CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	Division of Neurology 2
Reviewer Name(s)	David E. Jones, M.D.
Review Completion Date	3/17/2021
Established Name	Ponesimod
Trade Name	Ponvory
Applicant	Janssen Pharmaceuticals, Inc.
Dosage Form	Film-coated tablets
Dosing Regimen	20 mg daily after a 14-day dose titration
Applicant Proposed Indication	Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Recommendation on Regulatory Action	Approval

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Glossary

ALC	absolute lymphocyte count
ANC	absolute neutrophil count
AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
ARR	annualized relapse rate
AST	aspartate aminotransferase
BMI	body mass index
BRF	Benefit Risk Framework
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CM	cryptococcal meningitis
CMC	chemistry, manufacturing, and controls
CNS	Central Nervous System
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
EDSS	Expanded Disability Status Scale
FIS	Fatigue Impact Scale
FDA	Food and Drug Administration
FEV1	forced expiratory volume at one second
FVC	forced vital capacity
IBD	inflammatory bowel disease
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IR	information request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
LDL	low density lipoprotein
LFT	liver function test
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MERP	macular edema review panel
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OCT	optical coherence tomography
OLE	open label extension
OLP	open label phase
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PT	preferred term
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
RMS	relapsing multiple sclerosis
S1P	sphingosine-1-phosphate
SAE	serious adverse event
SCS	summary of clinical safety
SOC	system organ class
TB	total bilirubin
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell

1. Executive Summary

1.1. Product Introduction

Ponesimod (also known as JNJ-67896153 and ACT-128800) is an oral sphingosine-1-phosphate (S1P) receptor modulator that purportedly only binds to one ($S1P_1$) of the five known S1P receptors. As per Table 1, S1P receptors are ubiquitous in the human body and have protean biologic functions; their treatment effect in individuals with relapsing MS (RMS) is attributed to $S1P_1$, which regulates the egress of lymphocytes from secondary lymphoid tissue. This lymphocyte sequestration potentially modulates the adaptive immune system and reduces the number of auto-reactive lymphocytes in circulation, thereby reducing inflammatory activity in RMS. (Horga and Montalban, 2008)

Table 1. Reviewer Table. Distribution and biological activity of S1P receptors[1]

Subtype	Locations	Proposed Effects
$S1P_1$	Lymphocytes	Regulate lymphocyte egress from lymphoid tissue
	Thymocytes	Regulate thymocyte egress from thymus
	Mast cells	
	Eosinophils	
	Vascular smooth muscle	Modulate vasomotor tone
	Endothelial cells	Increased endothelial permeability
	Atrial myocytes	Cardiac conduction[2]
	Gastric smooth muscle	
	Neurons	Neurogenesis
	Astrocytes	Astrocyte migration
	Oligodendrocytes	Oligodendrocyte progenitor differentiation / survival
$S1P_2$	Vascular smooth muscle	Modulate vasomotor tone
	Gastric smooth muscle	Gastric smooth muscle contraction
	Neurons	Neuronal excitability
$S1P_3$	Endothelial cells	Increased endothelial permeability
	Vascular smooth muscle	Vasomotor tone regulation
	Atrial myocytes	Cardiac conduction
	Neurons	
	Astrocytes	
$S1P_4$	Lymphocytes	Cell shape and motility
$S1P_5$	Oligodendrocytes	Oligodendrocyte progenitor differentiation / migration

[1] Adapted from Table 1 in Horga and Montalban (2008).
[2] S1P1 is expressed on atrial myocytes (Camm et al 2014).

Currently, three S1P receptor modulators have been approved for the treatment of RMS,

which includes clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple (SPMS). The first of these that was marketed in the United States is fingolimod (Gilenya), which is a relatively non-selective S1P receptor modulator that was initially approved for adults on September 22, 2010 and is now approved for the treatment of RMS in individuals 10 years of age or older. Siponimod (Mayzent), which is purportedly selective for $S1P_1$ and $S1P_5$, and ozanimod (Zeposia), which is purportedly selective for $S1P_1 > S1P_5$, are also approved for the treatment of adults with RMS. Although one may expect that more selective S1P receptor modulators may have a fewer safety concerns than a less elective one, the safety profiles of the approved S1P receptors for RMS appear remarkably similar.

Ponesimod (Ponvory) is a new molecular entity (NME) that is purportedly selective for S1P1, for which the Applicant (Janssen Pharmaceuticals, Inc.) has submitted a New Drug Application (NDA) with a proposed indication for the treatment of adults with RMS. After a 14-day dose escalation (2, 2, 3, 3, 4, 4, 5, 6, 7, 8, 9, 10, 10, and 10 mg), the proposed maintenance dose of ponesimod is one 20 mg film-coated tablet per day.

1.2. Conclusions on the Substantial Evidence of Effectiveness

A large, Phase 3, active-controlled clinical trial, and a smaller, Phase 2, placebo-controlled study, provide substantial evidence of effectiveness for ponesimod in adults with RMS, as demonstrated by a statistically significant reduction in annualized relapse rate (ARR), a clinically relevant endpoint. This conclusion is further supported by ponesimod's robust effect on MRI metrics in both trials. Although a treatment effect on confirmed disability accumulation is not demonstrated in the Phase 3 study of ponesimod, it should be remembered that the active comparator used in this study (teriflunomide) has been shown to have a treatment effect on disability progression; however, this observation is tempered by the inconsistent results of other S1P receptor modulators on disability progression in subjects with RMS.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Ponesimod (Ponvory) is a sphingosine-1-phosphate (S1P) receptor modulator that is being developed for the treatment of relapsing forms of multiple sclerosis (RMS). Since it is purportedly selective for S1P1, ponesimod may be more selective than the other S1P receptor modulators that have been approved for the treatment of RMS given their robust treatment effects on relapse rates and new MRI activity. Ponesimod's development program includes two adequate and well-controlled studies in subjects with RMS, including a large Phase 3, active-controlled (teriflunomide) randomized clinical trial (RCT), a Phase 2, placebo-controlled, dose-finding RCT, and their open label extensions. The Phase 3 study provides substantial evidence that ponesimod results in a clinically relevant reduction in relapses compared to teriflunomide, which also has a treatment effect on relapses; both studies provide evidence that ponesimod has a treatment effect on MRI measures of inflammatory activity. Conversely, the Phase 3 study does not suggest that ponesimod has a treatment effect on disability as measured by Kurtzke's Expanded Disability Status Scale (EDSS) compared to teriflunomide; however, the clinical trials of this inhibitor of mitochondrial dihydroorotate dehydrogenase show a consistent treatment effect on disability metrics, so ponesimod may actually offer some potential benefit on disability progression. These benefits of ponesimod justify acceptance of a mild to moderate safety risk in subjects with RMS.

The safety signals identified with ponesimod appear similar to those of other S1P receptor modulators and include infections, lymphopenia, bradyarrhythmia and atrioventricular block (although all were first degree after implementation of an initial 14-day dose escalation), hepatic transaminase elevations suggestive of liver injury, hypertension, respiratory effects, and macular edema. Like other S1P receptor modulators, ponesimod may have an increased risk of (cutaneous) malignancies, for which enhanced pharmacovigilance would be appropriate.

As is typical in clinical trials for RMS, the inclusion / exclusion criteria for the ponesimod clinical trials selected a relatively healthy population of individuals with RMS; further, the study population was primarily from Europe and almost exclusively Caucasian, so the generalizability of this safety analysis to the overall RMS population may be somewhat limited.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The pathophysiology of RMS consists of a clear inflammatory (i.e., relapses and new MRI lesions) and a poorly understood "degenerative" (i.e., disease progression) component. Overall, it appears that MS becomes less "inflammatory" and more "degenerative" over time; however, both processes likely contribute to increasing disability. Worsening disability from "inflammatory" disease is due to incomplete recovery from inflammatory events; conversely, disability progression from "degenerative" disease is insidious but remains of unclear etiology. Currently, distinguishing disability progression due to "degeneration" from disability worsening from "inflammation" is difficult.	Reducing the inflammatory component of RMS with a S1P receptor modulator like ponesimod appears beneficial in that it may spare individuals with RMS from relapses and MRI activity; however, the effect of doing so on long term disability and the transition from RMS into a more "degenerative" phase of the disease is less clear, especially since ponesimod did not achieve statistical significance on its disability endpoints.
Current Treatment Options	There are over 18 agents approved for the treatment of RMS. Data for these agents strongly suggest that they reduce both relapse rates and MRI activity; however, the effectiveness of many of these agents in reducing disability progression at 12 or 24 weeks is questionable given less robust results and conflicting results among trials.	The RMS clinical trials demonstrate that ponesimod has a treatment effect on relapses and MRI metrics but did not show a convincing effect on disability worsening or progression.
Benefit	Two adequate and well-controlled trials provide substantial evidence that treatment with ponesimod 20 mg reduces the occurrence of relapses (and new MRI lesions) in a statistically significant and clinically relevant proportion of the RMS population. There is minimal uncertainty regarding this benefit. There is no clear indication that ponesimod offers a benefit on disability progression, although the clinical trials of the comparator used in the Phase 3 study (teriflunomide) showed a consistent treatment effect on disability metrics.	The benefits conferred by ponesimod justifies the acceptance of mild to moderate risk because a reduction in relapse rates (and new MRI lesions) are of value to individuals with RMS. The acceptance of more serious risk is not justified due to ponesimod's lack of a clear treatment effect on disability progression.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Safety Database The ponesimod safety database contains data from a large Phase 3, active-controlled (teriflunomide) and another Phase 2, placebo-controlled clinical trials in adults with RMS, and their long term extensions. These data are supported by placebo-controlled studies in adults with plaque psoriasis and clinical pharmacology studies, most of which were in healthy adult volunteers. Safety Concerns • The most common treatment emergent adverse events (TEAEs) in subjects randomized to ponesimod in the active-controlled Phase 3 study were ALT increase (19.5%), nasopharyngitis (19.3%), headache (11.5%), upper respiratory tract infection (10.6%), and hypertension (8.0%). Other TEAEs of interest include urinary tract infection (5.7%), dyspnea (5.3%), and dizziness (5.0%). • There were three deaths in subjects randomized to ponesimod during its clinical trials, including one from hepatic failure and sepsis in a Phase 1 study in subjects with hepatic impairment, another from sudden death in a subject with known vascular risk factors in the Phase 2 RMS study, and a third from cardiopulmonary insufficiency 55 days after the last dose of ponesimod. • Ponesimod is associated with lymphopenia and an increased risk of infections, potentially more so in individuals exposed to previous immunosuppressants. • Given the risk of bradycardia and atrioventricular (AV) block with	The degree of drug exposure to ponesimod 20 mg is adequate, and the demographics of the study subjects adequately reflects the intended population for use, although much of the study population is white and from Europe. Due to its risk of lymphopenia and infections, ponesimod's labeling should include a warning for an increased risk of infections, including herpes infections and progressive multifocal leukoencephalopathy, cryptococcal meningitis, and other opportunistic infections. Given the established relationship between initiation of other S1P receptor modulators and bradyarrhythmia, the studies of ponesimod excluded subjects with many pre-existing cardiac conditions and utilized a 14-day dose escalation. Ponesimod's labeling should recommend a baseline electrocardiogram (ECG), include a warning for the potential risk of bradyarrhythmia and atrioventricular block, and note which cardiac conditions were not studied in the ponesimod clinical trials. The labeling for ponesimod should also include the warnings established for other S1P

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	initiating other S1P receptor modulators, ponesimod was initiated with a 14-day dose escalation in the Phase 3 study. Second- and third-degree AV block were not observed in this study, and the incidence of bradycardia was 5.8% with ponesimod (compared with 1.6% with teriflunomide) after the first dose of the study drug, with the mean heart rate nadir occurring within three hours of that dose. • Ponesimod was also associated with hepatic transaminase elevations, hypertension, respiratory effects, macular edema, and probably cutaneous malignancies. These AEs are associated with other approved S1P receptor modulators and likely represent class effects. <u>Safety in the post-marketing setting</u> It is unclear if the risk of serious infections and malignancies will be increased with prolonged use of ponesimod in the post-marketing setting. <u>Risk management</u> Labeled warnings and a Medication Guide regarding the risks of infections, bradyarrhythmia and AV block, liver injury, macular edema, hypertension, respiratory effects, and PRES may mitigate the risk of serious outcomes from these events. The initial ponesimod dose escalation may further mitigate the risks of bradycardia and AV block in individuals without significant cardiac comorbidity, but first dose cardiac monitoring remains appropriate in select individuals with specific cardiac comorbidities. The risks of exposure to ponesimod during pregnancy, breast-feeding, childhood, and adolescence are unclear.	modulators, including liver injury, macular edema, hypertension, respiratory effects, posterior reversible encephalopathy syndrome (PRES), severe exacerbations in multiple sclerosis after discontinuation, and unintended immunosuppressive effects. The risk of malignancy, especially cutaneous malignancy, may rise in the postmarket setting as it did with other S1P receptor modulators for MS. In addition to increased pharmacovigilance to further define the magnitude of this risk, cutaneous malignancies should be included in Section 5 (Warnings and Precautions) of the labeling for ponesimod. Because ponesimod will be administered to women of childbearing potential, there will be postmarketing requirements for a pregnancy registry and a pregnancy outcomes study. There will also be a postmarketing requirement to perform pediatric and supportive nonclinical juvenile animal studies to establish the safety of ponesimod in children and adolescents with RMS, as per the Pediatric Research Equity Act (PREA).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

			Section where discussed, if applicable
☒	The patient experience data that was submitted as part of the application include:		
	☒	Clinical outcome assessment (COA) data, such as	See Sec 6.1 Study endpoints
		☒ Patient reported outcome (PRO)	See Sec 6.1 Study endpoints
		□ Observer reported outcome (ObsRO)	
		☒ Clinician reported outcome (ClinRO)	See Sec 6.1 Study endpoints
		□ Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:		
		□ Input informed from participation in meetings with patient stakeholders	
		□ Patient-focused drug development or other stakeholder meeting summary reports	
		□ Observational survey studies designed to capture patient experience data	
		□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.		

2. Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system (CNS) that likely occurs when a genetically susceptible individual is exposed to an environmental trigger. MS is one of the most common causes of non-traumatic neurologic disability in young

adults, and recent estimates suggest that almost one million people in the Unites States have this disease; therefore, the economic impact of MS (estimated at $10 billion annually in the US in 2013) is huge (Wallin et al., 2019; Reich et al., 2018). Approximately 50% of people with untreated MS have severe ambulatory limitations within 20 years of disease onset, and MS reduces life-expectancy by 5-10 years (Confavreux and Vukusic, 2006).

The International MS Genetics Consortium (IMSGC) has identified over 230 genetic loci that contribute to the risk of developing MS, and most of these are associated with the function of the immune system. The environmental triggers for MS are less well defined, although vitamin D deficiency and delayed exposure to the Epstein-Barr Virus (EBV) are considered to be risk factors for MS. The pathophysiology of MS includes a well-described inflammatory (or immune-mediated) component, which seems predominant earlier in the disease, and what is termed a "degenerative" component, which is less well understood but is felt to predominate later in the disease (Compston and Coles, 2008; Reich et al., 2018). The currently recognized clinical phenotypes of the disease include relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS); the modifier "active" is used to indicate either relapses or MRI activity, and the modifier "progression" indicates disability progression not attributable to relapses. Conversely, the term "worsening" should be used for disability progression attributable to relapses (Lublin et al. 2014).

About 85% of people who develop MS begin with RRMS, which has a predilection for women and an average age of diagnosis of approximately 30 years (Weinshenker et al., 1989). RRMS is characterized by recurrent inflammatory episodes, termed "relapses," in which auto-reactive lymphocytes marginate across the blood-brain barrier (BBB) and enter the CNS, leading to acute injury to myelin, oligodendrocytes, and axons and potentially causing new or worsening neurologic deficits. Potential targets of acute inflammatory injury include the subcortical white matter, brainstem, optic nerve, and spinal cord; however, recent data suggests that the grey matter and neurons can also be a target of this inflammatory attack and that these cortical lesions may correlate better with disability (Compston and Coles, 2008; Reich et al., 2018). The diagnostic criteria for RRMS require clinical or imaging evidence of dissemination of clinical events "in time and space," suggesting that a patient must experience at least two clinically or radiologically distinct episodes to be diagnosed with RRMS; however, after one clinical event, the most current iteration of the McDonald diagnostic criteria allows the coexistence of asymptomatic enhancing and nonenhancing lesions or intrathecal immunoglobulin synthesis to support dissemination in time (Polman et al., 2011; Thompson et al., 2018). Although early relapses may be followed by complete recovery, over time, relapses are associated with an accumulation of residual deficits and increasing disability (Confavreux et al., 1980; Weinshenker et al., 1989).

Over time, a slow, insidious progression of disability--that appears to be independent of the occurrence of relapses--is seen in many patients with RRMS (Weinshenker et al., 1989; Confavreux et al., 2000; Tremlett et al., 2009). On average, transition into this phase of the

disease, termed SPMS, occurs ~15 years after the diagnosis of RRMS, although frequent relapses soon after diagnosis (and incomplete recovery from early relapses) appears to hasten this transition (Confavreux 2003; Paz Soldan 2015), and drugs that treat RMS may delay this transition. The progression of disability in SPMS is felt to be driven by the poorly understood "degenerative" aspect of the disease. Hypotheses regarding the pathophysiology of this "degenerative process" in SPMS include a bioenergetic deficit from mitochondrial dysfunction, compartmentalized inflammation behind an intact blood-brain barrier, increased free radicals, an absence of any remaining functional reserve, or simply "neurodegeneration" (Mahad et al, 2015). Relapses and new MRI lesions can still occur in SPMS but are less frequent, especially later in this phase of the disease (Correale et al, 2017).

2.2. Analysis of Current Treatment Options

There are over 18 drugs that are FDA-approved to treat relapsing MS, including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active SPMS. Therapies for RMS reduce the annualized relapse rate in patients with RMS by approximately 30 to 70% but unfortunately achieve inconsistent results on disability progression, which is not surprising because of the different aspects of the pathophysiology of MS and the incomplete effect of relapses on disability progression. Even though meta-analyses of clinical trials in RMS (Sormani et al, 2009; Sormani and Bruzzi, 2013) suggest that the development of new MRI lesions may be a surrogate for relapses, the well-described "clinical-radiologic paradox" and the relatively weak correlation between MRI activity and disability suggest that MRI is not a good measure of how a patient functions, feels, or survives, thus lessening the importance of this endpoint from a regulatory point of view (Barkhof 1999, Sormani et al 2010). See Table 2 for a list of currently approved treatments for MS.

Table 2. Reviewer Table. FDA-approved treatments for relapsing multiple sclerosis

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency	Efficacy Information	Major Safety Concerns
Beta interferon 1b	Betaseron (Betaferon)	Relapsing forms of MS	1993	subcutaneous every other day	32% reduction in ARR	Hepatotoxicity, depression
Beta interferon 1a	Avonex	Relapsing forms of MS	1996	IM weekly	37% reduction in disability progression	Hepatotoxicity, depression
Glatiramer acetate[1]	Copaxone	Relapsing forms of MS	1996	subcutaneous daily[2]	29% reduction in ARR	None
Mitoxantrone	Novantrone	Relapsing forms of MS	2000	IV every 3 months	60% reduction in ARR; 64% reduction in disability progression	Cardiotoxicity, leukemia
Beta interferon 1a	Rebif	Relapsing forms of MS	2002	subcutaneous 3 times weekly	32% reduction in ARR	Hepatotoxicity, depression
Natalizumab	Tysabri	Relapsing	2004	IV every 28 days	61% reduction in	Progressive Multifocal

Approved Drug	Product Name	Relevant Indication	Year Approved	Route & Frequency	Efficacy Information	Major Safety Concerns
		forms of MS			ARR	Leukoencephalopathy,
Beta interferon 1b	Extavia	Relapsing forms of MS	2009	subcutaneous every other day	32% reduction in ARR	Hepatotoxicity, depression
Fingolimod[3]	Gilenya	Relapsing forms of MS	2010	orally once daily	55% reduction in ARR	1st dose bradycardia, lymphopenia, macular edema, fetal risk
Teriflunomide	Aubagio	Relapsing forms of MS	2012	orally once daily	31% reduction in ARR	Boxed warnings for hepatotoxicity and teratogenicity
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	2013	orally twice daily	44-53% reduction in ARR	Lymphopenia, PML, herpes zoster, liver injury
PEGylated Interferon Beta	Plegridy	Relapsing forms of MS	2014	subcutaneous every 2 weeks	36% reduction in ARR	Hepatotoxicity, depression
Alemtuzumab[4]	Lemtrada	Relapsing forms of MS after inadequate response to ≥ 2 MS treatments	2015	2 intravenous courses 12 months apart	49% reduction in ARR[5]	Boxed warnings for serious/fatal autoimmune conditions; serious and life-threatening infusion reactions, stroke, and increased risk of malignancies
Ocrelizumab	Ocrevus	Relapsing forms of MS and Primary Progressive MS (PPMS)	2016	IV every 2 weeks x 2 then IV x1 every 6 months	46% reduction in ARR (RMS)[5]; 24% reduction in disability progression (PPMS)	Infusion reactions, infections, reduction in immunoglobulins, increased risk of breast cancer
Siponimod	Mayzent	Relapsing forms of MS	2019	Oral once daily	38-48% reduction in ARR	1st dose bradycardia, lymphopenia, macular edema, fetal risk
Cladribine	Mavenclad	Relapsing forms of MS	2019	2 oral courses, one year apart	58% reduction in ARR	Malignancy, infections, lymphopenia, liver injury, teratogenicity
Diroximel fumarate[6]	Vumerity	Relapsing forms of MS	2019	orally twice daily	44-53% reduction in ARR	Lymphopenia, PML, herpes zoster, liver injury
Monomethyl fumarate[6]	Bafiertam	Relapsing forms of MS	2020	Oral twice daily	44-53% reduction in ARR	Lymphopenia, PML, herpes zoster, liver injury
Ozanimod	Zeposia	Relapsing forms of MS	2020	Orally once daily	38-48% reduction in ARR[7]	1st dose bradycardia, lymphopenia, macular edema, fetal risk
Ofatumumab	Kesimpta	Relapsing forms of MS	2020	Subcutaneously at week 0, 1, 2 and then every 4 weeks	51-59% reduction in ARR[8]	Infections, injection reactions, reduction in immunoglobulin, fetal risk

[1] Glatopa and other generic versions of the glatiramer acetate are now available.
[2] Daily and 3 times weekly formulations of glatiramer acetate are now available.
[3] Indicated for ≥ 10 years old
[4] Not indicated for use in patients less than 18 years of age due to safety concerns
[5] Compared to an active comparator (subcutaneous interferon β-1a).
[6] Utilized the 505(b)(2) regulatory pathway and relied on Tecfidera as the referenced product.
[7] Compared to an active comparator (intramuscular interferon β-1a).
[8] Compared to an active comparator (teriflunomide 14 mg).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ponesimod is a S1P receptor modulator that is purportedly selective for $S1P_1$ but otherwise has a similar mechanism of action to fingolimod (GILENYA), which was approved for the treatment of adults with RMS in 2010 and individuals aged 10 years and up in 2018. Other S1P modulators for RMS include siponimod (MAYZENT) and ozanimod (ZEPOSIA), which were approved for the treatment of adults with RMS in 2019 and 2020, respectively. Ponesimod is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND meeting: April 24, 2008

Original IND Submission: December 5, 2008
Although the initial studies of ponesimod were performed in France; the US IND (101722) was opened with Study AC-058-107, an open-label, pharmacokinetic study of a single dose of ponesimod 40 mg in ten healthy Japanese and ten healthy Caucasian subjects.

End of Phase 2 Meeting: December 6, 2011

(b) (4)

Type C Meeting Written Responses: October 3, 2014
Clinical topics discussed in this communication included the design (specifically the secondary endpoints and safety monitoring) of Study AC-058B301. The acceptability of the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS)

was also discussed; the Division noted that it will be "important to document support for a prespecified responder definition for the interpretation of clinically meaningful change on the FSIQ-RMS." The Applicant also initiated [redacted] (b) (4)

[redacted]

Type C Meeting Written Responses: May 21, 2018
The topics of this communication included changes to secondary endpoints and the multiplicity testing strategy for Study AC-058B301.

Type C Meeting Written Responses: February 1, 2019
The topics of this communication included the analyses of the primary and secondary endpoints in Study AC-058B301, ponesimod's first dose effect on cardiac conduction, and the need to determine a threshold for what constitutes a clinically meaningful change on the FSIQ-RMS.

Pre-NDA Meeting: September 4, 2019
The FSIQ-RMS was again discussed at this meeting; in brief, the Division did not agree that sufficient evidence or justification was provided to support the claim that "a [redacted] (b) (4) point change on the FSIQ Symptoms domain is an acceptable threshold for interpreting within-subject change from baseline at Week 108."

NDA Submission: March 18, 2020

4. Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the OSI review.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Control (CMC) review.

4.3. Clinical Microbiology

Please refer to the CMC/microbiology review.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology / toxicology review.

4.5. Clinical Pharmacology

Please refer to the clinical pharmacology review, from which this reviewer highlights the following points:

- "Ponesimod is a sphingosine 1-phosphate (S1P) receptor 1 modulator. Ponesimod binds with high affinity to S1P receptor 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 may involve reduction of lymphocyte migration into the central nervous system."

- "Ponesimod exposure increases in an apparent dose proportional manner at dose range from 1 to 75 mg/day. The time to reach maximum plasma concentration of ponesimod is 2 to 4 hours post-dose. … Food does not have a clinically relevant effect on ponesimod pharmacokinetics."

- "Ponesimod is extensively metabolized prior to excretion in humans, though unchanged ponesimod was the main circulating component in plasma. Two inactive circulating metabolites, M12 and M13, have also been identified in human plasma. M13 is approximately 20% and M12 is 6% of total drug related exposure."

- "Ponesimod is not recommended in patients with moderate and severe hepatic impairment. No therapeutic individualization for intrinsic or extrinsic factors is recommended."

- "Currently, limited data showed that concomitant use of strong PXR agonists may decrease the systemic exposure of ponesimod. It is unclear whether the impact of strong PXR agonists (e.g. rifampin, phenytoin, carbamazepine) on ponesimod systemic exposure would be considered of clinical relevance."

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

Table 3 delineates the clinical trials that were submitted to support this new drug application (NDA) for ponesimod.

Table 3. Reviewer Table. Clinical Studies of Ponesimod Submitted with NDA

Protocol #	Design	Exposure (n)
Phase 1 Studies		
AC-058-101	Double-blind, placebo-controlled, randomized, single ascending dose study to investigate the tolerability, safety, pharmacokinetics (including food interaction), and pharmacodynamics of ACT-128800 in healthy male subjects	Ponesimod: 36 Placebo: 12
AC-058-102	Single-center, double-blind, placebo-controlled, randomized, ascending multiple-dose study to investigate the tolerability, safety, pharmacokinetics, and pharmacodynamics of ACT-128800 in healthy male and female subjects	47
AC-058-103	Single-center, open-label, two-period, two-treatment, randomized, crossover study in healthy male subjects to investigate the pharmacokinetics of the polymorphic Forms A and C of ACT-128800	12
AC-058-104	Single-center, open-label, two-period, two-treatment, randomized, crossover study to investigate the effect of multiple-dose ACT-128800 on the pharmacokinetics of a single dose of Ortho-Novum® 1/35 in healthy female subjects	24
AC-058-105	A single-center, open-label, randomized, multiple dose, 3-treatment, 3-way crossover study to investigate the effects on heart rate and rhythm of three different up-titration regimens of ACT-128800, and of re-initiation of treatment in healthy male and female subjects.	30
AC-058-106	Single-center, open-label study with 14C-labeled ACT-128800 to investigate the mass balance, pharmacokinetics, and metabolism following single oral administration to healthy male subjects	6

AC-058-107	Single-center, open-label, parallel-group study to evaluate the pharmacokinetics, tolerability, and safety of a single dose of 40 mg ACT-128800 in Japanese and Caucasian healthy male and female subjects.	20
AC-058-108	Single-center, open-label, two-period, two-treatment, randomized, crossover study in healthy male and female subjects to compare the pharmacokinetics of 40 mg capsules and tablets of ACT-128800	14
AC-058-109	Single-center, double-blind, placebo-controlled, randomized, parallel-group, up-titration study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of increasing doses of ACT-128800 in healthy male and female subjects	16
AC-058-110	A single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group, multiple-dose, up-titration study of the electrocardiographic effects of ponesimod in healthy male and female subjects.	116
AC-058-111	Single-center, open-label, randomized, two-part, two-way crossover study to investigate the effects on heart rate, blood pressure, and pharmacokinetic interactions of ACT-128800a combined with a calcium channel blocker or a beta-blocker in healthy subjects	23
AC-058-112	Single-center, open-label, single-dose Phase 1 study to investigate the pharmacokinetics (PK), tolerability, and safety of ponesimod in subjects with mild, moderate, or severe hepatic impairment due to liver cirrhosis, and in healthy subjects.	32
AC-058-113	Single-center, open-label, single-dose Phase 1 study to investigate the pharmacokinetics, safety, and tolerability of ponesimod in subjects with moderate or severe renal function impairment	24
AC-058-114	Single-center, open-label, randomized, two-way crossover study to investigate the absolute bioavailability of a single oral dose of ponesimod in healthy male subjects	17
AC-058-115	Single-center, double-blind, placebo-controlled, randomized, two-way crossover, multiple-dose study to investigate the effects on heart rate and rhythm of two up-titration regimens of ponesimod in healthy male and female subjects.	32
AC-058-117	A Randomized, Double-blind, Parallel group, 2-period, Placebo-controlled, Phase 1 Study to Investigate the Effects on Heart Rate, Blood Pressure, and Pharmacokinetic Interactions of the Uptitration Regimen of Ponesimod in Healthy Adult Subjects Receiving Propranolol at Steady State	52
Clinical Trials in Subjects with Plaque Psoriasis		
AC-058A200	Multicenter, randomized, double-blind, placebo-controlled, Phase IIa study to evaluate the efficacy, safety, and tolerability of ACT-128800, an S1P1 receptor agonist, administered for 6 weeks to subjects with moderate to severe chronic plaque psoriasis	Ponesimod 20 mg: 45 Placebo: 15
AC-058A201	A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of two doses of ponesimod (ACT-128800), an oral S1P1 receptor agonist,	Ponesimod 20 mg:126 Ponesimod 40 mg: 133 Placebo: 127

	administered up to twenty-eight weeks in patients with moderate to severe chronic plaque psoriasis	
Clinical Trials in Subjects with Relapsing MS (RMS)		
AC-058B201	Multicenter, double-blind, randomized, 4-arm, parallel-group, dose-finding, placebo-controlled superiority study to evaluate efficacy, safety, and tolerability of ponesimod in subjects with RRMS (Duration 24 weeks)	Ponesimod 10 mg: 108 Ponesimod 20 mg:116 Ponesimod 40 mg: 119 Placebo: 121
AC-058B301	Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study designed to compare the efficacy and safety and tolerability of ponesimod versus teriflunomide in subjects with RMS (Duration 108 weeks)	Ponesimod 20 mg: 567 Teriflunomide 14 mg: 566
RMS Extension Studies[1]		
AC-058B202	Double-blind, randomized, multiple dose, parallel-group uncontrolled extension to Study AC-058B201 to explore long-term safety, tolerability, and efficacy of ponesimod in subjects with RRMS	Ponesimod 10 mg: 139 Ponesimod 20 mg:145 Ponesimod 40 mg: 151
AC-058B303	Multicenter, non-comparative, single arm, extension of AC-058B301 to evaluate long-term safety, tolerability, and disease control of ponesimod 20 mg in subjects with RMS	Ponesimod 20 mg: 877

[1] As of data cutoff date (31MAR2019 for AC-058B202 and 30May2019 for AC-058B303)

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. AC-058B301: Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study designed to compare the efficacy and safety and tolerability of ponesimod versus teriflunomide in subjects with RMS

6.1.1. Study Design

Overview and Objective

Study AC-058B301 is a Phase 3 clinical trial designed to compare the treatment effects, safety, and tolerability of ponesimod and teriflunomide in subjects with RMS.

Trial Design

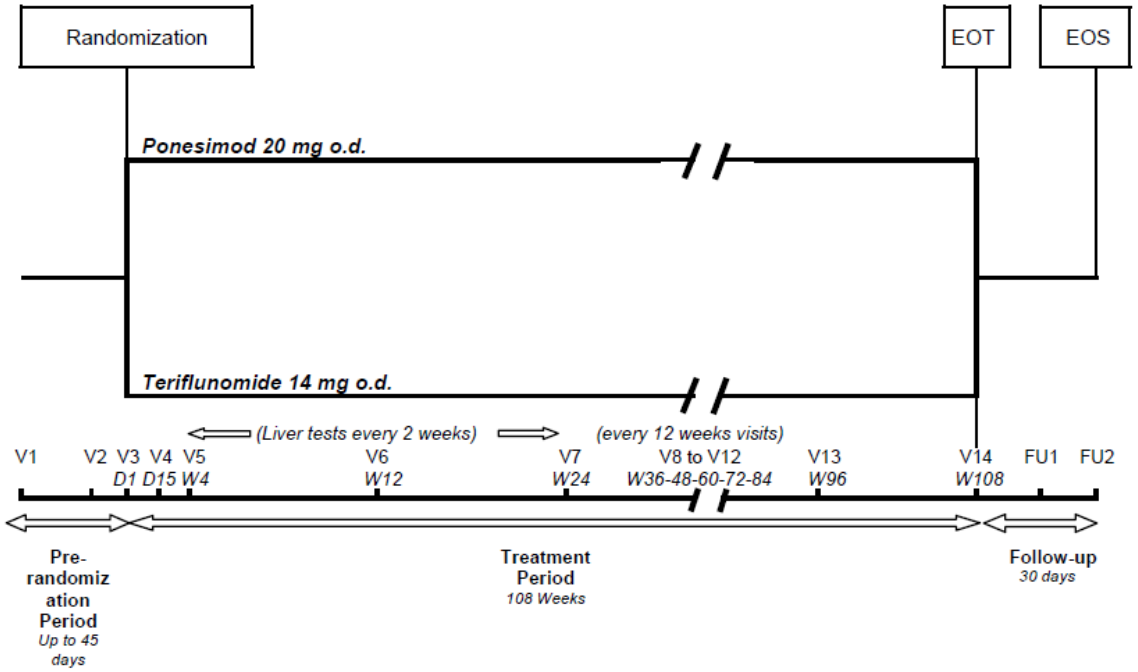
Study AC-058B301 is a prospective, multicenter, 1133-subject, double-blind, active-controlled, 1:1 randomized, double-blind, superiority study to evaluate the effectiveness, safety, and tolerability of ponesimod 20 mg daily compared to teriflunomide 14 mg daily in subjects with RMS. The primary efficacy endpoint of this study is annualized relapse rate (ARR), which is defined as the number of confirmed relapses per subject-year. Key secondary endpoints include the change in MS fatigue

(as measured by the Fatigue Severity Impact Scale – Relapsing Multiple Sclerosis [FSIQ-RMS]), an MRI metric (combined unique active lesions [CUAL]), and confirmed disability accumulation (CDA) at 3 and 6 months.

After completion of the 108-week Treatment Period (TP), randomized subjects were to have an End-of-Treatment (EOT) visit within seven days of the last dose of the study medication and to undergo an acceleration elimination procedure to remove teriflunomide, which undergoes enterohepatic recirculation, from the body. Subjects completing the TP were to attend a post-treatment safety follow-up (FU) visit 15 days after the last dose of the study drug was taken. Subjects completing Study AC-058B301 were eligible to enroll in a single-armed, long-term extension study of ponesimod (AC-058B303); those declining enrollment in this study were asked to attend a 30-day post-treatment safety FU visit.

Subjects who decided to prematurely discontinue the study drug were ineligible to participate in the AC-058B303 long term extension but were asked to undergo the accelerated elimination procedure, to attend 15- and 30-day post-treatment safety FU visits, and if possible, to remain in the study (albeit with an abbreviated schedule of assessments) for 108 weeks after randomization. See Figure 1.

Figure 1. Applicant Figure. AC-058B301 Study Design



D = day; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; M = month; V = visit; W = week.

Blinding

Study AC-058B301 employed a double-blind design in which the subjects, investigators, site study staff (including those performing the study assessments), study sponsor, and contract research organization (CRO) were to remain blinded to the identity of the study drug from the time of randomization until the database was locked for final study analysis.

To prevent unblinding during the double-blind treatment period, the protocol implemented the following procedures:

- The investigational treatment and the active comparator (and their packaging) were indistinguishable.
- Access to first date heart rate / atrioventricular conduction information, lymphocytes counts, and teriflunomide plasma concentrations was restricted unless required for subject safety.
- Relapse and disability accumulation assessments were performed by an efficacy assessor who was not involved in any other aspects of patient care and management throughout the study.
- Subjects were instructed not to discuss adverse events, heart rate, pulmonary function, or concomitant medications with the efficacy assessor, and the principal investigator / treating neurologist and the first-dose administrator were instructed to refrain from discussing clinical information about subjects unless necessary for that subject's safety.
- Study MRI's were evaluated by a central reading facility in a blinded fashion.

Reviewer Comment: The procedures implemented to reduce the risk of unblinding appear reasonable and appropriate.

Key Eligibility Criteria

Inclusion Criteria

1. "Signed informed consent prior to initiation of any study-mandated procedure.
2. Males and females aged 18 to 55 years (inclusive).
3. Subjects of reproductive potential are eligible only if the following apply:
   - WOCBP:
     - must have a negative serum pregnancy test at Visit 1 (Screening) and a negative urine pregnancy test at Visit 2 (Baseline);
     - must agree to undertake 4-weekly urine pregnancy tests during the study and up to 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L;
     - must agree to use reliable methods of contraception from Visit 1 until 6 weeks after the first of two tests showing teriflunomide level < 0.02 mg/L.

- Fertile male subjects participating in the study who are sexually active with WOCBP:
  - must agree to use a condom during the treatment period and for an additional 6 weeks after the first of two tests showing teriflunomide level < 0.02 mg/L.

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

Exclusion Criteria

1. "Lactating or pregnant women.
2. Subjects wishing to parent a child during the study.
3. Evidence of a relapse of MS with onset within 30 days prior to baseline EDSS assessment or between baseline EDSS assessment and randomization
4. Presenting with a diagnosis of MS with progressive course from onset (i.e., primary progressive MS or progressive relapsing MS).
5. Treatment with the following medications within 7 days prior to randomization:
   - IFN β-1a, IFN β-1b, or glatiramer acetate
6. Treatment with the following medications within 15 days prior to randomization:
   - β-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR lowering systemic therapy
   - Cholestyramine or activated charcoal
7. Treatment with the following medications within 30 days prior to randomization:
   - Adrenocorticotropic hormone (ACTH) or systemic corticosteroids (for any reason)
   - Dimethyl fumarate
   - Vaccination with live vaccines
8. Treatment with the following medications within 90 days prior to randomization:
   - Plasmapheresis, cytapheresis
   - i.v. immunoglobulin
   - Treatment with an investigational drug (within 90 days or five half-lives of the drug, whichever is longer), except biological agents

9. Treatment with the following medications within 180 days prior to randomization:
   - Azathioprine, methotrexate, or cyclophosphamide
   - Natalizumab
   - Other systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, mycophenolic acid)
   - Non-lymphocyte-depleting experimental biological agents (e.g., daclizumab)
10. Treatment with the following medications within 24 months prior to randomization:
   - Lymphocyte-depleting biological agents such as rituximab or ocrelizumab
   - Cladribine
11. Treatment with the following medications at any time prior to randomization:
   - Alemtuzumab
   - Mitoxantrone, leflunomide, or teriflunomide
   - Fingolimod
   - Ponesimod
   - Other investigational S1P modulators
   - Stem-cell transplantation
12. Ongoing known bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), positive hepatitis B surface antigen test at Visit 1 (Screening) (unless hepatitis B vaccination has occurred within 4 weeks prior to a positive screening test and a repeat hepatitis B surface antigen test performed ≥ 2 weeks after the initial test has been negative) or hepatitis C antibody tests at Visit 1 (Screening).
13. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Visit 1 (Screening).
14. Negative antibody test for varicella-zoster virus at Visit 1 (Screening).
15. Known Progressive Multifocal Leukoencephalopathy (PML) infection or evidence of new neurological symptoms or MRI signs within 6 months prior to randomization which are compatible with a diagnosis of PML infection
16. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation.
17. Presence of pre-cancerous (e.g., actinic keratosis, atypical moles) or cancerous skin lesions (e.g., basal cell carcinoma, squamous cell carcinoma) at Visit 2 (Baseline).
18. Presence of macular edema.
19. Any of the following cardiovascular conditions:
   - Resting HR < 50 bpm as measured by the pre-randomization 12-lead ECG on Day 1
   - Myocardial infarction within 6 months prior to randomization or ongoing unstable ischemic heart disease
   - Cardiac failure (New York Heart Association class III or IV) or any severe cardiac disease at the time of Visit 1 (Screening) or randomization
   - 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 (e.g., 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 QTcF interval > 470 ms (females), > 450 ms (males) as measured by 12-lead ECG at Visit 1(Screening) or Visit 2 (Baseline) or by the pre-dose ECG at Visit 3 (Randomization / Day 1)
- History of syncope associated with cardiac disorders
- Systemic arterial hypertension not controlled by medication according to the investigator's judgment

20. 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.
21. 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 6 months prior to randomization
    - Abnormal PFTs: FEV1 or forced vital capacity (FVC) < 70% of the predicted normal value at Visit 2 (Baseline)
22. Active or latent TB, as assessed by CXR performed at Visit 1 (Screening) or within 90 days prior to Visit 1 (Screening), or IFN gamma release assay (QuantiFERON-TB-Gold®) at Visit 1 (Screening), except if there is documentation that the subject has received adequate treatment for latent TB infection or TB disease previously
23. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline):
    - Hemoglobin (Hb) < 100 g/L
    - White blood cell (WBC) count < 3.5 × 109/L (< 3500/mm3)
    - Neutrophil count < 1.5 × 109/L (< 1500/mm3)
    - Lymphocyte count < 0.8 × 109/L (< 800/mm3)
    - Platelet count < 100 × 109/L (< 100,000/mm3)
24. Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within 3 years prior to randomization.
25. Presence of chronic liver or biliary disease.
26. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin, serum albumin, International Normalized Ratio (INR) and as well as on presence/absence and severity of ascites and hepatic encephalopathy.
27. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline):
    - ALT/SGPT > 2 × the upper limit of normal (ULN)
    - AST/SGOT > 2 × ULN
      Total bilirubin > 1.5 × ULN (unless in the context of known Gilbert's Syndrome).
28. Hypoproteinemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin < 3.0 g/dL.

29. Severe renal insufficiency defined as a calculated creatinine clearance < 30 mL/min (Cockroft-Gault) at Visit 1 (Screening) or Visit 2 (Baseline).
30. Known history of clinically significant drug or alcohol abuse.
31. Known allergy to any of the ponesimod formulation excipients.
32. Known allergy to any of the Aubagio® formulation excipients.
33. Known hereditary problems of galactose intolerance (e.g., Lapp lactase deficiency, glucose-galactose malabsorption).
34. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the subject at risk by participating in the study.
35. Contraindications for MRI such as:
    - Pacemaker, any metallic implants such as artificial heart valves, aneurysm/vessel clips and any metallic material in high-risk areas which are contraindicated for MRI according to the local procedures
    - Known allergy to any gadolinium (Gd)-containing contrast agent
    - Claustrophobia if its nature or severity is prohibitive for performing MRI according to the investigator's judgment
36. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for FU visits, or known likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study."

Reviewer Comment: These inclusion / exclusion criteria appear reasonable and appropriate.

Treatment

Rationale for dose selection

The 20 mg dose of ponesimod was chosen for Study AC-058B301 based on the results of Study AC-058B201, a Phase 2, placebo-controlled, dose-finding study of ponesimod in subjects with RRMS investigating the safety and efficacy of ponesimod doses ranging from 10 to 40 mg. The primary outcome measure of this 24-week study was the cumulative number of new gadolinium-enhancing lesions on MRI performed at Weeks 12, 16, 20, and 24. Per the CSR for Study AC-058B201, "A significant dose-response relationship ($P < 0.0001$) was identified for the primary endpoint using a multiple comparison modeling technique (MCP-Mod) … the treatment effect (ratio) vs placebo with ponesimod 10 mg was 0.566 (95% CLs: 0.337, 0.952, $P = 0.0318$), with ponesimod 20 mg 0.170 (95% CLs: 0.100, 0.289, $P < 0.0001$), and with ponesimod 40 mg 0.226 (95% CLs: 0.133, 0.384, $P < 0.0001$)."

Reviewer Comment: As noted in the regulatory history, although the Division recommended continued exploration of the 10 and 20 mg dose of ponesimod, ponesimod 20 mg daily was the only dose of ponesimod in this Phase 3 study.

First Dose Monitoring

Although it appears that the 14-day dose titration from 2 mg to the 20 mg maintenance dose of ponesimod (Table 4) may reduce its risk of early bradyarrhythmia, subjects who were initiating the study drug for the first time (or re-initiating it after missing at least one dose of the titration or more than 3 consecutive days of the maintenance dose) received the first dose of this dose titration in a monitored setting. Since heart-rate reductions (or bradyarrhythmia) would suggest randomization to ponesimod, this first-dose monitoring (electrocardiograms [ECG] and blood pressure checks) was overseen by a separate physician (first-dose administrator) to preserve the study blind. Subjects were eligible for discharge after four hours of monitoring if the following criteria were met; however, the study drug was to be permanently discontinued in those subjects who did not meet these criteria after 12 hours:

- "ECG-derived resting HR > 45 bpm, and if HR < 50 bpm it must not be the lowest value post-dose;
- SBP > 90 mmHg;
- QTcF < 500 ms and QTcF increase from pre-dose < 60 ms;
- No persisting significant ECG abnormality (e.g., AV block second- or third-degree) or ongoing AE requiring continued cardiac monitoring or prohibiting study continuation as an out-patient."

Table 4. Reviewer Table: Titration and Re-titration Regimen, AC-058B301

Day(s)	1-2	3-4	5-6	7	8	9	10	11	12-14	14+
Dose (mg)	2	3	4	5	6	7	8	9	10	20

Reviewer Comment: Even though ponesimod is deemed to selectively modulate $S1P_1$, some subjects developed bradyarrhythmia after starting the agent, thereby necessitating a 14-day dose titration and initial cardiac monitoring, particularly in subjects with cardiac comorbidities.

Concomitant Medications

Per the protocol for Study AC-058B301, all-concomitant therapies (including contraceptives or traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) were to be recorded in the eCRF.

The protocol allowed enrollment of subjects who had been treated with a stable dose of (dal)fampridine for at least 90 days before randomization. Subjects were not to start or increase the dose of (dal)fampridine during the study, and stopping or decreasing the dose of (dal)fampridine during the study was only to occur when absolutely necessary.

The following concomitant therapies were allowed:

- Atropine for symptomatic bradycardia
- Short-acting ß2-agonists for respiratory symptoms
- Vaccination with non-live vaccines.

The following concomitant medications were allowed, albeit with caution:

- Warfarin
- "QT-prolonging drugs with known risk of Torsades de Pointes
- CYP2C8 substrates, such as repaglinide, paclitaxel, pioglitazone, or rosiglitazone
- Medicinal products metabolised by CYP1A2 such as duloxetine, alosetron, theophylline, and tizanidine
- Substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, zidovudine
- Substrates of breast cancer resistant protein (e.g., topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OAT polypeptide family (e.g., nateglinide, repaglinide, rifampicin), especially HMG-CoA reductase inhibitors (e.g., rosuvastatin, simvastatin, atorvastatin, pravastatin)
- Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort
- Other treatments considered necessary for the subject's wellbeing and not categorized as prohibited concomitant medications"

The use of the following medications was prohibited in Study AC-058B301:

- Systemic corticosteroids and ACTH, except for the treatment of MS relapses and for short-term treatment with low dose corticosteroids
- "Disease-modifying drugs for MS other than prescribed as per protocol
- Immunosuppressive treatment
- i.v. immunoglobulin
- Plasmapheresis, cytapheresis, or total lymphoid irradiation
- Live vaccines
- β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR-lowering systemic therapy
- Cholestyramine or activated charcoal unless needed for an accelerated elimination procedure
- Any other investigational drug
- Any investigational therapeutic procedure for MS"

Treatment of Relapses

The protocol for Study AC-058B301 recommended treatment of confirmed MS relapses with a standard course of corticosteroids (1000 mg/day of methylprednisolone for three to five days) and discouraged the use of other corticosteroids, other doses, other routes of administration, or ACTH unless deemed necessary. The protocol prohibited the use of plasma exchange and tapering with oral corticosteroids.

Assessments

The schedule of assessments for Study AC-058B301 is summarized in the tables below.

Table 5. Applicant Table. Schedule of Assessments, Study AC-058B301

Periods	Name	PRE-RANDOMIZATION (1)		TREATMENT PERIOD						
	Duration	Up to 45 Days		108 Weeks						
Visits	Number	1	2	3	4	5	6	7	8–9	10
	Name	Screening	Baseline	Rand	W2	W4	W12	W24	W36 – 48	W60
	Time	Day −45 to −1		Day 1	Day 15	Week 4	Week 12	Week 24	Week 36 – 48	Week 60
	Visit window				± 1 day	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed consent*		X								
Inclusion/exclusion criteria*		X	X	X						
Demographics*		X								
Medical history / smoking status*		X	X							
MS history & treatment*		X								
McDonald criteria (revision 2010)		X								
EDSS/FS*		X	X				X	X	X	X
Relapse* (2)			X	X (2) <----------						-----------> X (2)
MSFC*, SDMT *		X(3)	X(3)	X(3)			X	X		X
FSIQ-RMS** (4), PGI-S**, CGI-C*			X(5)				X	X		X
SF-36v2**			X				X	X		X
Health care resource utilization* (6)					X	X	X	X	X	X
WPAI:MS**			X				X	X		X
Patient preference questionnaire** (7)		X	X							
Chest X-ray* (8)		X								
eC-SSRS**			X							X
MRI** (9)			X							X
Concomitant medications*		X	X	X	X	X	X	X	X	X
Physical examination*		X	X			X	X	X		X
Dermatological examination* (10)			X							X
Body weight and height* (11)		X								X
Body temperature*		X	X	X	X	X	X	X	X	X
SBP/DBP*		X	X	X(12)	X	X	X	X	X	X
12-lead ECG** (13)		X	X	X(14)	X	X	X(15)	X	X	X
Ophthalmological examination* / OCT* (16)		X					X	X		X
PFT** (17)			X			X	X			X
Hematology/Chemistry** (fasted)		X	X		X	X (18) <----------			X	X
Urinalysis		X				X	X	X		X
Tuberculosis test / Viral serology **		X								
Additional serum sample for viral serology			X							
Pregnancy test*/**		X (19)	X		X	X	X	X	X	X
PK sampling for ponesimod* (20)				X			X			X
Study drug dispensing & accountability (21)*/**				X	X	X	X	X	X	X
Study drug swallowing test (optional)			X							
AEs*/SAEs(22)		X	X	X	X	X	X	X	X	X

*Data collected in the eCRF
**Data electronically transferred to sponsor.
Day 1 (date of randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

(1) All pre-randomization assessments performed at Visit 1 (Screening) and Visit 2 (Baseline) may be conducted on days differing from the actual Visit 1 (Screening) date defined as the start of screening activities (i.e., signature of the informed consent form) and Visit 2 (Baseline)date defined as the date of baseline EDSS assessment. However, all pre-randomization assessments performed at Visit 1 and repeated at Visit 2 (Baseline; e.g., hematology, blood chemistry, urinalysis, physical examination, central laboratory, 12-lead ECGs, and SBP/DBP) must be performed at least 7 days after the Visit 1 (Screening) assessments. For women of childbearing potential, the serum pregnancy test at Visit 1 (Screening) must be performed at least 3 weeks before the urine pregnancy test performed pre-randomization at Visit 2.The blood draw at Visit 2 (Baseline) should happen early enough in order obtain the results from the central laboratory and confirm the eligibility prior to randomization.

(2) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsening neurological symptoms. In addition, the site will contact the subject in between the 12-weekly visits (e.g., Visit 6–Week 12, Visit 7–Week 24,…) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, and 102 (+/− 7 days), or 6 weeks after the last 12-weekly visit (+/− 7 days). Whenever, between visits, a subject experiences any new or worsening neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a relapse assessment questionnaire [see Appendix 17].

(3) During pre-randomization, two practice tests and a third test serving as baseline assessment will be performed. Ideally, the three tests should be performed ≥ 5 days apart (i.e., second test practice ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first test practice may be done at Visit 1 (Screening), the second test practice may be done at Visit 2 (Baseline) and the third test serving as baseline may be performed pre-dose at Visit 3 (Randomization).

(4) The symptoms scale (with a 24-h recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit). During pre-randomization, subjects during Visit 1 (Screening) will be provided with the FSIQ-RMS and will be instructed to complete the symptoms domain (i.e., section 1) of the FSIQ-RMS on 7 consecutive days prior to randomization at home (provided no other assessment performed in the meantime exclude the subject). Once the results from the laboratory tests confirm the subject's eligibility, the site coordinator will contact the subject to instruct him/her to start the completion of the symptoms domain of the FSIQ-RMS at latest 7 days before the randomization.

(5) No CGI-C assessment at Baseline.
(6) Health care resource utilization data, including number of intensive care unit admission for MS relapses and emergency medical services facility visits for MS
(7) Only for subjects participating in the patient preference substudy. The Multiple Sclerosis Patient Preference Questionnaire will be completed at home twice during pre-randomization (after Visits 1 and 2 [Screening and Baseline]).
(8) Any CXR that has been performed within 90 days prior to screening can be used (in this case, no need to repeat CXR at Screening). In case of re-screening, CXR does not need to be repeated if CXR was performed within 90 days prior to the date of re-screening.
(9) Brain MRI to be performed at any time an opportunistic infection in the central nervous system is suspected. In addition, non-conventional MRI techniques (MTR and DIR) will be performed at selected sites only.
(10) Dermatological examination to be performed by a dermatologist. In case of re-screening, skin examination does not need to be repeated if skin examination from initial screening was performed within 90 days prior to the date of re-screening
(11) Height only at Visit 1 (Screening).
(12) SBP/DBP: Pre-dose and hourly (+/− 15 min) for at least 4 h post-dose and up to 12 h.
(13) Only pre-dose ECGs at all visits except Day 1 and Week 12.
(14) Pre-dose and hourly (+/− 15 min) for at least 4 h post-dose and up to 12 h.
(15) Pre-dose and 3-h (+/− 15 min) post-dose ECGs.
(16) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms or findings suggestive of macular edema or active uveitis [see Section 5.1.13.7].
(17) Pulmonary function tests include spirometry to be performed pre-dose in all subjects and DL_{CO} to be performed in a subset of approximately 400 subjects at selected sites only.
(18) In addition, liver tests (ALT, AST, INR, alkaline phosphatase and total bilirubin) at Weeks 6, 8, 10, 14, 16, 18, 20, and, 22 will be collected, sent to, and analyzed at the central laboratory. Furthermore, total white blood cell and total lymphocyte counts will be assessed at Weeks 8, 16, and 20. The test window is ± 3 days. Note: No relapse assessment questionnaire is needed when blood sample is drawn.
(19) Serum pregnancy test at Screening, urine pregnancy test at all subsequent visits. Urine pregnancy tests (performed at home) on a 4-weekly (+/− 4 days) basis between the visits during the study (results to be communicated by telephone call to the principal investigator / treating neurologist). At all visits and telephone calls, the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.
(20) Pharmacokinetic sampling pre-dose at Weeks 12, 60 and 108, and 3 h (+/− 15 min) post-dose on Day 1 and Week 12.
(21) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
(22) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CGI-C = Clinician's Global Impression of Change of the patient's relapsing MS; CXR = chest X-ray; DBP = diastolic blood pressure; DIR = double inversion recovery; DL_{CO} = diffusing capacity for the lungs measured using carbon monoxide; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; FS = functional system; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; INR = International Normalized Ratio; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MTR = magnetization transfer ratio; OCT = optical coherence tomography; PFT = pulmonary function test; PGI-S = Patient's Global Impression of Severity of Fatigue; PI = principal investigator; PK = pharmacokinetics; SAE = serious adverse event; SBP = systolic blood pressure; SDMT = Symbol Digit Modalities Test; WPAI:MS = Work Productivity and Activity Impairment Index: Multiple Sclerosis.

Table 6. Applicant Table. Schedule of Assessments Study AC-058B301, Cont'd

Periods	Name	TREATMENT PERIOD				FOLLOW-UP		UNSCHEDULED			
	Duration	108 Weeks				30 Days					
Visits	Number	11	12	13	14	15	16	R1, R2, …	U1, U2, …	I1, I2, …	
										d1	d15
	Name	W72	W84	W96	EOT	FU1	FU2	Relapse	Unscheduled (19)	Re-initiation	
										Day 1 of re-initiation	Day 15 after re-initiation
	Time	Week 72	Week 84	Week 96	Week 108 or earlier in case of premature discontinuation (18)	Last study drug intake +15 days	Last study drug intake +30 days	Any day between Day 1 and EOS			
	Visit window	± 7 days	± 7 days	± 7 days	± 7 days	−1 day, +7days	+7 days (22)	+7 days	NA	NA	± 1 day
EDSS/FS*		X	X	X	X		X	X	X		
Relapse* (1)		X(1)<----------X(1)				X	X	X	X (21)		
MSFC*, SDMT*			X		X						
FSIQ-RMS** (2), PGI-S**, CGI-C *			X		X			X	X		
SF-36v2**			X		X			X			
Health care resource utilization* (3)		X	X	X	X			X			
WPAI:MS**			X		X						
Patient preference questionnaire** (4)						X					
Chest X-ray* (5)					X						
MRI** (6)					X				X		
eC-SSRS**					X						
Concomitant medications*		X	X	X	X	X	X	X	X		
Physical examination*			X		X			X	X		
Dermatological examination* (7)					X				X		
Body weight*					X				X		
Body temperature*		X	X	X	X	X	X	X	X	X	X
SBP/DBP*		X	X	X	X	X	X		X	X(8)	X
12-lead ECG** (9)		X	X	X	X	X	X		X	X(9)	X
Pulse rate*								X	X(20)		
Ophthalmological examination / OCT* (10)					X				X		
Pulmonary function tests** (11)					X	X	X		X		
Hematology/Chemistry**(fasted)		X	X	X	X	X	X		X		
Urinalysis			X		X	X			X		
Viral serology									X		
Pregnancy test*/** (12)		X	X	X	X	X	X (12)		X		
Serum sample vaccination* (13)									X		
PK sampling for ponesimod*					X				X (14)		
Teriflunomide plasma concentration									X (23)		
Accelerated elimination procedure					X	X (15)					
Accelerated elimination procedure compliance review						X	X (24)				
Study drug dispensing/accountability (16)		X	X	X	X			X	X	X	X
AEs/SAEs* (17)		X	X	X	X	X	X	X	X	X	X

*Data collected in the eCRF
**Electronically transferred to sponsor.
Day 1 (date of randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

(1) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsening neurological symptoms. In addition, the site will contact the subject in between the 12-weekly visits (e.g., Visit 6–Week 12, Visit 7–Week 24,…) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, and 102 (+/− 7 days), or 6 weeks after the last 12-weekly visit (+/− 7 days). Whenever, between visits, a subject experiences any new or worsening neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a relapse assessment questionnaire [see Appendix 17].
(2) The symptoms scale (with a 24-h recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit).
(3) Health care resource utilization data, number of intensive care unit admission for MS relapses and emergency medical services facility visits for MS.
(4) Only for subjects-participating in the patient preference sub-study. The Multiple Sclerosis Patient Preference Questionnaire will be completed at home during follow-up period (before Visit 15 [FU1]).
(5) In case of premature study drug discontinuation, the chest X-ray at EOT does not need to be performed if the EOT visit occurs within less than 24 weeks of the pre-randomization chest X-ray.
(6) Brain MRI to be performed at any time an opportunistic infection in the CNS is suspected. In addition, non-conventional MRI techniques (MTR and DIR) will be performed at selected sites only. Note: in case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within less than 4 weeks of the MRI assessment at Visit 10 (Week 60).

(7) Dermatological examination to be performed by a dermatologist.
(8) SBP/DBP: Pre-dose and hourly (+/− 15 min) for at least 4 h post-dose and up to 12 h.
(9) Pre-dose ECGs at all visits (when applicable) except re-initiation visits. At re-initiation, pre-dose and hourly (+/− 15 min) for at least 4 h post-dose ECGs and up to 12 h.
(10) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.13.7].
(11) PFTs include spirometry to be performed pre-dose in all subjects and DL_{CO} to be performed in a subset of approximately 400 subjects at selected sites only.
(12) Serum pregnancy test at FU2. Urine pregnancy test at all other visits. Urine pregnancy tests (performed at home) on a 4-weekly basis between the visits during the study and continued after last study drug intake on a 4-weekly basis (+/− 4 days) (performed at home) until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L (results of the pregnancy tests to be communicated by telephone call to the principal investigator / treating neurologist). At all visits and telephone calls, the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.
(13) Pre- and post-vaccination sampling for vaccine-specific antibody titers for subjects having received non-live vaccination while on study treatment (sub-study)
(14) When possible, collect PK sample upon experiencing SAE. Preferably, sample will be collected pre-dose, as early as possible after SAE onset, and no later than 7 days after the last dose of study drug.
(15) If the subject was not compliant with the accelerated elimination procedure, the procedure must be repeated or missing intakes completed.
(16) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
(17) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.
(18) The EOT visit will take place at Week 108 (or earlier in case of premature discontinuation of study drug). In all cases, the EOT visit should take place 1 day after the last dose of study drug but no later than 7 days after the last dose of study drug.
(19) Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.
(20) Only if no 12-lead ECG is performed at this visit.
(21) Only at unscheduled visits when the subject meets with the treating neurologist (but not at other unscheduled visits (e.g., conducted for repeat ALT or AST testing, repeat PFT testing,…).
(22) For subjects not continuing in the AC-058B303 extension study, FU2 will be performed 30 to 37 days after last study drug intake. For subjects continuing in the AC-058B303 extension study, an abbreviated FU2 will be performed 23 to 37days after last study drug intake, if needed for compliance reasons. The abbreviated FU2 should include: Accelerated elimination procedure compliance review, AEs/SAEs, relapse, concomitant medications
(23) The testing of teriflunomide plasma concentration may be conducted for women of childbearing potential and fertile male subjects, if needed to confirm that contraception may be discontinued. Teriflunomide plasma concentration can also be assessed for any subjects not entering the extension study if deemed necessary for the subject's safety, at the investigator's discretion. Testing must not be conducted earlier than i) 20 weeks after last drug intake if the subject's compliance with the accelerated elimination procedure has been assessed as sufficient [see Section 5.1.14.2]; ii) 35 weeks (i.e., 8 months) after last drug intake or EOS, whichever is last, if the subject's compliance with the accelerated elimination procedure has not been assessed as sufficient.
(24) Only if the accelerated elimination procedure has been repeated or missing intake was completed after FU1.

AE = adverse event; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; CGI-C = Clinician's Global Impression of Change of patient's relapsing MS; CNS = central nervous system; DBP = diastolic blood pressure; DL_{CO} = diffusing capacity for the lungs measured using carbon monoxide; DIR = double inversion recovery; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; EOS = End-of-Study; EOT = End-of-Treatment; FS = functional system; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; FU1 = follow-up visit 1; FU2 = follow-up visit 2; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MTR = magnetization transfer ratio; OCT = optical coherence tomography; PFT = pulmonary function test; PGI-S = Patient's Global Impression of Severity of Fatigue; PI = principal investigator; PK = pharmacokinetics; SAE = serious adverse event; SBP = systolic blood pressure; SDMT = Symbol Digit Modalities Test; WPAI:MS = Work Productivity and Activity Impairment Index: Multiple Sclerosis.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of Study AC-058B301 is annualized relapse rate (ARR), which is defined as the number of confirmed relapses per subject-year.

Reviewer Comment: This is a very reasonable, appropriate, and clinically relevant primary efficacy endpoint for a pivotal study in subjects with RMS.

Secondary Endpoints

The first secondary endpoint in the prespecified hierarchical analysis is the "change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the Fatigue Symptoms and Impact Questionnaire – Relapsing Multiple Sclerosis (FSIQ–RMS)." As noted in the regulatory history section, sufficient evidence or justification was not provided to support the claim that "a (b) (4) point change on the FSIQ

Symptoms domain is an acceptable threshold for interpreting within-subject change from baseline at Week 108."

Reviewer Comment: Since the threshold for a clinically-meaningful change on the unscaled 77-point FSIQ-RMS Symptoms domain (or its 100-pt scale) has not been established, the ability to confidently comment on the clinical significance of a (b) (4) *point change in this endpoint is limited; however, in general, a confirmed 20% change on an outcome assessment is deemed clinically meaningful.*

The second secondary endpoint in the prespecified hierarchical analysis is the "cumulative number of combined unique active lesions (CUAL; defined as new Gd+ T1 lesions plus new or enlarging T2 lesions [without double-counting of lesions]) from baseline to Week 108."

Reviewer Comment: Although it is not a measure of how one functions, feels, or survives and may not accurately predict an individual's clinical status, CUAL is a reasonable secondary efficacy endpoint, and MRI metrics have been reported in the labelling for other drugs, including other S1P receptor modulators, for RMS.

The third and fourth secondary endpoints in the prespecified hierarchical analysis are "time to 12-week confirmed disability accumulation (CDA) from baseline to EOS" and "time to 24-week CDA from baseline to EOS," in which EOS is reached when the treatment and safety follow-up (potentially including a post-treatment observation period) has been completed.

Reviewer Comment: Confirmed disability progression (or accumulation) endpoints based on the EDSS are reasonable and appropriate secondary endpoints in RMS studies.

Statistical Analysis Plan

Below is this reviewer's interpretation of the statistical analysis plan (SAP). See the Biometrics review by Dr. Xiang Ling for a more detailed discussion of the SAP.

Analysis Population

Efficacy analyses are performed on the set of all randomized subjects, termed the Full Analysis Set (FAS). The safety population consists of all randomized subjects who received at least one dose of the study medication. Subjects who stopped the assigned study medication were encouraged to continue to be followed in a post-treatment observation period (PTOP).

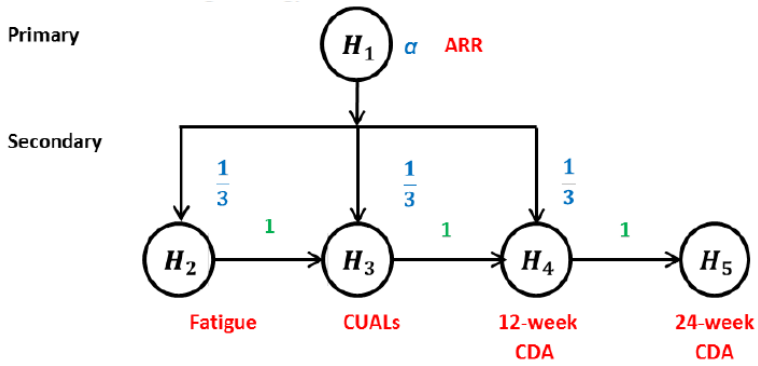
Endpoints

Per the protocol for Study AC-058B301,

> "The primary statistical analysis of the ARR endpoint will be performed on the FAS using a negative binomial model for confirmed relapses, with the stratification variables prior use of disease-modifying therapies (DMTs) and EDSS category as well as the number of relapses in the year prior to study entry, included in the model and time in the study as an offset variable ... The primary null hypothesis is that the ARR (μ) does not differ between ponesimod 20 mg and teriflunomide 14 mg. The alternative hypothesis is that the ARR differs between ponesimod 20 mg and teriflunomide 14 mg."

If the null hypothesis regarding the primary endpoint is rejected using a two-sided significance level of 0.01 for conclusive evidence and 0.05 for a positive study, analyses of the secondary endpoints will proceed using an overall two-sided significant level of 0.05 and a fallback method for allocating alpha as per Figure 2.

Figure 2. Applicant Figure. Overall testing strategy (alpha-sharing)



Power

Per the CSR,

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

Interim Analyses

Per the protocol for Study AC-058B301, "No unblinded interim analysis is planned for the study; however, a blinded interim analysis based on the first 291 randomized subjects will be performed in order to confirm the definition of FSIQ responders." The CSR and

Independent Data Monitoring Committee (IDMC) minutes do not mention other interim analyses.

Protocol Amendments

As shown in Table 7, there were six global protocol amendments to the original protocol for Study AC-058B301.

Table 7. Reviewer Table. Synopsis of Protocol Amendments, Study AC-058B301

Version	Release Date	Major Changes
2	29APR2015	Added substudy to assess subject outcome preferences with the electronic Multiple Sclerosis Patient Preference Questionnaire.
3	16JUL2015	Addressed comments from a Voluntary Harmonization Procedure (VHP) review in the EU: also added an exclusion criterion for signs of progressive multifocal leukoencephalopathy (PML), an electronic self-rated version of the Columbia-Suicide Severity Rating Scale (e-CSSRS) assessment, and every four week assessments of lymphocyte counts.
4	5FEB2016	Introduced a standardized stepwise procedure for confirming and reporting relapses, including a relapse assessment questionnaire.
5	14NOV2016	Modified procedure for testing teriflunomide plasma concentration after discontinuation of study drug.
6	30AUG2017	Allowed testing of teriflunomide plasma concentration in any subject who has discontinued study drug if deemed necessary for the subject's safety.
7	5DEC2018	Reduced the number of secondary endpoints in Study AC-058B301 from five to four to reduce the complexity of the testing strategy.

Data Quality and Integrity

Before a site could begin Study AC-058B301, a sponsor representative reviewed all of the essential study documents with the principal investigator (PI) and site personnel involved in the study at a site initiation visit. Site monitors also periodically visited study sites to review the completeness and accuracy of the collected data, adherence to the protocol and Good Clinical Practice (GCP), and study medication handling.

To ensure consistent EDSS scoring across time and subjects, sites were provided the interactive Neurostatus Training DVD-ROM. Efficacy assessors were to review this and demonstrate competency with the EDSS on a computerized assessment (Neurostatus

eTest) prior to enrollment of the first subject at the study site and every 2 years thereafter; however, the protocol did not specify the level of certification required.

Reviewer Comment: Many RMS studies utilize the Neurostatus program to certify EDSS raters. This reviewer would have more confidence in the validity of the EDSS assessments if the required level of certification had been specified, especially if level C certification (the highest level) was required of the efficacy assessors.

6.1.2. **Study Results**

Compliance with Good Clinical Practices

The Applicant reports that the protocol for Study AC-058B301 (and its six substantial global amendments and seven-country specific amendments) and any study documents provided to subjects (including the Informed Consent Form [ICF]) were reviewed (and approved) by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before use in the study. Additionally, the "Ethics" section at the beginning of the CSR states the following:

- "This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements."
- "Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment."
- "Personal data from subjects enrolled in this study were limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study agent(s) used in this study and were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations."
- "Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study."

The protocol for Study AC-058B301 allowed audits of investigator sites "to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations;" the CSR suggests that seven vendors and 16 investigator sites were audited. One of these audits led to investigation of a particular site, at which a "serious breach of GCP … due to serious violation of the ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles, informed consent process, Investigational Medicinal Product reconciliation, protocol adherence and PI oversight at the site" was discovered.

Financial Disclosure

Module 1, Section 1.3.4 of this NDA includes information regarding financial certification and disclosure. Form FDA 3455 identified one sub-investigator ((b) (6) at site (b) (6)) who reported no disclosable interests with Actelion but disclosed a > $50,000 USD equity interest in Johnson and Johnson, which acquired Actelion in June of 2017. Site (b) (6) randomized (b) (6) subjects in Study AC-058B301 and enrolled (b) (6) of these subjects in the AC-058B303 long term extension.

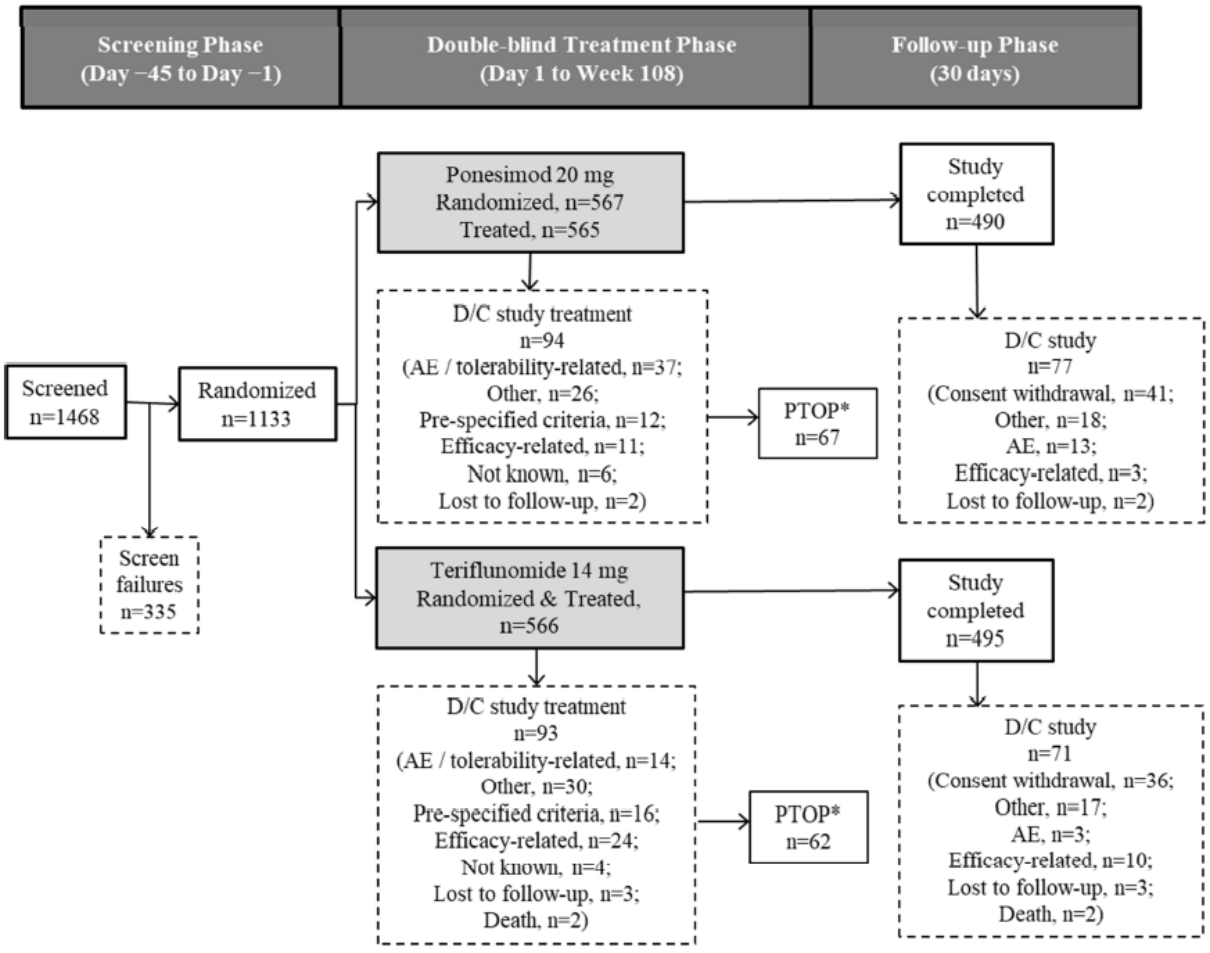
As per the two submitted Form FDA 3454s, most of the principal investigators and sub-investigators for Study AC-058B301 denied having disclosable financial interest in the Applicant; however, financial information (mostly follow-up information after Johnson and Johnson acquired Actelion in June 2017) was missing for 64 (5.5%) of the 1162 study site staff involved in studies of ponesimod.

Patient Disposition

First subject screened: 27APR2015
Last subject last visit: 16MAY2019
Clinical Study Report Approved: 05FEB2020

In Study AC-058B301, 1486 subjects were screened at 171 study sites in 28 countries, and 1133 of these were randomized and comprise the full analysis set (FAS) and the Intent to Treat (ITT) population. Of these 1133 subjects, 567 were randomized to ponesimod 20 mg daily, and 566 were randomized to teriflunomide daily; however, two subjects randomized to ponesimod were not treated with the study drug, so the safety population consists of 1131 subjects. The disposition of the subjects in Study AC-048B301 is shown in Figure 3.

Figure 3. Applicant Figure. Patient Disposition (CONSORT Diagram)



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

Of the 565 subjects who were treated with ponesimod in Study AC058-B301, 471 (83.4%) completed the Treatment Period (TP) on study drug; almost the same number of subjects (473) who were randomized to teriflunomide completed the TP on study drug. About two thirds of subjects who discontinued the study drug remained in the Post-Treatment Observation Period (PTOP) of the study. Unfortunately, many of the subjects who discontinued the study drug (or the study) did so for the reasons "Other" or "Consent withdrawal."

> *Reviewer Comment: Trying to identify the precise reason for discontinuing the study treatment would have been more beneficial. Although seemingly common practice, inclusion of "Other" and "Withdrew consent" in the list of potential reasons to discontinue a study treatment lessens the utility of this analysis, especially since these were the most common reasons for not completing the study on treatment.*

Protocol Deviations

A delineation of important protocol deviations occurring 20 or more times in the active-controlled RMS population in Study AC-058B301 is shown in Table 8.

Table 8. Reviewer Table. Important Protocol Deviations, Study AC-058B301

Demographic Parameter	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Two consecutive safety assessments not performed or performed but results not available and no re-test done	148	126
Any pre-randomization safety assessment required for eligibility not performed prior to randomization	28	37
Any site personnel made aware of any data with unblinding potential assessed as high or moderate not related to management of a clinical event (except day 1 or day of re-initiation of study drug data)	37	28
Any applicable follow-up visit not performed	28	26
Any EDSS assessment performed by personnel not qualified or not trained and certified or re-certified	23	24
Spirometry repeat testing not performed	31	14
During up-titration period, lack of compliance with study drug	25	15
EDSS for unconfirmed relapse performed after start of treatment with steroids or > 7 days after onset of symptoms	14	24
Liver function repeat testing not performed	21	14
During treatment period, treatment with beta-blocker, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR-lowering systemic therapy as listed in study protocol	16	16
During treatment period, treatment with systemic steroids or ACTH, except for MS relapses and short-term treatments with low dose/inhaled steroids for pulmonary conditions	9	20
Study drug taken from non-allocated kit: non-assigned treatment received	13	14
No EDSS assessment performed to confirm relapse	6	15
Informed consent form signed after first study procedure	8	12

Source: B301 ADDV where ADVDECOD='PROTOCOL DEVIATIONS,' FASFL and DVSCAT='Y' by TRT01A

Reviewer Comment: Since it displays the number of occurrences for common protocol deviations (and not the number of subjects who had that protocol deviation as the CSR does), Table 6 does not contain percentages because the same protocol deviation could occur more than once in the same subject. The degree of protocol deviations appears relatively balanced between the groups, and many of these refer to missed assessments; however, the numbers of potentially unblinding deviations (37 with ponesimod and 28 with teriflunomide) are obviously concerning.

Demographic Characteristics

The demographic characteristics of the safety population (subjects who received at least one dose of the study medication) of the active-controlled RMS population is shown is Table 9.

Table 9. Reviewer Table. Population Demographics, Study AC-058B301

Demographic Parameter	Ponesimod 20 mg n=565[1]	Teriflunomide 14 mg n=566
Age (years)[2]		
Mean (SD)	36.7 (8.7)	36.8 (8.7)
Median	36	37
Min, Max	18, 55	18, 55
≤40 years	372 (65.8%)	365 (64.5%)
> 40	193 (34.2%)	201 (35.5%)
Sex		
Female	363 (64.2%)	372 (65.7%)
Male	202 (35.8%)	194 (34.3%)
Race		
White	549 (97.2%)	553 (97.7%)
Black or African	3 (0.5%)	2 (0.4%)
Unknown / Other	13 (2.3%)	11 (1.9%)
Ethnicity		
Not Hispanic or Latino	524 (92.7%)	528 (93.2%)
Hispanic or Latino	27 (4.8%)	23 (4.1%)
Not reported / Unknown	14 (2.5%)	15 (2.7%)
Region		
European Union (EU) + UK	288 (51.0%)	284 (50.2%)
Europe Non-EU + Russia	233 (41.2%)	239 (42.2%)
North America	31 (5.5%)	24 (4.2%)
Rest of World	13 (2.3%)	19 (3.4%)
Body Mass Index (BMI, kg/m^2)		
Mean (SD)	24.7 (4.9)	24.6 (4.8)
Median	23.9	23.8
Min, Max	15.8, 44.4	15.3, 44.8

Source: B301 ADSL where SAFFL='Y' by TRT01A

[1] This does not include the two subjects who were randomized to ponesimod but not treated.
[2] Age at time of randomization

Reviewer Comment: The demographic characteristics of the two arms of Study AC-058B301 appear comparable. As is typical in RMS trials, the population of Study AC-058B301 is predominantly female and white; however, a more racially diverse study population would have enhanced the generalizability of the results. Most of the study subjects are from outside the US.

Baseline Disease Characteristics

The baseline disease characteristics of the subjects who received at least one dose of the study medication in Study AC-058B301 are shown in Table 10.

Table 10. Reviewer Table. Baseline Disease Characteristics, Study AC-058B301

Demographic Parameter	Ponesimod 20 mg n=565[1]	Teriflunomide 14 mg n=566
Time since RMS Symptom Onset (years)		
Mean (SD)	7.6 (6.8)	7.7 (6.8)
Median	5.8	5.7
Min, Max	0.2, 40.8	0.2, 30.8
Time since RMS Diagnosis (years)		
Mean (SD)	4.3 (5.3)	4.8 (5.6)
Median	2.1	2.9
Min, Max	0.1, 32.4	0.1, 29.3
Number of Relapses in Past Year		
Mean (SD)	1.2 (0.6)	1.3 (0.7)
Median	1	1
Min, Max	0, 4	0, 5
EDSS		
Mean (SD)	2.6 (1.2)	2.6 (1.2)
Median	2.5	2.5
Min, Max	0, 5.5	0, 5.5
Gadolinium Enhancing Lesions (%)		
# subjects with ≥ 1	226 (40.0%)	256 (45.4%)
# subjects with 0	339 (60.0%)	308 (54.6%)
# of T2 lesions (%)		
# subjects with < 9	63 (11.2%)	45 (8.0%)
# subjects with ≥ 9	501 (88.8%)	519 (92.0%)
Disease Phenotype (%)		
RRMS	550 (97.3%)	552 (97.5%)
SPMS with relapses	15 (2.7%)	14 (2.5%)
Disease Duration (%)		

Demographic Parameter	Ponesimod 20 mg n=565[1]	Teriflunomide 14 mg n=566
≤ 10 years	490 (86.7%)	480 (84.8%)
> 10 years	75 (13.3%)	86 (15.2%)

Source: B301 ADSL where FASFL='Y' by TRT01A
[1] This does not include the two subjects who were randomized to ponesimod but not treated.

Reviewer Comment: Fewer subjects randomized to ponesimod had gadolinium-enhancing lesions at baseline. Since the typical enhancing lesions only enhances for 3-6 weeks and the other baseline disease characteristics of the treatment arms of Study AC-058B301 appear comparable, this reviewer opines that the treatment arms are relatively well balanced.

Exposure

As shown in Table 11, the degree of exposure to both of the study medications in Study AC-058B301 is comparable.

Table 11. Reviewer Table. Exposure to Study Drug, Study AC-058B301

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Exposure (Patient Years)	1045.2	1057.1

Source: B301 ADEXS sum (AVAL) where PARAMCD='EXPIIY' by TRT01A

Treatment Adherence and Concomitant Medications

Treatment Adherence

As per Table 12, adherence to the study treatment in Study AC-058B301 appears quite good; also, per the Applicant's ADEXS dataset, 19 subjects randomized to ponesimod and 16 subjects randomized to teriflunomide had to reinitiate the dose titration.

Table 12. Reviewer Table. Percent Adherence to Study Drug, Study AC-058B301

	Mean (%)	Stdev (%)	Median (%)	< 90% (%)
Ponesimod 20 mg	99.2	3.0	100	1.6
Teriflunomide 14 mg	99.2	2.8	99.9	0.7

Source: B301 ADEXS AVAL where PARAMCD='COMP' by TRT01A

Concomitant Medications

Table 13 lists the common concomitant medications used by subjects during Study AC-058B301.

Table 13. Reviewer Table. Common Concomitant Medications, Study AC-058B301

Standardized Medication Name	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
METHYLPREDNISOLONE	93	135
PARACETAMOL	86	97
METHYLPREDNISOLONE SODIUM SUCCINATE	79	100
IBUPROFEN	82	86
OMEPRAZOLE	79	92
COLECALCIFEROL	61	78
DROSPIRENONE W/ETHINYLESTRADIOL	50	55
GABAPENTIN	28	29
VITAMIN D NOS	41	32
BACLOFEN	24	29
ACICLOVIR	17	20
ASCORBIC ACID	25	30
THIOCTIC ACID	15	24
LEVONORGESTREL	30	34
AMOXICILLIN	20	32
AZITHROMYCIN	23	25
AMOXI-CLAVULANICO	30	25
TROPHICARD	17	21
MARVELON	25	23
PANTOPRAZOLE	15	27
ACETYLSALICYLIC ACID	23	17
PREGABALIN	15	13
KETOPROFEN	15	15
FEMODENE	20	21
NEUROBION /00176001/	10	20
LEVOTHYROXINE SODIUM	19	13
TIZANIDINE HYDROCHLORIDE	17	12
DIAZEPAM	11	18
NAPROXEN	16	11
ESCITALOPRAM	15	14

Source: B301 ADCM ncategories (USUBJID) where FASFL and ANL05FL='Y' by CMDECOD and TRT01A

Reviewer comment: Not surprisingly, many of these concomitant medications are commonly used in people with MS, including methylprednisolone (for MS relapses), vitamin D, baclofen and tizanidine (for spasticity from MS), and pregabalin and gabapentin (for neuropathic pain from MS). The use of steroids was higher in the teriflunomide group, which may suggest that this group had more relapses and

inflammatory disease activity than the group randomized to ponesimod. Presumably, the relatively high frequency of antibiotic use is attributable to respiratory tract and urinary tract infections, the latter of which are not uncommon in individuals with RMS.

Efficacy Results – Primary Endpoint

Annualized Relapse Rate

Relapse rates, including annualized relapse rates (ARR), are clinically meaningful measures of how an individual with RMS functions, feels, and survives and are thus commonly used (and are typically accepted) as a primary endpoint in studies of potential treatments in this population. As per the protocol for Study AC-058B301,

> "A relapse was defined as new, worsening or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 hours, in the absence of fever or infection."

The occurrence of new, worsening, or recurrent neurological symptoms in Study AC-058B301 was to be evaluated by the subject's treating neurologist to ensure that there was not a better explanation for the symptoms (e.g., Uhthoff's phenomenon in the setting of a fever or infection). Unless a better explanation was found, the symptoms were deemed attributable to a potential relapse, in which case the efficacy assessor was to rate the subject's Functional Systems (FS) and Expanded Disability Status Scale (EDSS). A relapse was classified as confirmed if one (or more) of the following was true in comparison to a previous stable FS/EDSS assessment that was performed at least 30 days after a relapse:

- "An increase of at least half a step (0.5 points; unless EDSS=0, then an increase of at least 1.0 points was required) or
- An increase of at least 1.0 point in at least two FS scores, or
- An increase of at least 2.0 points in at least one FS score (excluding bladder/bowel and cerebral)."

The numbers of confirmed and unconfirmed relapses that occurred in each treatment arm of the FAS of Study AC-058B301 are shown in Table 14.

Table 14. Reviewer Table. Number of Relapses by Treatment Group, Study AC-058B301

Clinical Events	Ponesimod 20 mg	Teriflunomide 14 mg
Confirmed Relapses	242 (86.7%)	344 (88.2%)
Unconfirmed Relapses	31 (11.1%)	31 (7.9%)
Unspecified	6 (2.2%)	15 (3.8%)
Total	279	390

Source: B301 ADCE where FASFL and ANL02FL='Y' by CRIT01FL and TRT01A

Reviewer Comment: Although more relapses occurred in the teriflunomide arm, the percentages of relapses that were confirmed in the ponesimod 20 mg and the teriflunomide 14 mg arms of Study AC-058B301 appear comparable. Most of the relapses were confirmed, and subsequent analyses will focus on confirmed relapses.

When interpreting the treatment effect of ponesimod on ARR, it is important to remember that the active comparator in Study AC-058B301 (teriflunomide 14 mg daily) is an approved therapy for RMS that reduced ARR by 31-36% in its pivotal trials. (O'Connor et al., 2011; Confavreux et al., 2014). The unadjusted confirmed annualized relapse rates (ARRs), calculated with either the duration of treatment exposure or the study duration as the denominator, for the treatment arms of the FAS of Study AC-058B301 are shown in Table 15.

Table 15. Reviewer Table. Unadjusted confirmed ARRs, Study AC-058B301

	Ponesimod 20 mg n=567	Teriflunomide 14 mg n=566
Confirmed Relapses[1]	242	344
Treatment Exposure (Pt/yr)[2]	1045.2	1057.1
Treatment Exposure ARR	0.232	0.325
Study Duration (Pt/yr)[3]	1118.5	1136.9
Study Duration ARR	0.216	0.303

[1] Source: B301 ADCE where FASFL, CRIT1FL, and ANL02FL='Y' by TRT01A
[2] Source: B301 ADEXS sum (AVAL) where PARAMCD='EXPIIY' by TRT01A
[3] Source: B301 ADSL sum (STDDURY) where FASFL='Y' by TRT01A

Reviewer Comment: The reduction in the unadjusted treatment exposure ARR with ponesimod is 28.6%, although it should be remembered that teriflunomide is an active comparator that also has a treatment effect on ARR. Since the effect of a study drug may persist after the study drug is withdrawn, calculating ARR using the study duration may be preferable to doing so with the treatment exposure. The study duration ARRs shown above are identical to the raw ARR's shown in Table 11 of the CSR for Study AC-058B301. Adding this relative difference to the treatment effect that teriflunomide demonstrated in its pivotal trials (a relative risk reduction of 31%) approximates the ARR reduction observed with S1P receptor modulators that were studied versus placebo.

Refer to the biometrics review by Dr. Xiang Ling for a negative binomial regression analysis of this primary endpoint and the confidence intervals for the adjusted ARRs.

Table 16 compares the treatment effect of ponesimod 20 mg to that of teriflunomide 14 mg in the FAS of Study AC-058B301 by several relapse characteristics, including treatment with corticosteroids, the need for (or prolongation of) hospitalization, and the relapse outcome.

Table 16. Reviewer Table. Unadjusted confirmed ARRs by relapse characteristics, Study AC-058B301

Relapse Criterion	Ponesimod 20 mg (n=567; 1118.5 pt/yr)		Teriflunomide 14 mg (n=566; 1136.9 pt/yr)		% ARR reduction
	Relapses	ARR	Relapses	ARR	
All confirmed relapses	242	0.216	344	0.303	28.7
Relapses Treated with Corticosteroids (B301 ADCE CORTICO)					
Yes	221	0.197	325	0.286	31.1
No	21	0.019	19	0.17	+1.2
Hospitalized for Relapse(B301 ADCE CESHOSP)					
Yes	1	.001	3	0.003	33.3
No	241	0.215	341	0.300	28.3
Relapse Outcome					
Recovered / Resolved	188	0.168	279	.245	31.4
Recovered with sequelae	52	0.046	58	0.051	9.8
Not recovered	2	.002	7	.006	33.3

Source: B301 ADCE where FASFL, CRIT1FL, and ANL02FL='Y' by TRT01A

Reviewer Comment: The treatment effect of ponesimod on confirmed relapses appears to be relatively preserved across multiple relapse characteristics, although it is notable that the treatment effect of ponesimod appears less robust for relapses that recovered with sequelae. As expected, most confirmed relapses were treated with corticosteroids; however, this reviewer is of the understanding that individuals in the EU are commonly hospitalized for treatment with corticosteroids and is surprised by the relative rarity of relapses requiring hospitalization.

Table 17 compares the treatment effect of ponesimod 20 mg on relapses to that of teriflunomide 14 mg by several subject characteristics, including age, sex, baseline EDSS, and baseline gadolinium enhancing (GdE) lesions in the FAS of Study AC-058B301.

Table 17. Reviewer Table. Unadjusted confirmed ARRs by subject characteristics, Study AC-058B301

Subject Characteristic	Ponesimod 20 mg (n=567; 1118.5 pt/yr)			Teriflunomide 14 mg (n=566; 1136.9 pt/yr)			% ARR reduction
	Pt/year[1]	Relapses[2]	ARR	Pt/year[1]	Relapses[3]	ARR	
Age							
< 40 years	693.8	164	0.236	681.2	228	0.335	29.6
≥ 40 years	424.7	78	0.184	455.7	116	0.255	27.8
Sex							
Female	725.0	153	0.211	747.2	228	0.305	30.8
Male	393.6	89	0.226	389.6	116	0.298	24.2

Subject Characteristic	Ponesimod 20 mg (n=567; 1118.5 pt/yr)			Teriflunomide 14 mg (n=566; 1136.9 pt/yr)			% ARR reduction
	Pt/year[1]	Relapses[2]	ARR	Pt/year[1]	Relapses[3]	ARR	
Baseline EDSS							
≤ 3.5	941.0	157	0.167	954.4	268	0.281	59.4
> 3.5	177.5	85	0.479	182.5	76	0.416	-15.1
GdE at baseline[3]							
Yes	452.5	110	0.243	512.5	178	0.347	30.0
No	666.0	132	0.198	620.1	166	0.277	28.5
Disease Phenotype							
RRMS	1090.6	231	0.212	1107.2	335	0.303	30.0
SPMS w/ rel	27.9	11	0.394	29.7	9	0.303	-22.2
Disease Duration (years)[4]							
≤ 10	980.7	212	0.216	973.2	292	0.300	28.0
> 10	137.9	30	0.218	163.7	52	.318	31.4

[1] Source: B301 ADSL sum (STDDURY) where FASFL='Y' by TRT01A
[2] Source: B301 ADCE where FASFL, CRIT1FL, and ANL02FL='Y' by TRT01A
[3] B301 ADSL baseline GdE data was missing for two subjects randomized to teriflunomide.
[4] Joined B301 ADCE where FASFL, CRIT1FL, and ANL02FL='Y' with B301 ADSL MSDIAGY where FASFL='Y'

Reviewer Comment: Although the difference in ARRs between ponesimod 20 mg and teriflunomide 14 mg daily did not favor ponesimod in subjects with secondary progressive MS or in subjects with an EDSS above 3.5 (some of whom may have had SPMS), ponesimod's response on ARR (compared to that for teriflunomide) stratified by subject characteristics mostly favored ponesimod with percent reductions similar to those of the overall population.

The number of confirmed relapses per subject in each treatment arm of the FAS of Study AC-058B301 are shown in Table 18.

Table 18. Reviewer Table. Number of Confirmed Relapses by Subject, Study AC-058B301

# of confirmed relapses	Ponesimod 20 mg n=567	Teriflunomide 14 mg n=566
0[1]	401 (70.7%)	343 (60.6%)
1	116 (20.5%)	143 (25.3%)
2	33 (5.8%)	51 (9.0%)
3	12 (2.1%)	18 (3.2%)
4	3 (0.5%)	10 (1.8%)
5	1 (0.2%)	1 (0.2%)
6	0	0
7	1 (0.2%)	0

Source: B301 ADCE where FASFL and ANL02FL='Y' by CRIT01FL and TRT01A
[1] Some relapses were not confirmed by the efficacy assessor.

Reviewer Comment: Although some subjects had relapses that were not confirmed by the efficacy assessor, it appears that more subjects who were randomized to ponesimod 20 mg remained free of relapses, and fewer experienced 1, 2, 3, or 4 relapses, which aligns with the overall statistical superiority of ponesimod 20 mg on ARR.

Data Quality and Integrity

Per the protocol for Study AC-058B301, EDSS assessments were performed by efficacy assessors who were to remain unaware of each subject's adverse events, concomitant medications, vital sign and ECG data, laboratory data, and MRI results. Efficacy assessors were to be trained and certified in the administration and scoring of the EDSS, and they were not to refer to previous EDSS scores when performing an EDSS. Whenever possible, the same efficacy assessor was to be used for a given subject for the duration of the study; however, a back-up assessor could be used if required.

Efficacy Results – Secondary and other relevant endpoints

FSIQ-RMS

MS fatigue is distinct (and often described differently) than other types of fatigue, and it is one of the most common and disabling symptoms of RMS. Some of the distinguishing factors of MS fatigue include its rapidity of onset, persistence, and potential sensitivity to heat; indeed, functional brain MRIs of individuals with fatigue from MS demonstrate increased and more widespread cortical activation compared to those without MS fatigue and healthy controls. Fatigue from MS can be confused with (or confounded by) numerous factors, including depression / anxiety, sleep disturbances (including obstructive sleep apnea), pain, nocturia, deconditioning, and medication side effects. (Krupp et al., 2010)

The FSIQ-RMS (Fatigue Symptom and Impact Questionnaire-RMS) is a 20-item patient reported outcome (PRO) instrument that was developed by the Applicant to evaluate two domains of fatigue, specifically the symptoms (FSIQ-RMS-S) and impact (FSIQ-RMS-I) of fatigue, in individuals with MS. The FSIQ-RMS-S consists of seven items assessing fatigue-related symptoms over seven consecutive days (with a recall period of 24 hours) measured on an 11-point numeric rating scale; therefore, the unscaled symptom domain score of the FSIQ-RMS ranges from 0 to 77 with a higher score indicating greater fatigue. Conversely, the FSIQ-RMS-I refer to the impact of fatigue over the past 7 days and is retrospectively assessed with a 5-point Likert scale on day 7. (Hudgens et al, 2019) In Study AC-058B301, subjects input this data into an electronic device (e-diary) at baseline and at Weeks 12, 24, 60, 84, and 108; however, the protocol notes "The individual questionnaires will be completed only in countries for which validated translations are available."

Reviewer Comment: It is not clear how this instrument (or Study AC-058B301) accounts for the numerous symptoms that the word "fatigue" can be used to describe; however,

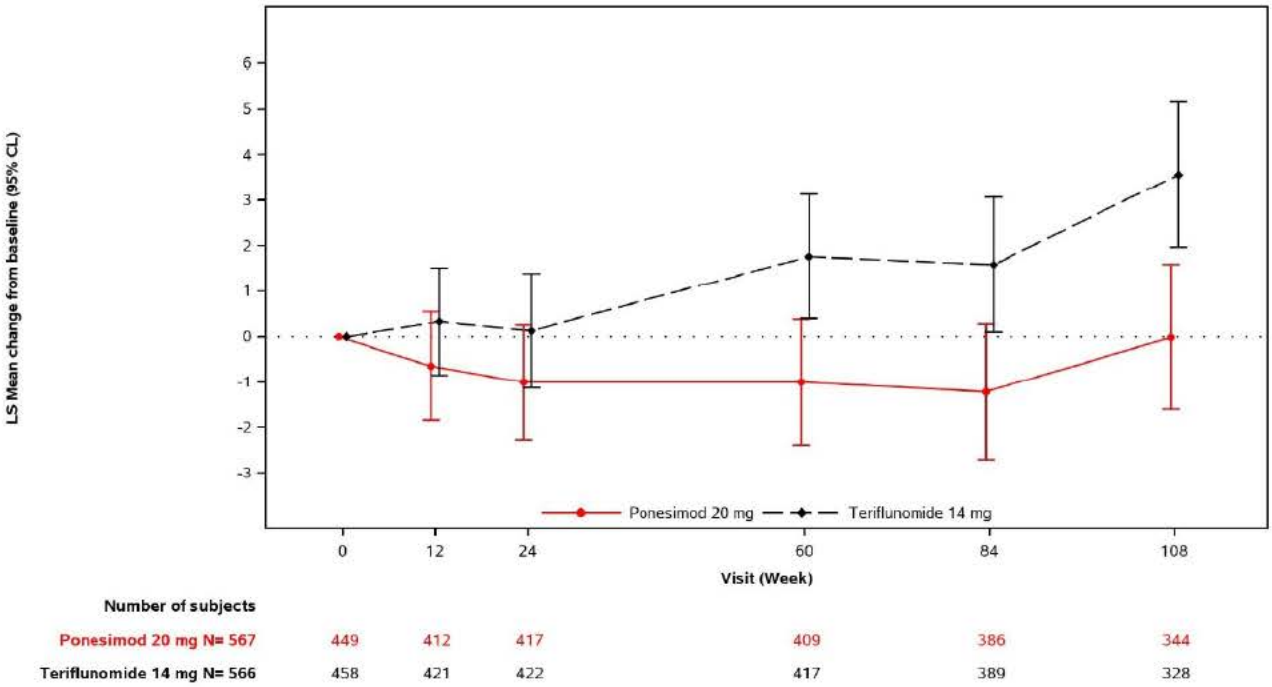
this lack of symptom specificity is arguably an issue with many of the instruments that have attempted to quantify MS fatigue. In addition, although successful randomization would likely mitigate the effect of potential confounders of MS fatigue (e.g., obstructive sleep apnea, medication side effects, nocturia, depression), the number (and prevalence) of these potential confounders is concerning.

Because Study AC-058B301 is an active-controlled study, one also needs to consider whether teriflunomide has an effect (positive or negative) on fatigue in general and the FSIQ-RMS in particular. In one of its pivotal studies in RMS (O'Connor et al, 2011), teriflunomide did not have a statistically significant effect on the Fatigue Impact Scale (FIS); the other (Confavreux et al, 2014) had a statistically significant effect on the FIS at the end of the study (p=0.0429) but not at week 48.

Reviewer Comment: It is unclear whether teriflunomide has a beneficial (or detrimental) effect on fatigue as measured by the FIS, an instrument that is arguably less specific for MS fatigue than the FSIQ-RMS. In its response to the 17NOV2020 Information Request about the effect of teriflunomide on fatigue in individuals with RMS, the Applicant was unable to provide additional clinical trial information about the effect of teriflunomide on the FIS but offered "real world" data suggesting stabilization of fatigue with teriflunomide. Conversely, after the late cycle meeting (LCM), the Applicant submitted a meta-analysis suggesting that teriflunomide does not have an effect on MS fatigue, at least as measured by the FIS.

The first key secondary efficacy endpoint of Study AC-058B301 is the change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ-RMS (FSIQ-RMS-S). The Applicant's and this reviewer's analysis of this endpoint at a population level are shown in Figure 4 and Table 19, respectively; further, the Applicant's assessment of subject level improvement in the FSIQ-RMS-S using a cumulative distribution change from baseline in subjects with available results is shown in Figure 5.

Figure 4. Applicant Figure. FSIQ-RMS Weekly Symptoms Score: Mean (95% CLs) Change From Baseline up to Week 108



Number of subjects						
Ponesimod 20 mg N= 567	449	412	417	409	386	344
Teriflunomide 14 mg N= 566	458	421	422	417	389	328

FSIQ-RMS=Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis, CL=Confidence Limit.
MMRM = Mixed effects repeated measurements model with unstructured covariance, treatment, visit, treatment by visit interaction, baseline by visit interaction as fixed effects, baseline FSIQ score, EDSS strata (<=3.5,>3.5), DMT in last 2 years prior randomization strata (Y,N) as covariates. Least square (LS) means and 95% CLs are displayed.
Includes subjects with baseline and at least one post baseline assessment. N = subjects in analysis set.
A negative change from baseline indicates an improvement in fatigue symptoms.

Reviewer Comment: This review notes that the confidence intervals for the change from baseline in the FSIQ-RMS-S appear to overlap at every time point except week 108 and that a large number of subjects appear to be missing data, even at baseline. Figure 4 *also suggests that fatigue, as measured by the FSIQ-RMS-S stabilized (but did not improve) in individuals randomized to ponesimod.*

Table 19. Reviewer Table. Change in baseline FSIQ-RMS weekly symptoms at week 108, Study AC-058B301

CHG	Ponesimod 20 mg n=567	Teriflunomide 14 mg n=566
N	344	328
Mean (SD)	0.3 (16.8)	2.3 (17.0)
Median	-0.1	1.4
Min, Max	-58.9, 80	-59.4, 52.5

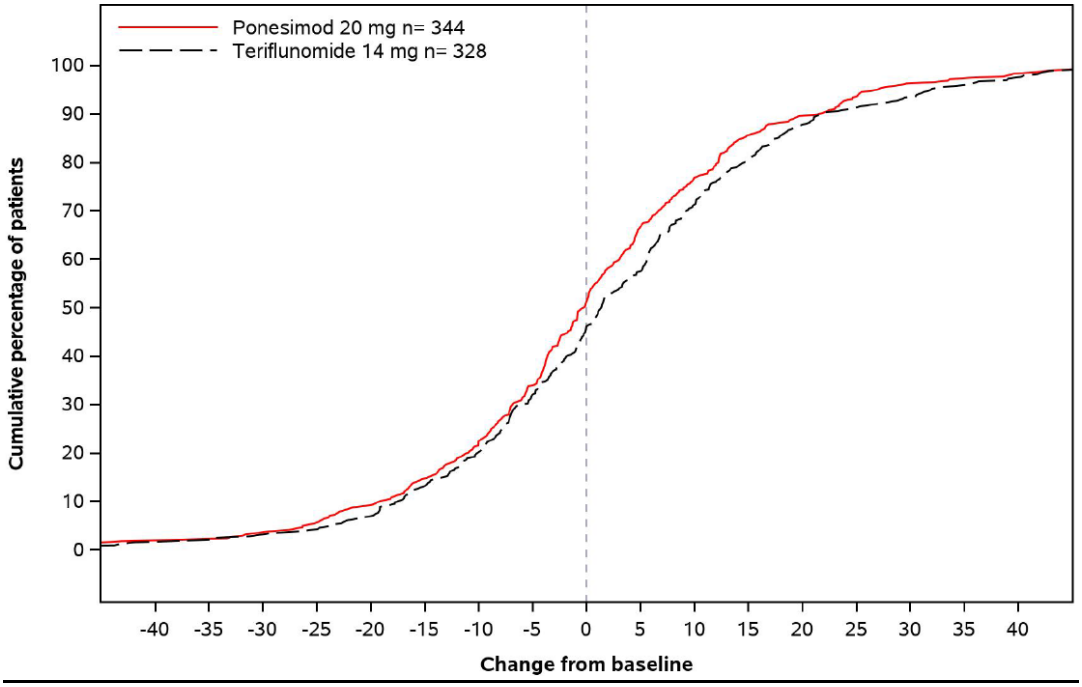
Source: B301 ADFSIQ where FASFL and ANL01FL='Y,' PARAMCD='S1SWS,' AVISIT='Visit 14 - Week 108, and CHG is not missing by TRT01A

Reviewer Comment: This reviewer defers to biometrics for more complex analyses (Mixed effect Model Repeated Measures[MMRM]), confidence intervals, and statistical significance of this key secondary endpoint but notes that the "raw" difference of -2.0 shown in Table 19 is identical to the Week 108 data shown in the T_FSIQ_SS_09_F FSIQ-RMS weekly symptoms score analysis of the CSR. It is again clear that many subjects are missing FSIQ-RMS-S data and that the magnitude of ponesimod's treatment effect on this endpoint is less than excepted since the Applicant noted suggested that a (b) (4) *change may be clinically meaningful in the SAP for Study AC-058B301 and later asked the following question at the 04SEP2019 pre-NDA meeting.*

> *"Does the Agency agree that a* (b) (4) *-point change on the FSIQ Symptoms domain is an acceptable threshold for interpreting within-subject change from baseline at Week 108?"*

As noted in Section 3.2 of this review, at the pre-NDA meeting, the Division opined that there were neither "sufficient evidence or justification to support that your proposed (b) (4) *point change threshold in the FSIQ Symptoms domain score is clinically meaningful." Indeed, it is difficult to justify that an unadjusted change of* (b) (4) *is clinically relevant, especially since a 20% change on outcome assessments is generally considered clinically meaningful.*

Figure 5. Applicant Figure. Cumulative Distribution Function of Change From Baseline to Week 108 in FSIQ-RMS Symptoms Weekly Score, Full Analysis Set



Reviewer Comment: Figure 5 suggests that most subjects did not experience much of a change, much less an improvement, in the FSIQ-RMS-S regardless of whether they were randomized to ponesimod or teriflunomide.

Given the number of subjects for whom FSIQ-RMS-S data are not available in Figure 4 and Table 19, the availability of FSIQ-RMS-S data by visit is quantified in Table 20.

Table 20. Reviewer Table. Availability of FSIQ-RMS weekly symptoms data by visit, Study AC-058B301

N	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Baseline	474 (83.9%)	468 (82.7%)
Visit 6 - Week 12	412 (72.9%)	421 (74.4%)
Visit 7 - Week 24	417 (73.8%)	422 (74.6%)
Visit 10 - Week 60	409 (72.4%)	417 (73.7%)
Visit 12 - Week 84	386 (68.3%)	389 (68.7%)
Visit 14 - Week 108	344 (60.9%)	328 (58.0%)

Source: B301 ADFSIQ where FASFL and ANL01FL='Y,' PARAMCD='S1SWS' by AVISIT and TRT01A

Reviewer Comment: Given the observed degree of missing data for the FSIQ-RMS endpoint in Figure 4 and the preceding two tables (even at baseline), an Information Request (IR) was sent to the Sponsor on 11SEP2020 to inquire if the missing data was attributable to a lack of validated translations for the FSIQ-RMS testing materials or to alternative / additional reasons. The Applicant confirmed that all necessary translations of the testing material were available and noted that the reason for missing baseline data was subject adherence to the administration procedure for the 7-day questionnaire. The Applicant provided the following table of the number of days for which baseline FSIQ-RMS data were available, noting that a valid baseline result could be derived from four or more days of baseline FSIQ-RMS-S data.

Table 21. Applicant Table. Number of FSIQ-RMS Daily Symptoms Scores Available at Baseline (FAS)

	Ponesimod 20 mg N=567 n (%)	Teriflunomide 14 mg N=566 n (%)
Baseline		
≥ 1 day	543 (95.8)	545 (96.3)
≥ 2 days	507 (89.4)	509 (89.9)
≥ 3 days	488 (86.1)	480 (84.8)
≥ 4 days *	**474 (83.6)**	**468 (82.7)**
≥ 5 days	451 (79.5)	446 (78.8)
≥ 6 days	420 (74.1)	404 (71.4)
7 days	337 (59.4)	315 (55.7)

* Minimum days required for a valid FSIQ-RMS baseline score.

With the low magnitude of the difference in the weekly FSIQ-RMS-S data between baseline and week 108, the noted degree of missing data (and its potential to represent bias) is especially concerning; indeed, one could wonder if more fatigued subjects would be less (or more) likely to adhere to the completion of this instrument. The Applicant submitted further sensitivity analyses after the Late Cycle Meeting (LCM), but these do not negate the concern regarding missing data.

Individuals with RMS often describe "non-specific" symptoms, including overwhelming fatigue, both before and during a relapse; in addition, some will even note these symptoms may worsen around the time that active disease (i.e., gadolinium-enhancing lesions) is noted on a surveillance MRI. An IR was sent to the Applicant on 17SEP2020 requesting two further sensitivity analyses of this endpoint: one restricted to those subjects who did not experience a confirmed relapse during Study AC-058B301, and the other excluding all FSIQ-RMS assessments obtained within 90 days of a confirmed relapse.

Reviewer Comment: The Applicant's response to this IR does not suggest that confirmed relapses (or their absence) drove the observed small effect on the FSIQ-RMS-S.

Combined Unique Active Lesions

A count of combined unique active lesions (CUALs) is a magnetic resonance imaging (MRI) metric referring to the sum of the number of new gadolinium-enhancing (GdE) T1 lesions and the number of new or enlarging T2 hyperintense lesions. Another key secondary endpoint of Study AC-058B301 is the cumulative number of CUALs from baseline to Study Week 108, as determined from MRIs performed at baseline, at Study Weeks 60 and 108 (or at end of treatment), and at any unscheduled study visits. The results of this key secondary endpoint for the FAS of Study AC-058B301 are shown in Table 22.

Table 22. Reviewer Table. Cumulative CUAL from baseline to week 108, Study AC-058B301

AVAL	Ponesimod 20 mg n=567	Teriflunomide 14 mg n=566
N	539	536
Mean (SD)	3.1 (5.8)	6.9 (13.3)
Median	1	2
Min, Max	0, 46	0, 136

Source: B301 ADMO where FASFL='Y,' PARAMCD='CUAL,' and AVISIT='Visit 14 - Week 108' by TRT01A

Reviewer Comment: Table 22 shows that ponesimod 20 mg appears to have a robust treatment effect on the cumulative number of CUALs from baseline to Week 108 compared with teriflunomide, which is also known to have a treatment effect on similar MRI metrics. This reviewer defers to the biometrics review by Dr. Xiang Ling for the verification, confidence intervals, and statistical significance of this endpoint; however,

given ponesimod's seemingly robust response on the cumulative number of CUAL compared to teriflunomide, this reviewer defers further analyses of this key secondary endpoint.

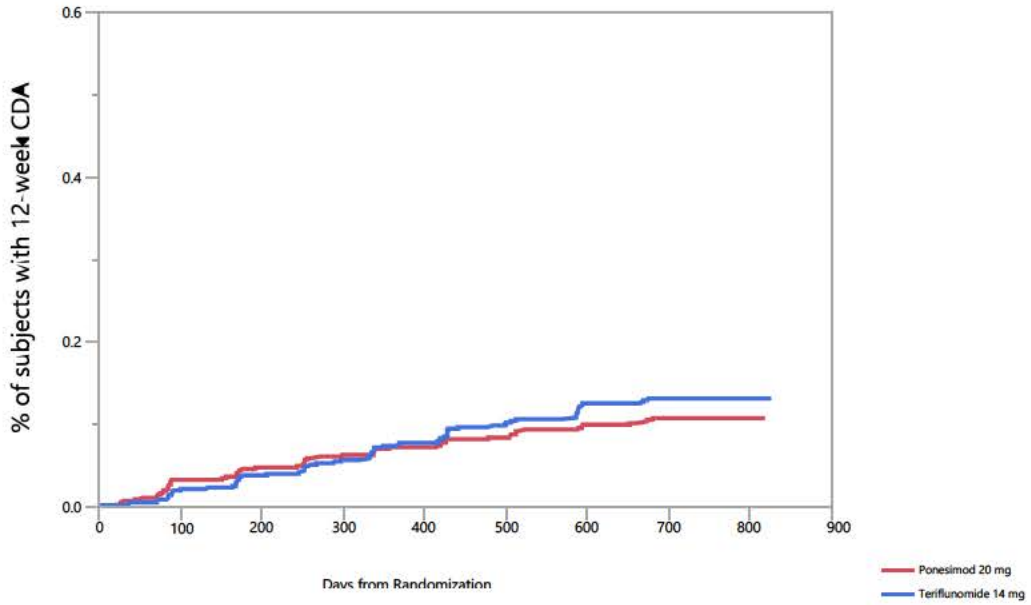
Time to 12-week confirmed disability accumulation

Another key secondary efficacy endpoint in Study AC-058B301 is the time to 12-week confirmed disability accumulation (CDA), which the Applicant defines as follows:

> "A 12-week CDA is an increase of at least 1.5 in EDSS for subjects with baseline EDSS score of 0.0 or an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for subjects with a baseline EDSS score ≥ 5.5 which is to be confirmed after 12 weeks.
>
> Baseline EDSS is defined as the last EDSS score recorded prior to randomization. The initial EDSS increase, meeting the above criteria, is defined as the onset of disability accumulation.
>
> All EDSS measurements (with or without relapse, at a scheduled or unscheduled visit) were used to determine the onset of disability accumulation. However, EDSS scores used for confirmation of disability accumulation were required to have been obtained at a scheduled visit (i.e., unscheduled visits were not to be used as confirmatory visits) outside any ongoing relapse. In this context, relapse duration was defined as the period between start and end dates if available and limited to 90 days from onset if end date was not available or duration was longer than 90 days."

This reviewer's unadjusted Kaplan-Meier analysis for this key secondary endpoint on the FAS of Study AC-058B301 is shown in Figure 5; in brief, this reviewer finds that ponesimod appears to achieve a 17.6% relative reduction in time to 12-week CDA, although this change does not appear statistically significant (hazard ratio 0.82, 95% CI from 0.58 to 1.17, p=0.28).

Figure 6. Reviewer Figure. Time to first 12-week-month CDA, Study AC-058B301



Source: B301 ADTTE where PARAMCD='CDA12W' by TRT01A

12-week CDA, FAS

Treatment Group	Number	3-month CDA	No 3-month CDA
Ponesimod 20 mg	565	57 (10.1%)	508 (89.9%)
Teriflunomide 14 mg	566	70 (12.4%)	496 (87.6%)

Group Comparison

Test	Chi-square	DF	Prob>ChiSq
Log-Rank	1.1787	1	0.2776
Wilcoxon	0.9396	1	0.3324

Risk Ratio

Test	Ratio	Prob>ChiSq	Lower 95%	Upper 95%
Ponesimod / Teriflunomide	0.8242162	0.2786	0.5810011	1.1692446

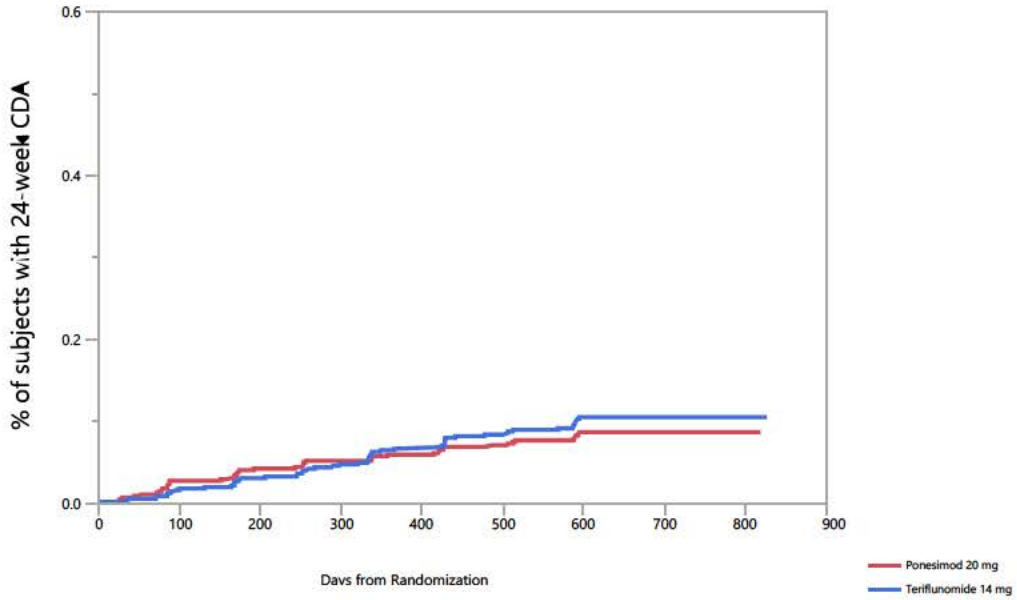
Reviewer Comment: Although this reviewer defers to the biometric analyses of Dr. Xiang Ling, Figure 5 suggests that ponesimod does not achieve statistical significance on its 12-week CDA endpoint in Study AC-058B301. This is not surprising, since studies of other S1P receptors for RMS have shown inconsistent results on analysis of their disability progression endpoints.

<u>24-week confirmed disability accumulation</u>

Similarly, 24-week confirmed disability accumulation (CDA) is another key secondary efficacy endpoint of Study AC-058B301. Although the preceding analysis suggests that no alpha is

remaining to formally evaluate the statistical significance of this endpoint, this reviewer's analysis of the time to 24-week CDA in the FAS of Study AC-058B301 follows below:

Figure 7. Reviewer Figure. Time to 24-week-month CDA, Study AC-058B301



Source: B301 ADTTE where PARAMCD='CDA24W' by TRT01A

24-week CDA, FAS

Treatment Group	Number	3-month CDA	No 3-month CDA
Ponesimod 20 mg	565	46 (8.1%)	519 (91.8%)
Teriflunomide 14 mg	566	56 (9.9%)	510 (90.1%)

Group Comparison

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.8407	1	0.3592
Wilcoxon	0.6734	1	0.4119

Risk Ratio

Test	Ratio	Prob>ChiSq	Lower 95%	Upper 95%
Ponesimod / Teriflunomide	0.83	0.36	0.56	1.23

Reviewer Comment: Although this reviewer defers to the biometric analyses of Dr. Xiang Ling, Figure 6 suggests that ponesimod would not achieve statistical significance on its 24-week CDA endpoint in Study AC-058B301 (if there were any remaining alpha) either. Again, this is not overly surprising, since studies of other S1P receptors for RMS have shown inconsistent effectiveness on their disability endpoints, and some suggest that an effect on 6-month disability progression is more difficult to achieve than one on 3-month

disability progression and partially attribute this to delayed recovery from MS relapses (i.e., disability worsening).

Table 23 compares the relative change between the baseline and the final study EDSS's in both treatment arms of Study AC-058B301.

Table 23. Reviewer Table. Baseline and End of Study EDSS, Study AC-058B301

	Ponesimod 20 mg n=567	Teriflunomide 14 mg n=566
Baseline EDSS		
N	565	566
Mean (SD)	2.6 (1.2)	2.6 (1.2)
Median	2.5	2.5
Last Study EDSS		
N	509	517
Mean (SD)	2.5 (1.3)	2.7 (1.4)
Median	2.5	2.5

Source: B301 ADEDSS where FASFL='Y,' PARAMCD='EDSS0101,' and AVISIT={'Baseline,' 'Premature End of Treatment,' or 'Visit 14-Week 108'} by TRT01A

Reviewer Comment: Table 23 suggests that ponesimod and teriflunomide had minimal (if any) effect on the change in EDSS between baseline and the end of Study AC-058B301.

Dose/Dose Response

Dose vs. response was not assessed in Study AC-058B301.

Durability of Response

The durability of the response to ponesimod was not assessed in this trial. An open-label extension of AC-058B301 remains ongoing, but the lack of a comparator arm in this study limits the ability to confidently assess the continued efficacy (or durability) of the response to ponesimod.

Persistence of Effect

Efficacy following withdrawal of treatment was not assessed in this trial. With that said, given the presumed mechanism of action of S1P receptor modulators like ponesimod (sequestration of circulating lymphocytes in lymph nodes and other lymphoid tissue), one could posit that the effect of the drug would last at least until these lymphocytes were released from the lymphoid tissue (usually within 15-30 days of treatment cessation). It should also be considered that lymphocyte-depleting therapies given after cessation of ponesimod may not be effective until the sequestered lymphocytes have egressed from the lymphoid tissue.

6.2. AC-058B201: A multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-finding study to evaluate the efficacy, safety, and tolerability of three doses of ponesimod (ACT-128800), an oral S1P1 receptor agonist, administered for twenty-four weeks in patients with relapsing-remitting multiple sclerosis

6.2.1. Study Design

Overview and Objective

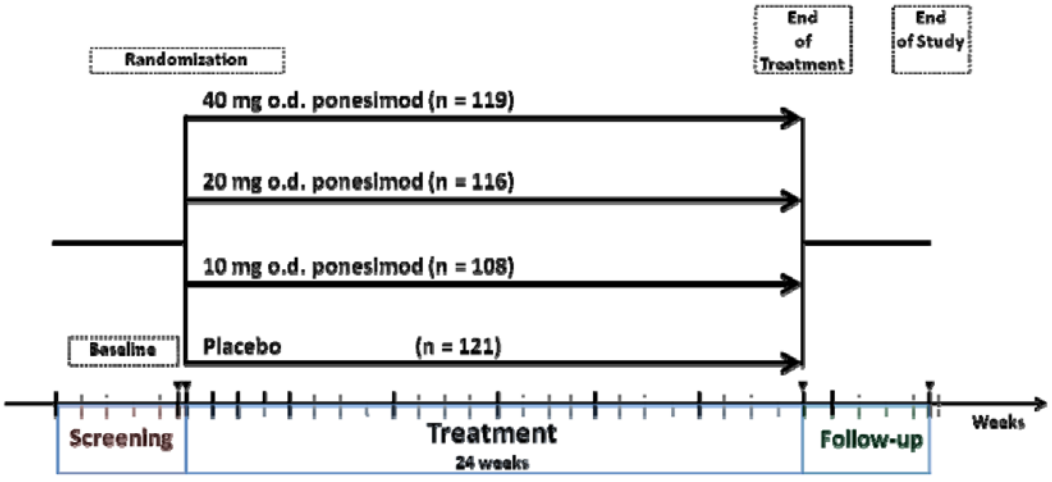
Study AC-058B201 is a Phase 2 randomized clinical trial designed to compare the efficacy, safety, and tolerability of three different doses of daily ponesimod to placebo in adults with RRMS.

Trial Design

Study AC-058B201 is a randomized, double-blind, multi-center, dose-finding, placebo-controlled, 24-week trial that evaluated the efficacy and safety of three doses of ponesimod in 464 subjects with RRMS as defined by the revised 2005 McDonald Diagnostic criteria. The primary objective of this study was to demonstrate the efficacy of three doses (10, 20, and 40 mg) of ponesimod on the cumulative number of new T1 gadolinium-enhancing (GdE) lesions per subject on MRI scans performed at Study Weeks 12, 16, 20, and 24. The secondary objectives of this study include relapse and safety / tolerability metrics. Subjects who completed the study were potentially eligible to receive ponesimod in an open label extension study (Study AC-058B202). The design of Study AC-058B201 is summarized in Figure 8.

An independent Data Safety Monitoring Board (DSMB) was used to allow independent safety assessments during the study.

Figure 8. Applicant Figure. AC-058B201 Study Design



Blinding

The investigational drug and its matching placebo (and their packaging) were reportedly indistinguishable in appearance. Except for the DSMB, Study AC-058B201 was performed in a double-blind fashion, so the primary investigators, treating neurologists, evaluating neurologists (EDSS raters), clinical coordinators/study nurses, subjects, monitors, CRO staff, and the study sponsor remained blinded to the identity of the study treatment from the time of randomization until the study database was locked. Because bradycardia with the first dose of ponesimod could lead to potential unblinding, study-independent first dose administrators were used. The primary endpoint of the study is based on MRI scans that were evaluated by an independent and blinded institution. Unblinding was permitted in the case of patient emergencies and at the conclusion of the study.

Reviewer Comment: The aforementioned methods to preserve the study blind seem reasonable and appropriate.

Key Eligibility Criteria

Inclusion Criteria

1. Males and females aged 18 to 55 years (inclusive).
2. Women of childbearing potential:
   - Must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.
   - Must use two methods of contraception (one from each group) from the screening visit until 8 weeks after study drug discontinuation. The two groups were defined as follows:
     - Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives, intrauterine devices, female sterilization (tubal ligation), or partner's sterilization (vasectomy). If a hormonal contraceptive was selected from this group, it must have been taken for at least 1 month prior to randomization (i.e., Visit 3).
     - Group 2: Condoms, diaphragm or cervical cap, all in combination with a spermicide.

   Abstention and rhythm methods were not acceptable methods of contraception.

3. Women of non-childbearing potential:
   - With previous bilateral salpingo-oophorectomy or hysterectomy.
   - With premature ovarian failure confirmed by a gynecologist.
   - Age ≥ 50 years and not treated with any kind of hormone replacement therapy for at least 2 years prior to screening, with amenorrhea for at least 24

consecutive months prior to screening, and a serum follicle stimulating hormone (FSH) level of ≥ 40 IU/L at screening.

4. Diagnosis of RRMS as defined by the revised McDonald Diagnostic Criteria for MS (2005).
5. Ambulatory and with an EDSS score of 0 to 5.5 (inclusive).
6. With at least one of the following characteristics of RRMS:
   - One or more documented relapse(s) within 12 months prior to the screening visit,
   - Two or more documented relapses within 24 months prior to the screening visit.
   - At least one Gd-enhanced lesion detected on T1-weighted MRI scan at the screening visit (based on central reading).
7. In a stable clinical condition without a clinical exacerbation of MS for at least 30 days prior to randomization (exacerbation of MS is defined as one or more new symptom(s), or worsening of existing symptoms, not associated with fever or infection, and lasting for at least 24 hours).
8. Signed informed consent prior to initiation of any study-mandated procedure.

Exclusion Criteria

1. Breast-feeding women.
2. Diagnosis of MS categorized as primary progressive or secondary progressive or progressive relapsing.
3. Treatment with the following medications within 30 days prior to randomization:
   - Systemic corticosteroids or adrenocorticotropic hormone (ACTH)
   - β-blockers, diltiazem, verapamil or digoxin or QT-prolonging drugs, for any indication. QT-prolonging drugs with reported torsade de pointes included:
   - anti-arrhythmic drugs (e.g., ajmaline, clofilium)
   - vasodilators/anti-ischemic agents (e.g., bepridil, prenylamine)
   - psychiatric drugs (e.g., amitryptiline, citalopram)
   - antimicrobial and antimalarial drugs (e.g., amantadine, chloroquine)
   - anti-histaminics (e.g., astemizole, diphenhydramine)
   - miscellaneous drugs (e.g., budipine, cisapride, vasopressine)
4. Treatment with the following medications within 3 months prior to randomization:
   - Interferon or glatiramer acetate
   - Systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, mycophenolic acid)
   - Vaccination with live vaccines
   - Plasma exchange (plasmapheresis, cytapheresis)
   - Investigational drug (within 3 months or 5 half-lives, whichever is longer), except biologic agents
5. Treatment with the following medications within 6 months prior to randomization:
   - Azathioprine or methotrexate
   - Natalizumab (or previous failure to natalizumab treatment)

- Intravenous immunoglobulin
- Non-lymphocyte-depleting biologic agents (e.g., daclizumab)

6. Treatment with the following medications at any time prior to randomization:
    - Cyclophosphamide, mitoxantrone or cladribine
    - Lymphocyte-depleting biologic agents such as alemtuzumab or rituximab
7. Patients at the time of randomization treated for an autoimmune disorder other than MS.
8. Contraindications for MRI such as:
    - Patients with pacemaker, any metallic implants such as artificial heart valves, aneurysm/vessel clips and any metallic material in high-risk areas
    - Known allergy to any gadolinium contrast agent
    - Severe renal insufficiency defined as a creatinine clearance < 30 mL/min according to the Cockcroft-Gault formula
    - Claustrophobia
9. Patients with ongoing bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), positive hepatitis B surface antigen or hepatitis C antibody tests.
10. Congenital or acquired immunodeficiency or known human immunodeficiency virus (HIV) infection.
11. Negative antibody test for varicella-zoster virus at screening.
12. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesion), lymphoproliferative disease or history of total lymphoid irradiation or bone marrow transplantation.
13. Poorly controlled type I or type II diabetes.
14. Macular edema or diabetic retinopathy (as confirmed by ophthalmoscopy within 30 days prior to randomization).
15. History of clinically significant drug or alcohol abuse.
16. Patients with any of the following cardiovascular conditions:
    - Resting HR < 55 bpm, as measured by the pre-randomization ECG on Visit 3 (Day 1).
    - History or presence of ischemic heart disease.
    - History of or current valvular heart disease.
    - History of or current heart failure.
    - History or presence of rhythm disorders (e.g., sino-arterial heart block, sick sinus syndrome, second or third-degree AV-block, ventricular arrhythmias, symptomatic bradycardia, atrial flutter or atrial fibrillation) or ongoing antiarrhythmic therapy.
    - QTc > 470 msec (females) and QTc > 450 msec (males) in any of the ECGs performed at screening, baseline or Day 1 prior to randomization.
    - History of syncope.
    - Uncontrolled arterial hypertension.
17. Patients with any of the following pulmonary conditions:

- Moderate or severe bronchial asthma or chronic obstructive pulmonary disease (COPD) stage II‑IV, i.e., forced expiratory volume in 1 second (FEV1) < 70% of the forced vital capacity (FVC), i.e., FEV1/FVC ratio < 0.7.
- History of pulmonary fibrosis (scarring of the lung) or pulmonary Langerhans cell histiocytosis.
- History of tuberculosis, chest X-ray findings at screening or within the previous 3 months, suggestive of active or latent tuberculosis or absence of a negative test result for tuberculosis at screening based on an interferon gamma release assay.

18. Abnormal liver function tests (LFTs) as defined by elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2-fold the upper limit of the normal range (ULN) or total bilirubin > 1.5-fold ULN.
19. Any of the following abnormal laboratory values:
    - White blood cells (WBC) count < 3,500/µL.
    - Hemoglobin (Hb) < 10 g/dL.
    - Lymphocyte count < 1,000/µL.
    - Platelets < 100,000/µL.
20. Known allergy to any of the study drug excipients.
21. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the patient at risk by participating in the study.
22. Patients who are confined by order of either judicial or administrative authorities.
23. Patients unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits or known likelihood of not completing the study, including mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study.

    Reviewer Comment: The aforementioned I/E criteria seem reasonable and appropriate.

In addition, "A local protocol amendment for the USA modified [the] exclusion criteria to exclude patients with bronchial asthma or COPD," and "A local amendment for Germany modified [the] exclusion criteria to exclude patients with PR interval > 200 ms, as measured by the pre-randomization ECG on Visit 3 (Day 1), and FEV1 < 50% of predicted value."

Treatment

Rationale for dose selection

After a dose uptitration, the maintenance doses of ponesimod in Study AC-058B201 were 10, 20, or 40 mg daily. The 10 mg dose was well-tolerated in the multiple ascending dose (MAD) study (AC-058B102) and led to an approximately 30% reduction in peripheral lymphocyte counts. At the 40 mg dose of ponesimod, the circulating lymphocyte count was reduced by approximately 70%, similar to the reduction seen

with a non-selective S1P receptor modulator shown to have efficacy in RMS (fingolimod).

First Dose Monitoring

Since bradyarrhythmia and atrioventricular conduction blocks are associated with the use of S1P receptor modulators, hourly blood pressure and ECG assessments were performed for six (or more) hours after the first dose of ponesimod (10 mg) or placebo was administered; if the discharge criteria were met, subjects were discharged with a sufficient study medication to last until the next study visit on Study Day 8. After initial blood pressure and ECG assessments, the next dose of ponesimod (either 10 or 20 mg depending on the treatment arm to which the subject was randomized) was administered on Study Day 8, after which hourly blood pressure and ECG assessments were again performed for six hours. If the discharge criteria were again met, subjects were discharged with a sufficient study medication to last until the next study visit on Study Day 15, at which the aforementioned procedures were repeated after a dose of ponesimod (10, 20, or 40 mg depending on the treatment arm to which the subject was randomized) or placebo was administered.

Treatment of Relapses

The protocol for Study AC-058B201 recommended that acute exacerbations of MS be treated with methylprednisolone 1g intravenously daily for 3 to 5 days.

Concomitant Medications

The following concomitant therapies were also allowed in Study AC-058B201:

- "Intravenous Atropine for in the event of symptomatic bradycardia.
- Vaccination with non-live vaccines … if the vaccination is advised by the primary investigator/treating neurologist ...
- Other treatments considered necessary for the patient's benefit and not categorized as a prohibited concomitant medication."

The following concomitant medications were prohibited in Study AC-058B201:

- "Systemic corticosteroids except for the treatment of acute MS exacerbations as defined in the protocol.
- Inhaled corticosteroids or ACTH.
- Immunomodulating treatment (e.g., interferon beta, glatiramer acetate, natalizumab or other monoclonal antibody therapy).
- Immunosuppressive treatment (e.g., cladribine, mitoxantrone or other systemic immunosuppressive drugs such as azathioprine, cyclophosphamide, cyclosporine or methotrexate).
- Intravenous immunoglobulin.

- Plasmapheresis, cytapheresis, or total lymphoid irradiation.
- Vaccination with live-vaccines.
- β-blockers, diltiazem, verapamil, digoxin, or any anti-arrhythmic therapy.
- QT-prolonging drugs
- Any investigational drug"

Assessments

The schedule of assessments for Study AC-058B201 are shown in Table 24 and Table 25 below:

Table 24. Applicant Table. Schedule of Assessments, Study AC-058B201

PERIODS	Name	PRE-RANDOMIZATION		TREATMENT PERIOD									
	Duration	4 weeks	3 days	24 weeks									
VISITS	Number	1	2	3	4	5	---	6	7	8	9	10	11
	Name	Screening	Baseline[1]	Randomization			Phone call[2]						EOT[3]
	Time	Day -28	Day -3 to -1	Day 1	Day 8	Day 15	Day 22	Week 4[4]	Week 8	Week 12	Week 16	Week 20	Week 24
	Visit window	± 7 days	---	---	± 1 day	± 1 day	± 1 day	± 2 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
* Informed Consent[5]		X											
* Inclusion/Exclusion criteria		X	X	X									
Demographics[6]		X											
Medical history		X	X										
MS history & treatment		X											
* Revised McDonald's criteria		X											
EDSS / Functional Systems		X	X										X
MSIS-29 & mFIS			X							X			X
* Chest X-ray		X											X
MRI		X[7]	X					X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X		X	X	X	X	X	X
* Physical Examination		X	X[8]		X	X		X	X	X[8]	X	X	X[8]
Systolic/diastolic blood pressure		X	X	X[9]	X[9]	X[9]		X	X	X	X	X	X
* 12-lead ECG		X	X	X[9]	X[9]	X[9]		X	X	X	X	X	X
Ophthalmologic examination[10]		X						X		X			X
Pulmonary function tests[11]		X	X		X	X		X	X	X	X	X	X
* Hematology/Blood chemistry		X[12]	X		X	X		X	X	X	X	X	X
* Urinalysis		X[12]	X		X	X		X	X	X	X	X	X
* Viral serology[13]		X[12]											
* Additional serum sample[14]			X										
* Pregnancy Test[15]		X[12]	X		X	X		X	X	X	X	X	X
* Postmenopausal test		X[12]											
PK Sampling[16]				X	X	X		X		X			X
* Study Drug Dispensing/Return				X	X[17]	X[17]		X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X	X	X	X	X
Serious Adverse Events		X[18]	X[18]	X	X	X	X	X	X	X	X	X	X
* Test for Tuberculosis		X											
* Echocardiography[19]		X								X			X

Table 25. Applicant Table. Schedule of Assessments, Study AC-058B201, cont'd

PERIODS	Name		SAFETY FOLLOW-UP[1]	
	Duration		4 weeks	
VISITS	Number	11	12	13
	Name	EOT	Follow-up 1	Follow-up 2
	Time	Week 24	Week 24 + 7 days[3]	Week 24 + 30 days[4]
	Visit window	---	± 1 day	± 5 days
EDSS / Functional Systems		X		X
MRI		X		X
Concomitant Medications		X	X	X
* Physical Examination		X[5]	X	X[5]
Systolic/diastolic blood pressure		X	X	X
* 12-lead ECG		X	X	X
Ophthalmologic examination[6]		X		X
Pulmonary function tests		X	X	X
* Hematology/Blood chemistry		X	X	X
* Urinalysis		X	X	X
* Pregnancy Test		X		X[7]
Adverse Events		X	X	
Serious Adverse Events		X	X	X

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of Study AC-058B201 is the cumulative number of new T1 gadolinium-enhancing lesions (GdE) per subject on MRI's performed at Study Weeks 12, 16, 20, and 24. This endpoint requires comparison to previous studies, so techniques need to be followed to ensure image comparability, including similar sequences, slice thickness (without gap), and orientation (subcallosal line). Enhancing lesions in MS typically enhance for 3-6 weeks and are relatively easy to identify, although it is necessary to ensure that the abnormal enhancement is not representative of a blood vessel or vascular anomaly. Enhancing lesions are typically hypointense on non-contrasted T1 scans. These T1 hypointense lesions ("black holes") can be persistent but are not necessarily so, especially if they appear less hypointense ("greyer"). At 6 months, almost 40% of T1 black holes will remain hypointense, and these persistent black holes are thought to correlate well with the degree of axonal loss in the lesion and resultant disability (Cotton 2003, Sahraian 2010, van Waesberghe 1998).

Secondary Endpoints

The secondary endpoints include the following:

- Annualized confirmed relapse rate within 24 weeks of study drug initiation.
- Time to first confirmed relapse within 24 weeks of study drug initiation.

Statistical Analysis Plan

Below is this reviewer's interpretation of the statistical analysis plan (SAP) for Study AC-058B201.

The primary analysis was performed on the per-protocol set (PPS), which consisted of all randomized subjects patients who received at least one dose of that treatment, had a baseline MRI, had a follow-up MRI after Study Week 12, and were considered "sufficiently treated with the study drug ($\geq$ 80% study drug intake without any interruption longer than 14 consecutive days) from study drug initiation to the date of the last available MRI examination." The Applicant used a Negative Binomial (NB) regression model for this primary analysis.

Per the CSR for Study AC-058B201, "enrolling 90 evaluable patients per group, the study would have 90% power to detect a reduction of 50% in the cumulative number of new gadolinium-enhancing lesions in at least one of the (ponesimod) groups, as compared with the placebo group (i.e., a reduction from 8 to 4 lesions)."

The annualized confirmed relapse rate secondary endpoint was also analyzed with an NB regression model, and the time to first relapse secondary endpoint was analyzed with a Cox regression model "with the treatment arm as a four level classification explanatory variable, testing individual comparisons between each of the active treatment groups and placebo."

Protocol Amendments

The first global protocol amendment (26OCT2009) included the addition of echocardiography (at selected study sites), allowance for vaccination with non-live vaccines during the study, the addition of an interferon gamma release assay to screen for tuberculosis, and discussion of a subject in a psoriasis trial who experienced asymptomatic second degree Mobitz Type I (Wenkebach) atrioventricular block after the first dose of ponesimod.

The second global protocol amendment (9MAR2010) included 24-hour Holter ECG monitoring, the addition of a QTc exclusion criterion, and prohibition from using QTc-prolonging drugs during the study.

Data Quality and Integrity

A study monitor reviewed the study protocol and CRFs with study staff site at the site initiation visit and periodically visited study sites to review the completeness and

accuracy of the data entered in the CRFs, adherence to the protocol and Good Clinical Practice (GCP), and study medication handling.

6.2.2. Study Results

Compliance with Good Clinical Practices

Per the CSR for Study AC-058B201,

- "Prior to the start of the trial, each study center consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and wellbeing of human subjects involved in a clinical investigation … The protocol and any material provided to the patient (such as a patient information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC or IRB before the study was started."
- "The investigator ensured that this study was conducted in full conformance with principles of the 'Declaration of Helsinki' and with the laws and regulations of the country in which the clinical research was conducted. A copy of the Declaration of Helsinki & International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines was provided to the investigator site. Documentary evidence of adequate GCP training of the investigator was collected prior to site initiation."
- "Written informed consent was obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study."

Financial Disclosure

Module 1, Section 1.3.4 of this NDA includes information regarding financial certification and disclosure. One Form FDA 3455 suggests that none of the investigators in Study AC-058B201 had a disclosable financial interest, although another Form FDA 3455 lists those investigators in Study AC-058B201 for which complete financial certification and disclosure was not available, reportedly because Johnson and Johnson acquired Actelion in June of 2017 and because the financial disclosures for some subinvestigators for this study were unable to be located.

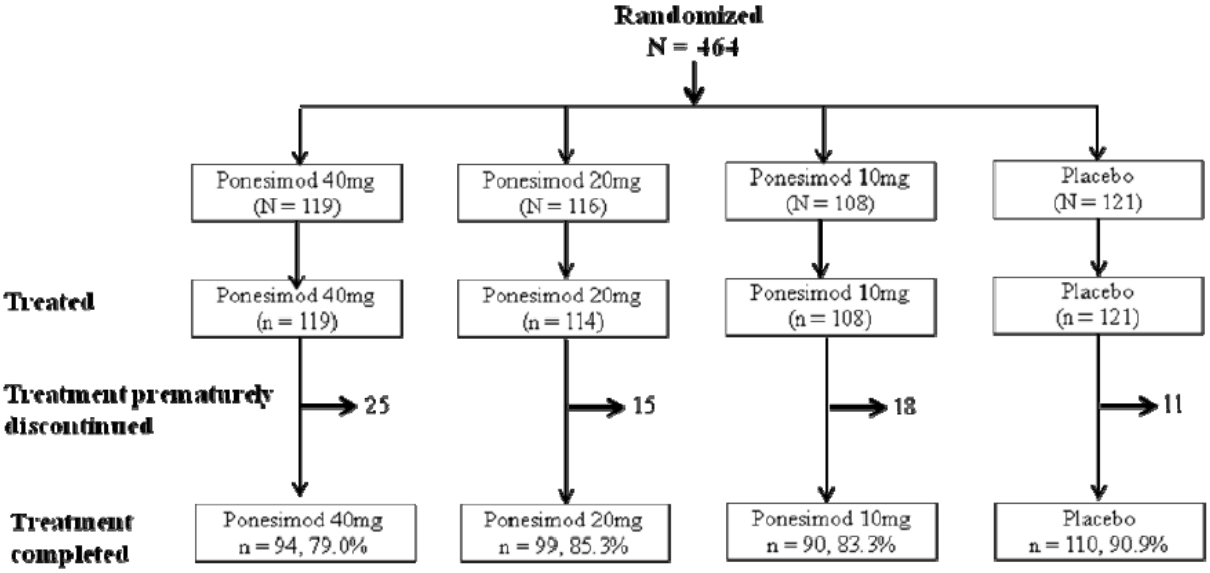
Patient Disposition

First subject, first visit: 23AUG2009
Last subject, last visit: 17JUN2011
Clinical Study Report Approved: 31JAN2013

In Study AC-058B201, 621 subjects were screened, and 464 of these were randomized (108 to ponesimod 10 mg, 116 to ponesimod 20 mg, 119 to ponesimod 40 mg, and 121 to placebo). Two subjects who were randomized to ponesimod 20 mg were not treated with the study drug, so the intent to treat (ITT) population consists of 462 subjects. The disposition of the subjects

in Study AC-048B201 is shown in Figure 9; of note, 25, 15, 18, and 11 subjects randomized to ponesimod 40 mg, ponesimod 20 mg, ponesimod 10 mg, and placebo, respectively, prematurely discontinued the study drug.

Figure 9. Applicant Figure. Disposition of Subjects, Study AC-058B201



Reviewer Comment: Compared to other RMS studies, a seemingly typical percentage (85%) of subjects in the ITT population did not complete Study AC-058B201 on the assigned study drug.

Protocol Violations / Deviations

Table 26 contains an excerpt from Table 50 of the CSR for Study AC-058B201, which contains a delineation of the more common protocol deviations in the study; many of these involve assessments being performed outside of the study window (if at all).

Table 26. Applicant Table. Summary of Protocol Deviations, Study AC-058B201

ACT-128800, Protocol: AC-058B201
Summary of all protocol violations
Analysis set: All-randomized

	Ponesimod 40 mg N=119	Ponesimod 20 mg N=116	Ponesimod 10 mg N=108	Placebo N=121	Total N=464
Protocol Deviations					
Individual visits outside of protocol-allowed windows	118 99.2%	112 96.6%	108 100%	121 100%	459 98.9%
Any PFT assessment not performed as per protocol requirement.	39 32.8%	30 25.9%	37 34.3%	33 27.3%	139 30.0%
Any ECG assessment not performed as per protocol requirement.	39 32.8%	23 19.8%	32 29.6%	30 24.8%	124 26.7%
Any blood pressure not performed as per protocol requirement.	24 20.2%	14 12.1%	18 16.7%	25 20.7%	81 17.5%
Any ophtalmological not performed as per protocol requirement.	20 16.8%	15 12.9%	21 19.4%	23 19.0%	79 17.0%
QoL questionnaire procedure not performed according to protocol requirements	25 21.0%	17 14.7%	18 16.7%	19 15.7%	79 17.0%
Prohibited concomitant treatment	19 16.0%	19 16.4%	21 19.4%	15 12.4%	74 15.9%
Any Holter assessment not performed as per protocol requirement.	19 16.0%	14 12.1%	15 13.9%	18 14.9%	66 14.2%
Not sufficiently treated with the study drug (< 80% study drug intake) from study drug initiation to the planned end of treatment (i.e. 168 days).	24 20.2%	15 12.9%	16 14.8%	9 7.4%	64 13.8%
PK sampling not performed at the appropriate timing.	16 13.4%	13 11.2%	11 10.2%	24 19.8%	64 13.8%
More than 2 missing or invalid MRIs between Week 12 and Week 24	23 19.3%	17 14.7%	13 12.0%	8 6.6%	61 13.1%
MRI performed within 14 days following systemic (i.v., i.m., oral) corticosteroids treatment.	8 6.7%	8 6.9%	11 10.2%	17 14.0%	44 9.5%
Holter started more than 15 minutes before or after the study drug intake time at Visit 4	9 7.6%	6 5.2%	7 6.5%	12 9.9%	34 7.3%
Holter started more than 15 minutes before or after the study drug intake time at Visit 5	7 5.9%	6 5.2%	5 4.6%	13 10.7%	31 6.7%
Holter started more than 15 minutes before or after the study drug intake time at Visit 3	5 4.2%	6 5.2%	8 7.4%	11 9.1%	30 6.5%
Violation of informed consent procedure	6 5.0%	7 6.0%	9 8.3%	8 6.6%	30 6.5%
EDSS assessment not performed according to the protocol	7 5.9%	4 3.4%	8 7.4%	9 7.4%	28 6.0%
More than two MRIs are missing between Week 12 and Week 24	8 6.7%	4 3.4%	8 7.4%	1 0.8%	21 4.5%

Demographic Characteristics

Table 27 delineates the demographics of the ITT RRMS population in Study AC-058B201.

Table 27. Reviewer Table. Baseline Demographic Characteristics, Study AC-058B201

Demographic Parameter	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Age (years)				
Mean (SD)	35.5 (8.5)	36.6 (8.6)	36.9 (9.2)	36.5 (8.5)
Median	35	35	38	38
Min, Max	19, 55	18, 55	18, 55	18,55
<40 years	37 (32.5%)	45 (37.2%)	44 (40.7%)	48 (40.3%)
≥40 years	77 (67.5%)	76 (62.8%)	64 (59.3%)	71 (59.7%)
Sex				
Female	77 (67.5%)	85 (70.2%)	71 (65.7%)	79 (66.4%)
Male	37 (32.5%)	36 (29.8%)	37 (34.3%)	40 (33.6%)
Race				

Demographic Parameter	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Caucasian / White	112 (98.2%)	114 (94.2%)	105 (97.2%)	114 (95.8%)
Black or African	2 (0.2%)	6 (5.0%)	2 (1.9%)	2 (1.7%)
Other	0	1 (0.8%)	1 (0.9%)	3 (2.5%)
Region				
Northern Europe	24 (21.1%)	32 (26.4%)	25 (23.1%)	27 (22.7%)
Southern Europe	35 (30.7%)	31 (25.6%)	28 (25.9%)	36 (30.3%)
Eastern Europe	33 (28.9%)	36 (29.8%)	33 (30.6%)	33 (27.7%)
North America	22 (19.3%)	22 (18.2%)	22 (20.4%)	23 (19.3%)
Body Mass Index (BMI, kg/m^2)				
Mean (SD)	26.0 (5.3)	25.2 (5.2)	26.4 (5.2)	25.1 (4.7)
Median	24.5	23.9	25.6	24.4
Min, Max	17.3, 44.6	16.0, 56.7	17.5, 43.7	16.4, 46.1

Source: ADSL where ITTFL='Y' by TRT01P

Reviewer Comment: The treatment arms of Study AC-058B201 appear relatively well-matched, but as expected in a trial of RRMS, the typical subject is a white woman in her thirties.

Baseline Disease Characteristics

Table 28 shows the baseline disease characteristics of the RRMS population in Study AC-058B201.

Table 28. Reviewer Table. Baseline Disease Characteristics, Study AC-058B201

Demographic Parameter	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Duration since RMS Symptom Onset (years)				
Mean (SD)	7.3 (6.3)	6.9 (5.7)	6.7 (6.6)	8.0 (7.1)
Median	5.5	5.0	4.3	6.0
Min, Max	0.4, 31.2	0.2, 28.0	0.2, 30.3	0.4, 35.8
Duration since RMS Diagnosis (years)				
Mean (SD)	4.4 (5.1)	4.0 (4.6)	4.1 (4.7)	4.3 (4.7)
Median	2.2	2.4	2.3	2.4
Min, Max	0.1, 22.5	0.1, 20.8	0.0, 19.8	0.0, 23.3
Relapses with the past 12 months				
Mean (SD)	1.2 (0.6)	1.3 (0.7)	1.4 (0.7)	1.3 (0.8)
Median	1	1	1	1
Min, Max	0, 3	0, 3	0, 3	0, 4

Demographic Parameter	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Relapses with the past 24 months				
Mean (SD)	1.8 (1.0)	1.8 (0.8)	1.8 (1.1)	1.8 (1.0)
Median	2	2	2	2
Min, Max	0, 5	0, 4	0, 7	0, 6
Baseline EDSS				
Mean (SD)	2.2 (1.3)	2.2 (1.2)	2.4 (1.3)	2.2 (1.2)
Median	2.0	2.0	2.0	2.0
Min, Max	0, 5.5	0, 5.5	0, 5.5	0, 5.5
Baseline GdE lesions				
Mean (SD)	2.4 (6.6)	1.7 (3.3)	2.6 (6.0)	1.7 (3.6)
Median	0	0	1	0
Min, Max	0, 59	0, 20	0, 53	0, 24

Source : BSL where ITTFL='Y' by TRT01P
EDSS EDSBINDN where ITTFL='Y' and EDS_VISD='Visit 2 - Baseline' by TRT01P
MRI MRI_T1R where ITTFL='Y' and MRI_VISD='Visit 2 - Baseline' by TRT01P

Reviewer Comment: The baseline disease characteristics seem typical for a relapsing MS trial, and the treatment arms appear reasonably well-matched in regard to disease characteristics.

Exposure

The numbers of days that subjects remained on study drug appear similar in the ponesimod and placebo arms of the study, as per Table 29.

Table 29. Reviewer Table. Days of Exposure, Study AC-058B201

Days of Exposure	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Total	17293	19294	16150	16986
Median	151.7	159.5	149.5	142.7

Source : ADEX sum(EXPRDURN) by TRT01P

Treatment Adherence and Concomitant Medications

Treatment Adherence

Records of the number of capsules used and returned were collected during the study. Study drug accountability (i.e., capsule counts) was performed on a regular basis by the study staff and checked by the study monitor during site visits and at completion of the study.

Although it may not be the best measure of treatment adherence, the number of subjects with an interruption in the study treatment in Study AC-058B201 is shown in Table 30.

Table 30. Reviewer Table. Subjects with an interruption in treatment, Study AC-058B201

	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Subjects with treatment interruption	1 (0.9%)	8 (6.6%)	3 (2.8%)	9 (7.6%)

Source : ADEX ncategories (USUBJID) where EXPINTN>0 by TRT01P

Reviewer Comment: At least by this measure, adherence to the study medication in Study AC-058B201 appears good, especially with the 20 mg dose of ponesimod.

Concomitant Medications

Table 31 lists the common concomitant medications used by subjects in Study AC-058B201.

Table 31. Reviewer Table. Common Concomitant Medications, Study AC-058B201

Concomitant Medication	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
PARACETAMOL	29	21	21	22
IBUPROFEN	19	17	21	18
METHYLPREDNISOLONE	22	14	12	10
ALPRAZOLAM	5	4	9	5
ERGOCALCIFEROL	8	8	9	6
MULTIVITAMINS	6	8	7	6
OMEPRAZOLE	7	6	3	8
ASCORBIC ACID	7	3	8	7
PHENYLEPHRINE	8	4	8	1
BACLOFEN	3	7	5	7
CYANOCOBALAMIN	7	5	6	4
NAPROXEN	6	6	6	5
ACETYLSALICYLIC ACID	5	6	4	3
GABAPENTIN	4	5	3	7
DROSPIRENONE W/ETHINYLESTRADIOL	5	4	6	6
DICLOFENAC	3	4	4	5
DIAZEPAM	1	6	3	1
IRON	6	3	5	1
MODAFINIL	7	3	3	4

Concomitant Medication	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
SALBUTAMOL	6	3	3	5
FLUOXETINE	2	3	4	6

Source ADEX ncategories (USUBJID) where ITTFL='Y' by OTPREF and TRT01P

Reviewer comment: Not surprisingly, many of these concomitant medications are commonly used in people with MS, including vitamin D, methylprednisolone for MS relapses, baclofen for spasticity, gabapentin for neuropathic pain, modafinil for fatigue, and fluoxetine for depression.

Efficacy Results – Primary Endpoint

Cumulative Number of GdE

The primary efficacy endpoint of Study AC-058B201 is the cumulative number of new gadolinium enhancing (GdE) lesions on T1-weighted MRI scans performed between Study Weeks 12 and 24. Because this endpoint relies on MRI data over a period of time, it is reasonable to analyze the endpoint on the per-protocol set (PPS), which is defined as follows:

- "Patients who presented with RRMS as stated in the protocol, who had received ≥ 80% of study drug from study drug initiation to the planned EOT (i.e., 168 days), and with at least two valid post-baseline MRIs between Weeks 12 and 24.
- In addition, the patient was required not to have received any forbidden treatment which has an effect on MS or on immune system, prior to study drug initiation, and not received a study treatment different from the treatment allocated originally by the IVRS at any time during the study."

Reviewer Comment: Although this reviewer understands the rationale for using the PPS in this analysis, it should be recognized that this set only consisted of 389 (84.2%) of the 462 subjects treated in Study AC-058B201, as delineated in Table 32.

Table 32. Reviewer Figure. Per Protocol Set, Study AC-058B201

	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Per Protocol Set	98 (86.0%)	110 (90.9%)	88 (81.5%)	93 (78.2%)

Source ADSL where PPROTFL='Y' by TRT01P

As is typical in Phase 2 studies in RMS, Study AC-058B201 is a relatively short study that utilized frequent (every 4 week) MRI scans between Study Weeks 12 and 24 (inclusive). As MRI lesions can occur up to 10 times as commonly as relapses in RMS, a drug's ability to reduce MRI activity

may give some initial indication of its efficacy in MS; indeed, a large meta-analysis by Sormani et al 2009 (extended in Sormani and Bruzzi 2013) suggests a correlation between the development of new MRI and relapses. That said, the limited correlation between the degree of MRI disease and a subject's clinical status at a given point (clinico-radiographic paradox) and the relatively weak correlation between MRI activity and disability progression limit the utility of this potential surrogate (Barkhof 1999, Sormani et al 2010). Table 33 delineates the cumulative number of new GdE lesions between Study Weeks 12 and 24 in the PPS of Study AC-058B201.

Table 33. Reviewer Table. Cumulative New GdE Lesions Between Weeks 12 and 24, Study AC-058B201

	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
N	98	110	88	93
Mean (std)	1.1 (2.0)	5.9 (12.7)	3.4 (7.3)	1.4 (3.2)
Median	0	2	1	0
Min, Max	0, 11	0, 91	0, 42	0, 20

Source: B201 MRI where MRIDVISD='Visit 11 - Week 24' and PPROTFL='Y' by TRT01P

Reviewer Comment: It appears that ponesimod had a robust treatment effect on GdE lesions in Study AC-058B201. In addition to reproducing the Applicant's results (including imputation of missing data) on this endpoint as shown in Table 12 of the CSR, this reviewer performed a similar analysis, albeit without imputation, that also suggests that ponesimod has a treatment effect on GdE lesions, as shown in Table 33.

Efficacy Results – Secondary and other relevant endpoints

Annualized confirmed relapse rate within 24 weeks of study drug initiation

Annualized relapse rate (ARR) is a secondary endpoint of interest in Study AC-058B201. As per Table 34, this reviewer's analysis suggests that ponesimod may have a treatment effect on ARR in Study AC-058B201.

Table 34. Reviewer Table. Annualized Confirmed Relapse Rate, Study AC-058B201

	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Mean (std)	0.40 (1.02)	0.60 (1.66)	0.30 (0.80)	0.22 (0.78)
Median	0	0	0	0
Min, Max	0.0, 6.58	0.0, 14.61	0.0, 4.25	0, 4.2720

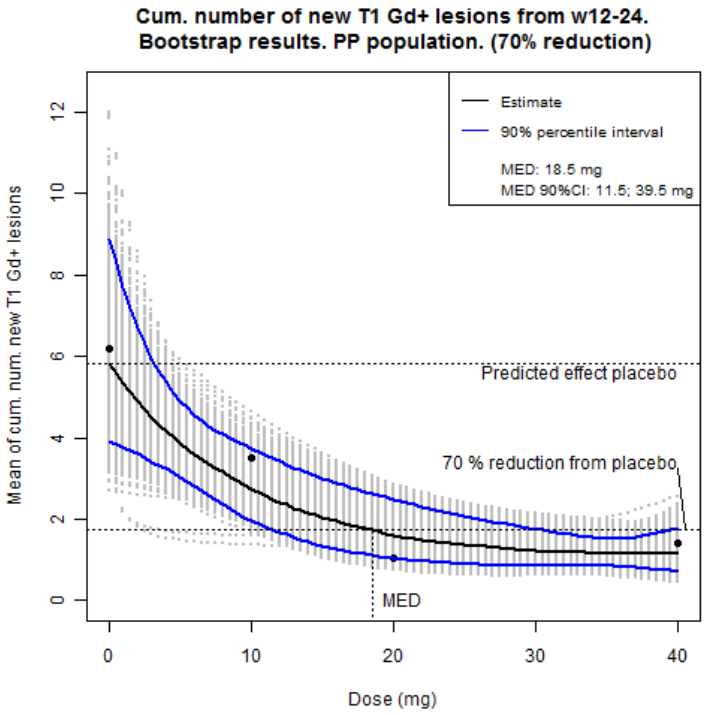
Source: B201 RELARR1 by TRT01P

Reviewer Comment: The annualized confirmed relapse rates for Study AC-058B201 shown in Table 34 are identical to those shown in Table 83 of the CSR and suggests that ponesimod may have a treatment effect on ARR.

Dose/Dose Response

As per Figure 3 of the CSR for Study AC-058B201, which is shown in Figure 10 below, there appears to be a dose-response treatment effect of ponesimod on new GdE lesions.

Figure 10. Applicant Figure. Dose-response Analysis for Cumulative Number of New T1 GdE Lesions



Reviewer Comment: Although this reviewer defers to the Biometrics and Clinical Pharmacology reviewers to assess the statistical significance for his finding, Figure 10 and Table 34 suggest that there is a dose-response relationship between the dose of ponesimod and the cumulative number of new gadolinium enhancing lesions.

Durability of Response

Durability of response was not assessed in Study AC-058B201. An open-label extension of AC-058B201, titled AC-058B202, remains ongoing, but the lack of a comparator arm in this extension limits the ability to confidently assess the continued efficacy (or durability) of

ponesimod's effect on cumulative GdE lesions or relapses.

Persistence of Effect

Efficacy following withdrawal of treatment was not assessed in Study AC-058B201. With that said, given the presumed mechanism of action of S1P receptor modulators (sequestration of circulating lymphocytes in lymphoid tissue), one could posit that the effect of ponesimod would last at least until these lymphocytes were released from the lymphoid tissue (typically within 15-30 days of cessation of ponesimod). It should be remembered that lymphocyte-depleting therapies may not be effective until the sequestered lymphocytes have egressed from the lymphoid tissue.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This integrated assessment of efficacy is limited to the two controlled clinical trials of ponesimod in subjects with RMS (albeit diagnosed with slightly different diagnostic criteria for RMS) that utilized different primary endpoints (new GdE lesions and ARR).

7.1.1. Primary Endpoints

The primary endpoint for the Phase 2 study of ponesimod in subjects with RRMS (Study AC-058B201) is the cumulative number of new GdE lesions on MRIs performed between Study Weeks 12 and 24 compared among 3 doses of ponesimod and placebo. As shown in Section 6.2, Study AC-058B201 suggests that ponesimod has a dose-response treatment effect on this endpoint.

ARR is the primary endpoint for the Phase 3 study of ponesimod 20 mg in subjects with RMS (Study AC-058B301), which uses teriflunomide 14 mg as an active comparator. In Section 6.1, this reviewer estimates the reduction in the unadjusted treatment exposure ARR with ponesimod is 28.6%, although it should be remembered that the active comparator also has a treatment effect on ARR, suggesting that ponesimod would have a greater absolute effect on ARR versus no treatment.

7.1.2. Secondary and Other Endpoints

ARR is a secondary endpoint of interest in Study AC-058B201, and this reviewer's analyses in Section 6.2 suggests that ponesimod has a significant treatment effect on this endpoint compared with placebo.

As noted in Section 6.1, the data for the FSIQ-RMS-S in Study AC-058B301 key secondary

endpoint is likely uninterpretable, but the treatment effect on the CUAL key secondary endpoint in this study appears robust. Unfortunately, Study AC-058B301 did not achieve a robust or clinically significant effect on its EDSS key secondary endpoints.

7.1.3. Subpopulations

Many (64.9%) of the subjects in Study AC-058B301 were women, and most (97.4%) were white. Although more diversity would have eased concerns about the generalizability of the results of this study, RMS does have a predilection for white women.

7.1.4. Dose and Dose-Response

See Figure 10 and Table 34 for the dose-response analyses of ponesimod on the cumulative number of new GdE lesions in Study AC-058B201. Study AC-058B301 only assessed one dose of ponesimod (20 mg).

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There were no dedicated onset, duration, or durability studies performed in the pivotal or supportive trials in this application.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Especially given the treatment effects demonstrated with other S1P receptor modulators approved for the treatment of RMS, this reviewer does not suspect that the efficacy of ponesimod in the postmarket setting will vary substantially from the treatment effect demonstrated in Studies AC-058B201 and AC-058B301.

7.2.2. Other Relevant Benefits

This reviewer does not foresee any other potentially relevant benefits of ponesimod at this time; as per Section 6.1, even though statistical significance appears to be reached on the FSIQ-RMS-S endpoint in Study AC-058B301, these data are uninterpretable and do not suggest that ponesimod has a clinically meaningful effect on fatigue.

7.3. Integrated Assessment of Effectiveness

Like the other S1P receptor modulators that have been approved for RMS, both the Phase 2 and the Phase 3 trial of ponesimod in subjects with RMS show a robust response on relapses and MRI metrics even though the Phase 3 trial used an active comparator (teriflunomide). Also similar to other S1P receptor modulators, the effect

on ponesimod on 12- and 24-week confirmed disability accumulation was not robust; indeed, these key secondary endpoints did not achieve statistical significance in Study AC-058B301. The design and conduct of these studies do not raise questions about the validity of the ARR and MRI results; therefore, this reviewer finds that there is substantial evidence of effectiveness to support the approval of ponesimod for the treatment of adults with relapsing forms of MS with inclusion of ARR and CUAL (preferably stratified by new GdE and new T2 lesions) in Section 14 of its labelling.

Conversely, as noted in Section 6.1 above, there is insufficient evidence of effectiveness to include the results of the FSIQ-RMS-S in any labelling of ponesimod.

8. Review of Safety

8.1. Safety Review Approach

This safety review of ponesimod will focus on the safety findings from the clinical trials of subjects with relapsing multiple sclerosis (RMS) since this is the indication for which the Applicant seeks approval. The smaller studies exploring the use of ponesimod in subjects of plaque psoriasis will be supportive as they consistent of a distinct population for a different disease state, one for which a combination immunosuppressive therapy is more common. The clinical pharmacology studies, most of which consist of healthy subjects, may help further inform the safety findings with ponesimod but are not a primary focus of this review.

The safety population for ponesimod's RMS development program includes a Phase 2, placebo-controlled, dose-finding study of 464 subjects with RRMS and a Phase 3, active-controlled (teriflunomide) study of 1131 subjects with RMS.

After discussing the overall ponesimod exposure in the RMS safety population, the relevant characteristics of this population, the categorization of adverse events, and the scheduled safety testing, this review will delineate deaths, serious adverse events, treatment emergent adverse events (TEAE) leading to discontinuation of the study medication, and TEAE graded as severe; narratives for events of particular interest will follow each of these sections. Additionally, common TEAEs in the RMS and plaque psoriasis safety population will be tabulated, after which the potential effect of ponesimod on laboratory values, vital signs, electrocardiography findings (ECG), and pulmonary function tests (PFTs) will be explored.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall exposure to ponesimod in its development program is shown in Table 35, which is copied from Table 7 of the Summary of Clinical Safety (SCS) for this NDA.

Table 35. Applicant Table. Overall exposure to ponesimod

Table 7: Overall Exposure

	Phase 1[a]	Multiple Sclerosis[b]					Plaque Psoriasis			GVHD	TOTAL	
		B201/B202[c]			B301/B303[d]		A200	A201		C202	MS	ALL
		10 mg[e]	20 mg[e]	40 mg[e]	20 mg[f]	20 mg[g]	20 mg	20 mg	40 mg	20 mg		
≥1 day	462[h]	139	145	151	565	438	45	126	133	1	1438	2205
>6 months		114	115	112	518	302		47[i]	51[i]		1161	1259
>1 year		111	113	105	502	196					1027	1027
>2 years		107	109	97	472						785	785
>3 years		99	102	88	237						526	526
>4 years		96	95	82							273	273
>5 years		92	84	77							253	253
>6 years		87	81	73							241	241
>7 years		84	78	70							232	232
>8 years		70	73	63							206	206
>9 years		11	19	11							41	41

[a] Subjects exposed to ponesimod in Phase 1 are healthy, renally impaired, or hepatically impaired.
[b] Not including subjects from Study B302 (who remain blinded).
[c] As of the cutoff date of 31 March 2019
[d] As of database lock of Study B301 on 27 June 2019 and the cutoff date of 30 May 2019 for Study B303
[e] Subjects are summarized based on their first randomized dose of ponesimod. Subjects initially randomized to ponesimod 40 mg were re-randomized to 10 or 20 mg in Treatment Period 2. All subjects received ponesimod 20 mg in Treatment Period 3.
[f] Subjects receiving ponesimod 20 mg in Studies B301 and B303 (P20 mg/P20 mg).
[g] Subjects naïve to ponesimod 20 mg in Study B303 (ie, initially randomized to teriflunomide 14 mg in Study B301) (T14 mg/P20 mg)
[h] The number represents subjects from 16 Phase 1 studies. Subjects were exposed to single doses of ponesimod (up to 75 mg) or multiple doses of ponesimod up to 100 mg for up to 22 days.
[i] Subjects with >24 weeks of exposure

Reviewer Comment: The overall exposure to ponesimod exceeds the ICH guidelines for chronically administered medications (i.e., n=1,500 exposed, n=300-600 for 6 months, n=100 for 1 year).

8.2.2. **Relevant characteristics of the RMS safety population:**

There is a well-recognized geographical distribution of RMS in which the prevalence of RMS increases with greater distance from the equator. This distribution may relate to vitamin D, since vitamin D is more easily synthesized closer to the equator and since there appears to be an inverse correlation between vitamin D levels and the risk of RMS activity; indeed, there are some subpopulations who prefer a diet high in Vitamin D (e.g., Alaskan Inuits) that have a much lower risk of RMS than expected given where they live. RMS is more common in women than in men (approximately 3:1) and in people of Northern European, Caucasian descent, although a recent study from Southern California suggests an increasing incidence in people of African descent. The prevalence of RMS is quite low in childhood, increases during adolescence, and is highest between 20-40 years of age. The classic epidemiologic characteristics of an individual diagnosed with MS is a 30 year old post-partum woman (Compston and Coles, 2008, Reich et al, 2018, Ascherio and Munger, 2016).

Reviewer Comment: Overall, the demographics of the safety population appear comparable among the treatment arms and are generally representative of what would be expected for a typical RMS population. With that caveat, this reviewer notes that the safety population is almost entirely white and worries that this may limit the generalizability of the results: although many people with RMS are of Caucasian descent, it does appear that people of African descent are at risk of worse outcomes from RMS. Further, much of the safety population is from Eastern Europe, leading this reviewer to worry about the generalizability of the safety results, especially given the seemingly low rates of adverse event reporting in applications with study populations predominantly from this region.

As is common in clinical trials of RMS, subjects with clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease, including specific cardiac conditions, poorly controlled diabetes mellitus type 2, and a history of uveitis, were excluded from participating in the clinical trials of ponesimod in subjects with RMS.

Reviewer Comment: Although the aforementioned exclusions are appropriate to enhance the safety of subjects participating in clinical trials, it should be recognized that these safety analyses may underestimate the risk of using ponesimod in the overall RMS population, so this reviewer recommends that the characteristics of the population enrolled in the ponesimod RMS studies be described in any labelling for ponesimod.

8.2.3. **Adequacy of the safety database:**

The ponesimod safety database includes a sufficient number of RMS subjects treated for an adequate duration to allow a satisfactory safety review capable of reaching meaningful conclusions about the safety of ponesimod in adults with RMS. The demographics and disease characteristics of this safety population are similar to that of a typical RMS population, although it would have been preferable if more non-white subjects and more subjects from outside of Eastern Europe had been enrolled. As is commonly done in RMS trials, the ponesimod RMS safety population does not include subjects with significant concomitant disease, potentially limiting the generalizability of this safety analysis to the overall RMS population.

8.3. **Adequacy of Applicant's Clinical Safety Assessments**

8.3.1. **Issues Regarding Data Integrity and Submission Quality**

The safety data provided by the Applicant are of sufficient quality to permit their review. A data fitness assessment by the Agency's Office of Computational Science (OCS)

concluded that the datasets submitted for review were substantially complete and found few examples of duplicated, inconsistent, or missing data. The Applicant responded appropriately to all queries about their submitted data with timely (and meaningful) responses to the Division's Information Requests (IRs).

This reviewer was able to replicate the key findings of the safety summaries provided by the Applicant. Comparing subject-level data across sources did not uncover gross discrepancies between datasets, narratives, supplied CRFs, listings, or summary tables.

8.3.2. **Categorization of Adverse Events**

The definitions of adverse event (AE) and treatment emergent adverse event (TEAE) in the protocol for Study AC-058B301 are reasonable and consistent with typical definitions of AEs and TEAEs:

> "An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment."
>
> "A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 15 days after study treatment discontinuation), whether or not considered by the investigator as related to study treatment."

Unless they were atypical in severity or some other characteristic, MS relapses and disability progression events were not considered AEs. Investigators' verbatim terms for AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 for Study AC-058B301 and version 14.0 for Study AC-058B201.

> *Reviewer Comment: The Applicant's definition of AEs / TEAEs and process for coding these AEs appear adequate to allow for reasonably accurate estimates of event risks by preferred term (PT) and System Organ Class (SOC).*

During the studies of ponesimod, investigators monitored subjects for the occurrence of AEs from the time that the informed consent form was signed until 30 days after the study drug was discontinued and were to record any AEs on electronic Case Report Forms (eCRFs). In addition to reviewing abnormal findings on physical examinations, laboratory results, and other testing for clinically significant changes, investigators solicited AEs by questioning subjects at each study visit, although subjects could also volunteer AEs between visits. Abnormal laboratory values or test results constituted AEs if they represented a clinically significant finding, symptomatic or not, that was not present at study start, worsened during the course of the study, or led to dose reduction, interruption or permanent discontinuation of the study treatment.

All AEs were to be included in the eCRF regardless of the investigator's impression regarding the relatedness of an AE to the study medication. In addition to a description of the event, the Investigator was to record the severity of the AE. Instead of using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), the severity of AEs was graded by three categories of intensity using the following definitions:

- "Mild: The event may be noticeable to the subject. It does not influence daily activities and does not usually require intervention.;
- Moderate: The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.;
- Severe: The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed."

Investigators were to follow all AEs until "they are no longer considered clinically relevant, or until the event outcome is provided." Other information collected about AEs on the eCRF included the onset, duration, action taken with the study treatment, and outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown) of the AE. Although of limited utility. the investigator's assessment of the relationship (unrelated or related) of the AE to the study medication was also recorded on the eCRF.

Reviewer Comment: The methods to ascertain AEs and the information collected on the eCRF appears reasonable and appropriate.

The Applicant defined a serious adverse event (SAE) as any untoward medical occurrence or effect that fulfills the following criteria:

- "Fatal
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above."

The following reasons for hospitalization are exempted from being reported:

- "Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for MS relapse (unless fatal .
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris."

In addition to deaths and SAEs, TEAEs leading to study withdrawal, study drug discontinuation, or treatment interruption are of special interest, as are those whose severity was graded as severe. The Applicant defined the following to be adverse events of special interest (AESIs):

- "Effect on HR and rhythm related AEs
- Hepatobiliary disorders / Liver enzyme abnormality related AEs
- Pulmonary related AEs
- Eye disorders related AEs
- Infection related AEs
- Skin malignancy related AEs
- Non-skin malignancy related AEs
- Cardiovascular related AEs
- Hypertension related AEs
- Stroke related AEs
- Seizure related AEs"

Reviewer Comment: The definition of SAEs is reasonable and appropriate, as is the Applicant's choice of AESIs, especially given the safety profiles of other S1P receptor modulators.

8.3.3. **Routine Clinical Tests**

Serologies

Testing for viral serologies was performed at screening, and the study exclusions included evidence of infection with HIV, tuberculosis, or hepatitis B or C. Subjects also had to demonstrate evidence of antibodies to the varicella zoster virus (VZV), although VZV seronegative subjects could be rescreened after VZV vaccination.

First Dose Cardiac Monitoring

Presumably because of the known risks of bradyarrhythmia and atrioventricular (AV) block with the administration of the first dose of other S1P receptor modulators (and cases of second degree AV block in the early studies of ponesimod), a 14-day dose escalation was implemented in Study AC-058B301 in an attempt to mitigate this risk. In

addition to a resting heart rate less than 50 beats per minute (bpm) on a 12-lead ECG on Study Day 1, the exclusion criteria for Study AC-058B301 included the following cardiac conditions:

- "Myocardial infarction within 6 months prior to randomization or ongoing unstable ischemic heart disease
- Cardiac failure (New York Heart Association class III or IV) or any severe cardiac disease at the time of Visit 1 (Screening) or randomization
- 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 (e.g., 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 QTcF interval > 470 ms (females), > 450 ms (males) as measured by 12-lead ECG at Visit 1(Screening) or Visit 2 (Baseline) or by the pre-dose ECG at Visit 3 (Randomization / Day 1)
- History of syncope associated with cardiac disorders
- Systemic arterial hypertension not controlled by medication according to the investigator's judgment"

As previously noted, a 14-day dose titration was implemented in Study AC-058B301 to reduce the risk of first dose bradyarrhythmia and AV block. After the first dose of ponesimod was administered on Study Day 1 (or on the first day of a required dose re-initiation for missed doses), subjects were closely monitored for cardiac AEs (by a first-dose administrator) at a site capable of managing symptomatic bradycardia. ECGs were performed before the first dose of the study medication was administered and then hourly for a minimum of four hours or until the following discharge criteria were met.

- "ECG-derived resting HR > 45 bpm, and if HR < 50 bpm it must not be the lowest value post-dose
- SBP > 90 mmHg;
- QTcF < 500 ms and QTcF increase from pre-dose < 60ms;
- No persisting significant ECG abnormality (e.g., AV block second- or third-degree) or ongoing AE requiring continued cardiac monitoring or prohibiting study continuation as an out-patient."

Subjects who did not meet the defined discharge criteria at 12 hours after the first dose of ponesimod was administered were required to permanently discontinue the study drug but were monitored until the ECG changes were no longer clinically relevant or until monitoring was no longer medically indicated.

Subsequent study ECGs were performed before the study medication was dosed for the day; at the visit on Study Week 12, an additional ECG was performed three hours after the dose of the study medication was taken.

Reviewer Comment: The methodology for cardiac monitoring after administration of the first dose of ponesimod appears reasonable and appropriate.

Vital Signs

In addition to the aforementioned ECGs (from which heart rates were derived), vital signs, including body temperature, weight, and systolic and diastolic blood pressure were routinely taken at study visits. Heart rates were directly assessed at unscheduled relapse visits. The height of subjects was collected at baseline, allowing the calculation of a body mass index (BMI).

Laboratories

Since lymphopenia occurs with other S1P receptor modulators, hematology laboratories (including white blood cell, lymphocyte, and platelet counts as well hemoglobin / hematocrit) were checked at baseline and periodically during the studies of ponesimod in subjects with RMS. The exclusion criteria for Study AC-058B301 included an absolute white blood cell count (WBC) < 3500/uL, an absolute lymphocyte count (ALC) < 800/uL, an absolute neutrophil count (ANC) < 1500/uL, a hemoglobin < 100 g/L, and a platelet count below 100 x 10^9/L.

Serum chemistries were also checked at baseline and periodically during the studies of ponesimod in subjects with RMS. Given the occurrence of transaminase elevations suggestive of liver injury with other S1P receptor modulators, the exclusion criteria for Study AC-058B301 included subjects with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x ULN and a total bilirubin (TB) > 1.5x ULN (except for known Gilbert's syndrome). Elevation in ALT, AST, and TB during the study were of special interest and were managed as follows.

Table 36. Applicant Table. Guidance for discontinuation for liver enzyme abnormalities

Item	Laboratory parameter	Guidance
1	ALT or AST ≥ 3 × ULN *	Start close observation. Repeat labs within 72 hours. See items 1a and 1b. * if ALT or AST ≥ 8 × ULN OR ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN or INR > 1.5 OR ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) and retest cannot be done within 72 hours, permanently discontinue study drug, and perform FU
1a	If at repeated labs, ALT or AST ≥ 3 × ULN < 8 × ULN	Continue close observation. Repeat labs twice weekly. See items 2a and 2b.
1b	If at repeated labs, ALT or AST < 3 × ULN	Resume regular labs schedule.
2a	If at repeated labs, ALT or AST ≥ 5 × ULN for > 2 weeks	Permanently discontinue study drug, and perform FU.
2b	If at repeated labs, ALT or AST ≥ 3 × ULN < 5 × ULN for > 2 weeks	Continue close observation. Repeat labs once or twice weekly.
3	If at repeated labs: • ALT or AST ≥ 8 × ULN • ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN or INR > 1.5 • ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)	Permanently discontinue study drug, and perform FU.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FU = follow-up; INR = International Normalized Ratio; ULN = upper limit of normal range.

Urinalyses and coagulation studies (i.e., INR) were checked at baseline and periodically during the studies of ponesimod in subjects with RMS.

Pulmonary Monitoring

Pulmonary function tests, including a forced vital capacity (FVC), a forced expiratory volume in one second (FEV1), and at certain sites , a diffusion capacity of the lungs for carbon monoxide (DLCO), were assessed at baseline and periodically during the studies

of ponesimod in subjects with RMS. Subjects with a baseline FEV1 or FVC < 70% of predicted were excluded from Study AC-058B301.

Ophthalmology Monitoring
Given the association of macular edema with other S1P receptor modulators, risk factors for macular edema, including a history of macular edema, diabetes mellitus type 1 or uncontrolled diabetes mellitus type 2, and diabetic retinopathy were among the exclusion criteria for the ponesimod studies. Optical coherence tomography (OCT) studies were performed at baseline and periodically during the studies of ponesimod in subjects with RMS. In cases of macular edema confirmed by a local ophthalmologist, subjects were to discontinue the study drug and be followed and managed until resolution of this AE. An Ophthalmology Safety Board (OSB) reviewed cases of suspected macular edema, including a central review of the OCT results.

Dermatology monitoring
As cutaneous malignancies have been reported with other S1P receptor modulators, a history of malignancy (except excised and resolved basal or squamous cell carcinoma of the skin) was among the exclusion criteria for the ponesimod clinical trials. Dermatologic examinations were performed at baseline, Study Week 60, and at end of treatment in Study AC-058B301.

Suicidality
The Columbia Suicide Severity Rating Scale (C-SSRS) was assessed at baseline and periodically throughout the study.

Reviewer Comment: The methodology for assessing for vital sign and laboratory abnormalities and monitoring for suicidality and pulmonary, ophthalmologic, and dermatologic abnormalities in the clinical studies of ponesimod in RMS appears reasonable and appropriate.

8.4. Safety Results

8.4.1. Deaths

Per the ISS, there were five deaths in the clinical studies of ponesimod, although two of these occurred in subjects randomized to teriflunomide 14 mg in Study AC-058B301. None of the deaths were deemed to be related to the study medication by the investigators.

- At enrollment, Subject (b) (6) was a 52yo man with a history of hypertension, dyslipidemia, and axillary artery thrombosis (s/p thrombectomy) who was randomized to ponesimod 20 mg in Study AC-058B201 and continued this dose in AC-058B202. Reportedly, he started smoking during the study. On Study Day 1987, he developed

chest pain and died, but an autopsy was not performed. The Major Adverse Cardiovascular Events (MACE) Adjudication Board considered this sudden death to be cardiovascular in etiology.

Reviewer Comment: Given this subject's vascular risk factors (including axillary artery thrombosis suggestive of baseline peripheral artery disease), this reviewer agrees that the role of ponesimod in this death (if any) is unclear.

- At enrollment, Subject (b) (6) was a 41yo woman with a complex medical history including cirrhosis, esophageal varices, stomach perforation, abdominal abscess, and diabetes mellitus who was taking ponesimod 10 mg in Study AC-058-112. On Study Day 5, she was hospitalized with fever, chills, and right lower quadrant abdominal pain, and she was diagnosed with Staphylococcus Aureus sepsis, hepatic encephalopathy, severe anemia, and high hyperbilirubinemia. Despite treatment, she died from this event.

  Reviewer Comment: Given this subject's complex medical history suggestive of end stage liver disease, this reviewer agrees that the role of ponesimod in this death (if any) is unclear.

- At enrollment, Subject (b) (6) was a 33yo man with a history plaque psoriasis who was randomized to ponesimod 40 mg in Study AC-058A201 but decided to discontinue the study drug on Study Day 31, presumably due to adverse events (tinnitus and sinusitis). Fifty-five days after stopping the study drug, he was found death in his bath and the cause of death was determined to be "acute cardiac and pulmonary insufficiency."

  Reviewer Comment: Since this death occurred almost eight weeks after stopping the study medication, this reviewer agrees that it is difficult to attribute this event to the study medication.

- At enrollment, Subject (b) (6) was a 52yo man with a history of hypertension, dyslipidemia, obesity, and impaired glucose tolerance who was randomized to teriflunomide 14 mg in Study AC-058B301. On Study Day 99, the subject experienced acute coronary insufficiency and died; his autopsy revealed generalized atherosclerosis and chronic ischemic heart disease with severe sclerosis of the coronary arteries.

  Reviewer Comment: This subject's vascular risk factors and coronary disease certainly predated initiation of the study drug, so the role of teriflunomide in this death (if any) is unclear.

- At enrollment, Subject (b) (6) was a 45yo man with a history of bilateral cataracts who was randomized to teriflunomide 14 mg in Study AC-058B301. The study drug was

discontinued on Study Day 295 "due to festive and family related activities," and two days later he reportedly developed facial pallor and respiratory difficulties before suddenly dying. An autopsy was not performed, and the primary cause of death was reported as multiple sclerosis.

Reviewer Comment: Given very little available information, it is difficult to confidently hypothesize about the cause of this subject's death two days after stopping the study drug, so the role of teriflunomide in this death (if any) is unclear.

No additional deaths were reported in the 120-day safety update for the ongoing AC-058B202 and AC-058B303 long-term extension studies.

8.4.2. **Serious Adverse Events**

Serious adverse events (SAE) are flagged in the ADAE datasets (AESER='Y') and are defined in the protocol for Study AC-058B301 as "any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above. Important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above."

The following exceptions apply to reporting a hospitalization as an SAE:

- "Hospitalization for cosmetic elective surgery, or social and/or convenience reasons."
- "Hospitalization for MS relapse" with the following exceptions:
  - "MS relapses with fatal outcome
  - MS relapses that, in the view of the investigator, warrant specific notice due to unusual frequency, severity or remarkable clinical manifestations"
- "Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris."

SAEs, active-controlled RMS population (Study AC-058B301)

This reviewer's analysis of the AC-058B301 ADAE dataset suggests that 125 SAEs were reported by 96 subjects in Study AC-058B301 and that most of these SAEs only occurred once. The SAEs that occurred more than once in Study AC-058B301 are delineated in Table 37.

Table 37. Reviewer Table. SAEs, Study AC-058B301

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Abdominal pain	3	0
Appendicitis	3	0
Lumbar radiculopathy	3	1
Abortion induced	2	0
Cholelithiasis	1	3
Endometrial hyperplasia	1	1
Endometriosis	1	1
Hypertensive crisis	1	1
Intervertebral disc protrusion	1	1
Multiple sclerosis relapse	1	1
Uterine leiomyoma	1	3
ALT increased	0	2
Concussion	0	2
Femur fracture	0	2
Metrorrhagia	0	2

Source: AC-058B301 ADAE where SAFFL, TRTEMFL, and AESER ='Y' by AEDECOD and TRT01A.

Reviewer Comment: Percentages are not calculated in Table 37 because of the very low incidence of SAEs in the active-controlled RMS population and because the same SAE could potentially be reported more than once by the same subject. The low number of SAEs is reassuring but complicates the identification of clear safety signals from background rates. Although many of the SAEs in *Table 37 occur relatively commonly in the general population, the hypertensive crisis SAE with ponesimod is of interest, especially since hypertension is recognized as a risk with other S1P receptor modulators.*

Hypertensive crisis

- At enrollment, Subject (b) (6) was a 53yo man who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 20, he presented with severe headaches and was found to have a hypertensive crisis with a blood pressure of 240/150 mmHg that improved to 222/150 after sublingual nitroglycerin was given en route to the hospital. The study treatment was stopped, and he was hospitalized on Study Day 21 because his blood pressure remained high despite starting ramipril and amlodipine. Transthoracic echocardiography showed "hypertensive heart disease

with massive hypertrophy of left ventricle without wall motion abnormalities and highly echogenic septum," and work-up for secondary causes of hypertension was reportedly unrevealing. With initiation of spironolactone, dihydralazine sulfate and hydrochlorothiazide, the episode was considered resolved on Study Day 31, albeit with the sequela of chronic renal insufficiency. He was started on mononidine and carvedilol on Study Day 34.

Reviewer Comment: Although the echocardiogram suggests that this subject had long standing issues with hypertension, the close temporal association between initiating ponesimod and the onset of this SAE suggests a possible contribution by ponesimod, especially since other S1P receptor modulators have a safety signal for hypertension and posterior reversible encephalopathy syndrome (PRES), which can be associated with accelerated hypertension.

Perusal of other SAEs that occurred once with ponesimod reveals several categories of interest, including malignancy (single cases of basal cell carcinoma, malignant melanoma, and squamous cell carcinoma of the cervix), seizures (cases of clonic convulsion, epilepsy, partial seizure with secondary generalization), and liver injury (drug-induced liver injury, hepatic enzyme increase). There are also solitary cases of herpes zoster, syncope, acute pancreatitis, thrombocytopenia, and tubulointerstitial nephritis.

Reviewer Comment: Although little can be gleaned from solitary cases, infections, seizures, malignancies, liver injury, and malignancies have occurred with other S1P receptor modulators, and there are post-marketing reports of thrombocytopenia with fingolimod. Since there were multiple SAEs for malignancies and seizures, these events are explored in more detail; further, given the risk of bradyarrhythmia with S1P receptor modulators, the case of syncope is of interest.

<u>Malignancy</u>

- At enrollment, Subject (b) (6) was a 48 yo woman with a reported personal history of dermatofibroma, whose father who had "non-melanoma malignant sign (sic) lesion," and who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 687, an "irregular pigment lesion of 6x4mm" was noted "on the left malar area." A biopsy revealed malignant melanoma with superficial extension. Other risk factors for skin cancer are not mentioned in the narrative.

- At enrollment, Subject (b) (6) was a 49 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. During a dermatologic evaluation on Study Day 757 (End of Treatment visit), atypical pigmentation was noted

on his neck, and a biopsy revealed basal cell carcinoma (BCC). Other risk factors for skin cancer are not mentioned in the narrative.

- At enrollment, Subject (b) (6) was a 39 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and who presented with vaginal spotting on Study Day 224. She was hospitalized on Study Day 260 and was found to have "nonkeratinizing squamous cell carcinoma infiltrating the uterine cervix." On Study Day 335, she had a total hysterectomy, salpingectomy, and iliac lymphadenectomy; the histopathology revealed "squamous cell carcinoma, non-keratinizing and poorly differentiated" with vessel invasion and five of eight sampled lymph nodes showing metastasis. The study medication was stopped, and the subject was treated with chemotherapy and radiation, seemingly with good effect.

  Reviewer Comment: Although Subject (b) (6) may have had risk factors for melanoma, it is certainly possible that ponesimod played a role in all three of these malignancies.

Seizure

- At enrollment, Subject (b) (6) was a 26 yo man with a reported history of hydrocephalus who was randomized to ponesimod 20 mg in Study AC-058B301. The subjects stated to experience weight loss on Study Day 610 and was hospitalized with "loss of consciousness and generalized cramps" on Study Day 692. An EEG revealed "generalized epileptiform activity," for which he started lamotrigine.

- At enrollment, Subject (b) (6) was a 33 yo woman with a history of partial seizures with secondary generalization who was randomized to ponesimod 20 mg in Study AC-058B301. She had a partial seizure with secondary generalization on Study Day 748 and was started on carbamazepine.

- At enrollment, Subject (b) (6) was a 37 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 13, she was hospitalized for a "clonic convulsion … in left hand and left half of face followed by decreased level of consciousness" with post-ictal (Todd's) paralysis. She was intubated until Study Day 15, after which she had an MRI and was started on carbamazepine. A subsequent EEG reportedly did not show any clinically significant abnormalities.

  Reviewer Comment: The medical histories of Subjects (b) (6) (hydrocephalus) and (b) (6) (partial seizures with secondary generalization) confound interpretation of the potential role of

ponesimod in these SAEs. Given the close temporal correlation between starting ponesimod and experiencing a seemingly new onset seizure, it is unclear why the investigator and sponsor did not consider the event experienced by Subject (b) (6) to be at least possibly related to the study medication; indeed, this reviewer suspects that ponesimod may have contributed to the occurrence of this SAE.

Herpes zoster

- At enrollment, Subject (b) (6) was a 21 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 32, she noted a skin rash on her right upper abdomen after vigorous exercise and soon developed blisters and pain at this site. She was diagnosed with herpes zoster and started on acyclovir.

Reviewer Comment: Herpetic infections, including varicella zoster virus infections, are reported with other S1P receptor modulators.

Syncope

At enrollment, Subject (b) (6) was a 58yo man with a history of diabetes mellitus, hypertension, and myopia who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Days 660 and 662, he experienced diaphoresis and syncope at night while urinating, suggestive of vasovagal syncope; reportedly, a follow-up ECG and 24-hour Holter showed normal sinus rhythm.

Reviewer Comment: This reviewer agrees that this event is suggestive of vasovagal syncope and is doubtfully related to the study drug.

SAEs, placebo-controlled RMS population (Study AC-058B201)

This reviewer's analysis of the AC-058B201 ADAE dataset suggests that 27 SAEs were reported by 22 subjects in Study AC-058B201 and that most of these SAEs only occurred once. The SAEs that occurred more than once in Study AC-058B201 are delineated in Table 38.

Table 38. Reviewer Table. SAEs, Study AC-058B201

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
Macular edema	2	0	0	0
Atrioventricular block 2nd degree	1	0	2	0
Appendicitis	1	0	0	1

Source: AC-058B201 ADAE where ITTFL, AETREMFL, and AESER ='Y' by AEDECOD and TRT01P.

Reviewer Comment: Percentages are not calculated in Table 38 because of the very low incidence of SAEs in the active-controlled RMS population and because the same SAE could be reported more than once by the same subject. Given the safety profile of other S1P receptor modulators, the SAEs for 2nd degree AV block and macular edema in subjects randomized to ponesimod are of interest.

Bradyarrhythmia and Atrioventricular Block

- Subject (b) (6) was a 44 yo woman with a known cardiac history who was randomized to ponesimod 20 mg in Study AC-058B201 and who reported dizziness two hours after receiving her first dose of ponesimod. An ECG at the time showed a heart rate of 47 with second degree AV block 2:1, and subsequent first-dose ECGs showed second degree AV block. A 24-hour Holter monitor on Study Day 1 showed "showed multiple episodes of Mobitz I (Wenckebach) second degree AV block (11563 episodes); 2:1 AV block (2295 episodes) throughout the entire recording, frequent VPCs (8363 in 24 hours)" so the study medication was permanently discontinued and the event was considered resolved on Study Day 16.

- Subject (b) (6) was a 36 yo woman with a history of migraines who was randomized to ponesimod 10 mg in Study AC-058B201. After the first dose of the study medication was administered, she reported palpitations, and an ECG at three hours after this dose showed first degree AV block. An ECG at four-hours showed a junctional rhythm with a HR of 68 bpm, and her five-hour ECG showed "second degree AV block Mobitz I (Wenckebach) and 1 junctional escape beat" with a HR of 47 bpm. The subject was hospitalized on Study Day 1, and a Holter assessment showed "second degree AV block Mobitz I (Wenckebach) (more than 200 episodes) and 2:1 second degree AV block (eleven episodes)." The subject was discharged from the hospital of Study Day 2.

- Subject (b) (6) was a 27 yo woman without a known cardiac history who was randomized to ponesimod 10 mg in Study AC-058B201 and who developed shortness of breath and wheezing 90 minutes after receiving the first dose of ponesimod. Since ECGs after this first dose showed first degree AV block and Mobitz I second degree AV block (Wenckebach), she was admitted to the hospital for observation, and the study medication was permanently discontinued. She was discharged from the hospital on Study Day 2, and a five-day cardiac monitor 22 days after the study drug was discontinued showed "sinus rhythm and borderline first degree AV block and second degree AV block Mobitz I (Wenckebach) in early hours of morning."

  Reviewer Comment: First-dose bradyarrhythmia and AV blocks are recognized risks with other S1P receptor modulators, and these SAEs strongly suggest that

ponesimod has the same risk, even if Subject (b) (6) experienced early morning bradyarrhythmia three weeks after stopping ponesimod. It is noted that the dose-escalation scheme in the Phase 2 studies of ponesimod was less gradual than it was Study AC-058B301.

Macular edema

- Subject (b) (6) was a 38 yo woman with a history of "mydriasis, iridocyclitis, extensive posterior synechial both eyes and cataracts" who was randomized to ponesimod 20 mg in Study AC-058B201. Since her foveal thickness in both eyes significantly increased between her baseline optic coherence tomography (OCT) and a scheduled OCT on Study Day 36, she was diagnosed with macular edema and the study drug was withdrawn. Follow-up OCTs showed improvement in her foveal thickness on Study Day 71 and a return to baseline on Study Day 147.

- Subject (b) (6) was a 34yo man who was randomized to ponesimod 20 mg in Study AC-058B201 and who noted visual impairment on Study Day 58. An ophthalmological evaluation was consistent with bilateral macular edema, so the subject was hospitalized and the study drug was discontinued on Study Day 59. A follow-up ophthalmological evaluation on Study Day 64 showed "visual acuity measurement normal" without macular edema in the right or left eye. An independent Ophthalmology Advisory Board found that "only (b) (6) from (b) (6) (Day 64), does not shown any edema (RNFL imaging was performed around the fovea, which does not allow to judge any potential swelling around the optic disk)." On Study Day 105, the event was reportedly resolved without sequelae.

Reviewer Comment: Although macular edema has been associated with the use of other S1P receptor modulators, factors in both of these cases complicate an analysis of the role of ponesimod: Subject (b) (6) had a significant ophthalmological history before starting ponesimod, and the rapid resolution (and seemingly unremarkable OCT) raise questions about the diagnosis of macular edema in Subject (b) (6)

Perusal of the SAEs that occurred once with ponesimod revealed several single cases of interest, including cases of breast cancer, QT prolongation, and coronary artery disease as well as a subject who experienced ALT and AST elevations and another who experienced dyspnea and a pleural effusion.

Malignancy

- Subject (b) (6) was a 53 yo woman with a family history (maternal aunt) of breast cancer who was randomized to ponesimod 10 mg in Study AC-058B201. On Study Day 107, screening mammography revealed a "2.9 x 4.1 cm mass of left breast with speculated margins and irregular contour." Biopsy of this lesion showed

"invasive poorly differentiated ductal carcinoma of NOS type," so the study drug was discontinued.

Reviewer Comment: Since breast cancer was diagnosed in this subject on Study Day 107, it is highly likely that the development of this malignancy predated initiation of ponesimod.

Bradyarrhythmia and Atrioventricular Block

- Subject (b) (6) was a 32 yo woman who was randomized to ponesimod 10 mg in Study AC-058B201. She had a heart rate of 44 bpm two hours after receiving her first dose of ponesimod; further, she experienced vertigo and somnolence and was found to have QT prolongation (512 ms) three hours and first degree AV block (PR of 261 ms) five hours after her first dose of ponesimod.

Reviewer Comment: Although this first-dose SAE was coded as "QT prolongation," the narrative also describes a bradyarrhythmia with first degree block, which are known to occur with other S1P receptor modulators.

Coronary Artery Disease

- Subject (b) (6) was a 50 yo woman with a one-year history of dyspnea and chest discomfort who was randomized to ponesimod 10 mg in Study AC-058B201. The investigator reported that she had angina pectoris when she received the first dose of the study drug (Study Day 1), and the subject stated that her chest discomfort occurred more often and lasted longer during the first week of taking the study drug. A scheduled ECG on Study Day 8 showed ST depression and flattened T-waves, so she was hospitalized on Study Day 11 and diagnosed with coronary artery disease based on ECG changes during a positive exercise stress test. The study medication was withdrawn on Study Day 15.

Reviewer Comment: Although the onset of coronary artery disease certainly predated initiation of ponesimod, it is concerning that the subject reported more frequent and longer episodes of chest pain after starting the study medication.

Transaminase Elevation

- Subject (b) (6) was a 40 yo woman with a history of "thyroid insufficiency (autoimmune origin)" who was randomized to ponesimod 10 mg in Study AC-058B201. Reportedly, her transaminases and bilirubin were normal at baseline, but on Study Day 8, her ALT and AST were 6.5 and 2.6 times the upper limit of normal (ULN). On Study Day 10, her ALT was 7.3 x ULN (380 U/L), and her AST was 4.9 x ULN (380 U/L); unfortunately, her bilirubin was not checked on Study Days 8 or 10. The study drug was discontinued on Study Day 11. Testing for hepatitis and HIV serologies was negative. On Study Day 15, her ALT and AST had improved (219 and

60 U/L, respectively), and her bilirubin was normal. On Study Day 29, her ALT and AST were normal.

Reviewer Comment: Liver injury has been reported with other S1P receptor modulators, and the temporal correlation between initiating ponesimod and the hepatic transaminase elevations in this case suggests a potential causative role for ponesimod. Since her bilirubin was normal on Study Day 15, it is likely that this case does not meet Hy's law criteria for drug-induced liver injury (DILI).

Dyspnea

- Subject (b) (6) was a 39 yo man who was randomized to ponesimod 40 mg in Study AC-058B201 and reported orthopnea and dyspnea with exertion on Study Day 15. His Forced Expiratory Volume at 1 second (FEV1) and Forced Vital Capacity (FVC) were reduced from baseline, and a chest X-ray showed a bilateral pleural effusion. An echocardiogram was normal, so his symptoms were not deemed to be attributable to heart failure. The study drug was withdrawn on Study Day 47, and the subject reported resolution of his dyspnea on Study Day 57.

Reviewer Comment: The temporal correlation between initiating ponesimod and the onset of dyspnea suggests that ponesimod may have played a role in this SAE, especially since respiratory effects have been reported with other S1P receptor modulators; however, the presence of bilateral pleural effusions may suggest an alternative mechanism.

SAEs, uncontrolled RMS population

One hundred and twenty-eight SAEs were reported by 93 subjects while taking ponesimod in the uncontrolled RMS trials (i.e., the long-term extensions of Studies AC-058B201 and AC-058B301), and those SAEs that occurred more than once in the uncontrolled RMS population are delineated in Table 39.

Table 39. Reviewer Table. SAEs, uncontrolled RMS population

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Invasive ductal breast carcinoma	3	0	1
Cholelithiasis	2	1	0
Uterine leiomyoma	2	1	0
Appendicitis	2	0	0
Multiple sclerosis relapse	2	0	0
Transient ischemic attack	2	0	0
Uterine hemorrhage	2	0	0

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Uterine polyp	2	0	0
Basal cell carcinoma	1	1	1
Pneumonia	1	0	2
Varicose vein	1	0	1
Anal abscess	0	0	2
Ankle fracture	0	2	0
Cervical dysplasia	0	0	2
Endometriosis	0	1	1
Seizure	0	1	1

Source: ISS LT ADAE where SAFFL, TRTEMFL, and AESER='Y' and ACAT1='Starts in Extension' by AEDECOD and TRT01A.

Reviewer Comment: Although the utility of a safety analysis of an uncontrolled population is inferior to one of a controlled population, there is value in this analysis as it may inform subsequent analyses, including potential risks that become more apparent with an increased duration of exposure. As previously noted, percentages are not calculated in Table 39 because of the very low incidence of SAEs and because the same SAE could be reported more than once by the same subject. The four cases of invasive ductal breast carcinoma, the three cases of basal cell carcinoma, the three cases of seizures (one coded as epilepsy), and the two cases of transient ischemic attack are of interest and are explored below.

Malignancy

- At enrollment, Subject (b) (6) was a 35 yo woman who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 20 mg in its long-term extension. After an abnormal mammogram, breast ultrasound, and biopsy, she was diagnosed with invasive ductal carcinoma of the left breast and intraductal papilloma of the right breast on Day 3043 of Study AC-058B202. Reportedly, she did not have a family history of breast cancer and was not tested for BRCA1 / BRCA2 mutations. She was treated with bilateral breast ablation and subcutaneous goserelin acetate, but reportedly no action was taken with the study drug.

- At enrollment, Subject (b) (6) was a 45 yo woman with a history of a uterine leiomyoma who was randomized to ponesimod 40 mg in Study AC-058B201 and remained on this dose until she was transitioned to ponesimod 10 mg in Treatment Period 2 of Study AC-058B202. On Day 952 of Study AC-058B202, she was diagnosed with invasive ductal breast carcinoma and underwent a partial resection of the right breast; reportedly, the surgical margins were clean, and the sentinel lymph node was negative. Her paternal grandfather had prostate cancer.

Reportedly, she was not tested for BRCA1 / BRCA2 mutations. The study drug was stopped on Study Day 1015, after which she started tamoxifen and radiotherapy.

- At enrollment, Subject (b) (6) was a 53 yo woman who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on this dose of ponesimod in its AC-058B202 extension. On Day 917 of Study AC-058B202, she was found to have an abnormal mammogram, which lead to a diagnosis of invasive ductal breast carcinoma. Reportedly, she did not have risk factors for breast cancer, although BRCA1/2 testing was not performed. She was treated with a partial breast excision and axillary lymphadenectomy on Study Day 992, and the study drug was discontinued on Study Day 1015.

- At enrollment, Subject (b) (6) was a 54yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on this dose in its extension. On Day 159 of Study AC-058B303, she "underwent prophylactic mammography and was diagnosed with invasive ductal breast carcinoma with metastasis in 9 out of 19 regional lymph nodes." She had a mastectomy on Study Day 198. The study drug was subsequently discontinued on Study Day 227, and she subsequently started chemotherapy.

- At enrollment, Subject (b) (6) was a 40 yo woman who was randomized to ponesimod 10 mg in Study AC-058B201 and remained on this dose in its extension. On Day 502 of Study AC-058B202, a dermatologist noticed a skin abnormality on her abdomen, and a biopsy revealed basal cell carcinoma (BCC). The subject did not have a history of excessive ultraviolet exposure or a family history of skin cancer.

- At enrollment, Subject (b) (6) was a 40 yo woman who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on this dose in its extension. On Day 2151 of Study AC-058B202, she was found to have a melanocytic nevus, and then on Day 2754, a dermatologist noted an abnormality in the left infraorbital region, a biopsy of which showed BCC. Reportedly, the subject did not have a history of excessive ultraviolet exposure or a family history of skin cancer.

- At enrollment, Subject (b) (6) was a 42 yo woman who was randomized to ponesimod 40 mg in Study AC-058B201 and continued this dose from Treatment Periods 1 and 2 of its extension before transitioning to ponesimod 20 mg in Treatment Period 3. On Day 1969 of Study AC-058B202, a skin lesion was noted in the left fronto-temporal region, and a biopsy showed that it was BCC. The BCC was excised on Study Day 2045. No action was taken with the study drug; indeed, she transitioned to ponesimod 20 mg on Study Day 2367. The narrative does not comment on potential risk factors of skin cancer.

Reviewer Comment: These narratives do not offer clear confounding factors for malignancy and may suggest an increased risk of malignancy with ponesimod, so care will be taken to continue to focus on this possible signal throughout this review.

Seizure

- At enrollment, Subject (b) (6) was a 34 yo woman who was randomized to ponesimod 10 mg in Study AC-058B201, remained on this dose during Treatment Periods 1 and 2 of Study AC-058B202, and transitioned to ponesimod 20 mg in Treatment Period 3 of that study. On Day 1611 of Study AC-058B202, she reportedly experienced the first "epileptic seizure" of her life, but the narrative does not provide further details about this SAE. For unclear reasons, this event was coded as "epilepsy."

  Reviewer Comment: The lack of information limits interpretation of this case.

- At enrollment, Subject (b) (6) was a 31 yo woman with a history of anxiety and depression who was randomized to ponesimod 10 mg in Study AC-058B201 and remained on this dose during Treatment Period 1 of Study AC-058B202. On Day 583 of Study AC-058B202, she experienced "a focal seizure (seizure) with secondary generalization of 2 min duration; after complaining of 'darkness' of vision, she developed clonic jerks on the left side of her face, which were followed by unresponsiveness and tonic body posturing." She was post-ictal after the event and received IV diazepam. She experienced another seizure about 2.5 hours later and was treated with IV diazepam and valproic acid. A head CT showed a "tumour-like multiple sclerosis plaque … in the right occipital lobe," and an EEG showed "focal epileptiform discharges in the right frontotemporal area." The event was considered resolved on Study Day 583. Since a brain MRI showed "13 new T1 Gd+ lesions and 6 new or enlarging T2 lesions," she was deemed a non-responder to the study medication, which was discontinued on Study Day 584.

  Reviewer Comment: Given the extensive active MS activity (including a potentially tumefactive lesion) in this individual, this reviewer agrees that it appears that this subject was a non-responder to ponesimod and suspects that the seizures were likely related to robust juxtacortical inflammation from MS.

- At enrollment, Subject (b) (6) was a 23 yo man who was randomized to ponesimod 40 mg in Study AC-058B201, remained on this dose during Treatment Period 1 of Study AC-058B202, and transitioned to ponesimod 10 mg in Treatment Period 2 of this extension study. On Day 892 of Study AC-058B202, he experienced "tonic/clonic seizures (seizure) and confusion post seizure (postictal state) and was taken to the hospital …developed respiratory failure due to increased secretions and

prolonged decreased mental status and was intubated." His temperature increased to 38.3°C and he was tachycardic with an elevated white blood cell count (19.4, units not provided). There were six white blood cells (neutrophils 31%) in his cerebrospinal fluid (CSF), so he was started on ceftriaxone and vancomycin; however, both were stopped after testing for herpes simplex virus was negative and his "CSF results did not indicate meningitis." The seizures were attributed to MS, and he was started on levetiracetam which was subsequently changed to topiramate. Although the event was considered resolved with sequelae on Study Day 899, he had persistent memory issues and was readmitted for this on Study Day 918, when he was not oriented to date and repeated himself often. His EEG was reportedly normal, and his MRI was consistent with MS. He was discharged from the hospital on Study Day 923 with persistent memory issues; the study medication was discontinued, and he was lost to follow-up.

Reviewer Comment: This is a complicated case. This reviewer expects that the initial seizure (or seizures?) was related to an infection, the source of which was not clarified; therefore, a drug that sequesters circulating lymphocytes like ponesimod does could have played a role in this SAE. There are many possibilities that may explain the ongoing memory impairment after this SAE, including initial unrecognized non-convulsive status epilepticus, a hypoxic-ischemic event in the setting of respiratory failure, an adverse effect of topiramate, an insufficiently treated CNS infection, or an autoimmune encephalopathy. Given the ambiguities in this case, it is hard to posit the contribution of ponesimod to this SAE.

Transient Ischemic Attack

- At enrollment, Subject (b) (6) was a 34 yo woman who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on this dose for the three treatment periods of Study AC-058B202. Her blood pressure was 142/103 at baseline, and she was started on an anti-hypertensive on Day 20 of Study AC-058B202. On Day 904 of Study AC-058B202, she experienced 15-30 minutes of "speech arrest and difficulties to find words," so she was diagnosed with a transient ischemic attack (TIA); however, no action was taken with the study drug. An echocardiogram showed left ventricular hypertrophy, suggesting a long history of hypertension.

- At screening, Subject (b) (6) was a 52yo woman with a history of hypertension, ischemic heart disease, and diabetes mellitus who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. On Day 309 of Study AC-058B303, she was hospitalized with "headache, nausea, weakness/numbness in the left extremities, walking dysfunction, gait disorder, speech disorder, dizziness, retching and urinary incontinence, and BP was 200/120 mmHg." Vessel imaging suggested "hypertensive angiopathy," and a spiral

chest CT showed "lung hypertension." Although this event is coded as a TIA, the head CT reportedly showed acute ischemia in the territory of the right middle cerebral artery; however, the event was considered "resolved" on Study Day 313.

Reviewer Comment: Interpretation of the role of ponesimod in both of these cases is confounded by pre-existing risk factors for vascular disease, although it is possible that ponesimod played a role in these events since vascular events are noted in Section 6 of the labelling for other S1P receptor modulators. Given the reported head CT findings, his reviewer deems that the SAE experienced by Subject (b) (6) was a stroke and not a TIA.

Review of those SAEs that were reported once in the uncontrolled ponesimod population (and have not been previously described) reveals multiple SAEs of interest, including infectious, macular, and malignancy SAEs as well as single reports of thrombocytopenia, syncope, and hepatosplenomegaly.

Infectious SAEs

- At enrollment, Subject (b) (6) was a 49 yo woman who was randomized to ponesimod 40 mg in Study AC-058B201 and remained on this dose for Treatment Period 1 of Study AC-058B202. A per protocol chest X-ray at the end of Study AC-058B201 showed bibasilar changes that were considered artifact, but a "control Chest X-ray" on Day 8 of Study AC-058B202 revealed signs of "bilateral bronchopneumonia." The subject was dyspneic and had a "subfebrile temperature with increased CRP of 90.3 mg/L" and a lymphocyte count of 0.38×10^9/L. The study drug was discontinued, and a bronchoalveolar lavage (BAL) culture was positive for Pneumocystis jiroveci. As the PCR and microscopy from a subsequent BAL were negative for P. jiroveci, this SAE was deemed to be bilateral bronchopneumonia. The event was considered resolved without sequelae on Study Day 68.

  Reviewer Comment: As the initial BAL was positive for P. jiroveci, this reviewer suspects that Subject (b) (6) had Pneumocystis jiroveci pneumonia (PJP), which usually occurs in individuals with a weakened immune system, suggesting a potential role for ponesimod in the occurrence of this SAE.

- At enrollment, Subject (b) (6) was a 38 yo man who was randomized to ponesimod 40 mg in Study AC-058B201, continued this dose for Treatment Period 1 of Study AC-058B202, and transitioned to ponesimod 20 mg for Treatment Periods 2 and 3 of the extension study. On Day 1753 of Study AC058-B202, he presented with a cough and a fever (38°C) and was hospitalized with bilateral pneumonia. No action was taken with the study drug, and the event was considered resolved without sequelae on Study Day 1961.

Reviewer Comment: Although the available information about this case is limited, bilateral pneumonia in a 38 yo man seems unusual and may suggest a causal role for ponesimod, which sequesters circulating lymphocytes in secondary lymphoid tissue.

- At enrollment, Subject (b) (6) was a 28 yo woman with a history of meningitis in 2007-2008 who was randomized to ponesimod 20 mg in Study AC-058B301 and continued on this medication in Study AC-058B303. On Day 91 of Study AC-058B303, she developed an intense headache with nausea and vomiting. Since she had meningeal signs, a lumbar puncture was performed, after which she was diagnosed with viral meningitis. This SAE was considered resolved on Study Day 100, and the study drug was reinitiated on Study Day 124.

  Reviewer Comment: Although the available information about this case is limited, it is certainly possible that ponesimod played a role in its development; however, her history of prior meningitis may be confounding.

- At enrollment, Subject (b) (6) was a 44 yo man with a history of hypertension, diabetes mellitus, and "leg scars secondary to flea bites" who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on this dose in the AC-058B303 long term extension. On Day 409 of Study AC-058B303, he noted furuncles in his right axilla and on his right leg; on Study Day 432, he presented to an emergency department with a "3-week history of right leg wound with signs of eschar, draining pus and subcutaneous emphysema." He was diagnosed with right leg cellulitis, a methicillin-resistant Staph aureus abscess, a group B strep infection of the right pretibial area, and an eschar and subcutaneous emphysema of his right lower shin. He was treated with intravenous antibiotics, and the leg wound required irrigation and debridement and application of a wound VAC. Of note, he also developed bilateral heel ulcers on Study Day 508. These events were considered resolved on Study Day 558.

  Reviewer Comment: Although S1P receptor modulators like ponesimod sequester circulating lymphocytes in lymph nodes and can thereby increase the risk of infection, the case confounded by the subject's history of diabetes mellitus and seemingly related poor wound healing, as suggested by a history of bilateral leg scars from flea bites and the development of bilateral heel ulcers.

- At enrollment, Subject (b) (6) was an 18 yo woman from the Russian Federation who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. She experienced five non-serious upper respiratory tract infections during Study AC-058B301, and on Day 200 of Study AC-058B303, she was hospitalized with a fever and a cough and was eventually found to

have a community acquired right upper lobe (RUL) pneumonia. Sputum culture was reportedly negative for tuberculosis. No action was taken with the study drug.

Reviewer Comment: A RUL pneumonia is suggestive of tuberculosis, especially in an area in which tuberculosis is endemic. Although a sputum culture was negative, it is difficult to grow Mycobacterium tuberculosis in culture; therefore, this reviewer is suspicious that this case may represent tuberculosis.

- At enrollment, Subject (b) (6) was a 50 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and continued on this dose in Study AC-058B303. On Day 116 of Study AC-058B303, she experienced rapidly increasing transaminase elevations and mild elevations in alkaline phosphatase (with a normal bilirubin). She was diagnosed with hepatitis B and hepatocellular injury on Study Day 120; therefore, the study drug was withdrawn on Study Day 122. On Study Day 123, she was hospitalized and reportedly had an abdominal ultrasound that showed chronic cholecystitis and pancreatitis but negative testing for hepatitis B and C. On Study Day 142,.her laboratory values showed "laboratory values showed positive results for hepatitis B core antibody and ANA, whereas negative for hepatitis B core antibody IgM, hepatitis B surface antigen, hepatitis A antibody IgM; and anti-mitochondrial antibody." The events of hepatocellular injury and hepatitis B were considered resolved on Study Day 131.

  Reviewer Comment: Although this case was coded as hepatitis B, this reviewer suspects that this individual had a past / resolved infection with hepatitis B (negative HBsAg, positive total anti-HBc but negative anti-Hbc IgM) and that the acute but temporary transaminase (and alkaline phosphatase) elevations were at least partially attributable to cholecystitis.

- At enrollment, Subject (b) (6) was a 30 yo man with a history of chronic gastritis, chronic duodenitis, chronic cholecystitis, hypertension, and tobacco use who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on this dose in the three Treatment Periods of its extension. On Day 85 of Study AC-058B201 and Day 2464 of Study AC-058B202, he experienced transaminase elevations; on Study Day 2472, he was found to have worsening cholelithiasis and had a cholecystectomy on Day 2505. On Study Day 2701, he presented with darkening of his urine and generalized weakness and was found to have marked transaminase elevations (ALT 1388 U/L, AST 810 U/L, total bilirubin 53.3 µmol/L, and LDH 433 U/L). Since anti-HCV antibody was detected, he was diagnosed with hepatitis C, and the study drug was discontinued.

  Reviewer Comment: Since this subject had an extensive history of abdominal issues, the chronicity of his hepatitis C is unclear, but it is certainly possible that

ponesimod played a role in the development (or severity) of this SAE.

SAEs involving the macula

- At enrollment, Subject (b) (6) was a 42 yo woman who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 40 mg in Treatment Period 1 of Study AC-058B202. Although she was asymptomatic, a scheduled OCT on Day 84 of Study AC-058B202 showed macular edema of her left eye; therefore, the study medication was discontinued. Dilated ophthalmoscopy on Study Day 120 suggested that this SAE was resolving, and the event was considered resolved when she saw an ophthalmologist on Study Day 332.

- At enrollment, Subject (b) (6) was a 51 yo woman who was randomized to ponesimod 10 mg in Study AC-058B201, remained on this dose in Treatment Period 1 of Study AC-058B202, and transitioned to ponesimod 20 mg in Treatment Period 2 of the extension study. On Day 431 of Study AC-058B202, she experienced worsening of vision in her left eye, and an ophthalmology visit on Study Day 532 (and an OCT on Day 534) revealed a macular hole.

- At enrollment, Subject (b) (6) was a 43 yo woman who was randomized to ponesimod 40 mg in Study AC-058B201, remained on ponesimod 40 mg in Treatment Period 1 of Study AC-058B202, and was transitioned to ponesimod 20 mg for Treatment Periods 2 and 3 of Study AC-058B202. On Day 1413 of Study AC-058B202, she experienced mild dizziness, a headache, and visual problems in both eyes; work-up of her visual symptoms revealed minor macular changes without edema. No action was taken with the study drug, and this SAE was considered resolved without sequelae on Study Day 1443.

  Reviewer Comment: Subject (b) (6) clearly had macular edema with a relatively close temporal correlation with starting ponesimod, but the correlation between ponesimod and the macular hole is less clear. As the minor macular changes seemingly resolved without stopping the study medication, this reviewer suspect that the SAE in Subject (b) (6) is unlikely related to the study drug.

Malignancy

- At enrollment, Subject (b) (6) was a 55 yo man with a history of angiolipoma who was randomized to ponesimod 40 mg in Study AC-058B201, remained on this dose in Treatment Period 1 of Study AC-058B202, and transitioned to ponesimod 10 mg in Treatment Period 2 of Study AC-058B202. Reportedly, his baseline EBV serologies suggested past (latent) EBV infection. On Day 753 of Study AC-058B202, he presented with right flank and back pain and was found to have diffuse lymphadenopathy and hepatosplenomegaly; biopsy of a right axillary lymph node revealed B-cell non-Hodgkin's lymphoma. The study medication was withdrawn,

and the subject was lost to follow-up; therefore, further information about the treatment or outcome of this SAE is not reported in the narrative.

- At enrollment, Subject (b) (6) was a 34 yo woman who was randomized to ponesimod 10 mg in Study AC-058B201, remained on this dose during Treatment Period 1 of Study AC-058B202, and was transitioned to ponesimod 20 mg in Treatment Period 2 of this extension. On Day 1333 of Study AC-058B202, cervical dysplasia was found on a routine gynecological evaluation, and a subsequent cone biopsy revealed adenocarcinoma of the cervix. Although the narrative suggests that she had a hysterectomy and bilateral oophorectomy on Study Day 1394, it also states that she had a right oophorectomy of Study Day 2386, after which the event was considered resolved without sequelae. No action was taken with the study drug, so she continued ponesimod 20 mg in Treatment Period 3.

- At enrollment, Subject (b) (6) was a 44 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and continued this dose in the three Treatment Periods of its AC-058B303 extension. On Day 2162 of Study AC-058B202, she was diagnosed with ductal carcinoma in situ of the left breast, which was treated with radiotherapy; no action was taken with the study drug.

  Reviewer Comment: Although previous EBV infection can be a risk factor for B-cell lymphoma, EBV infections are much more common than B-cell lymphoma, which commonly occurs in the setting of immunosuppression; therefore, it is possible that ponesimod played a role in the development of the B-cell lymphoma in Subject (b) (6). Similarly, is it possible that ponesimod played a role in the development of cervical adenocarcinoma in Subject (b) (6) and breast cancer in Subject (b) (6).

<u>Thrombocytopenia</u>

- At enrollment, Subject (b) (6) was a 45 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and continued this dose in its AC-058B303 extension. On Day 673 of Study AC-058B301, the subject experienced thrombocytopenia (platelet count $72x10^9$/L), which was worse on Day 8 of Study AC-058B303 ($72x10^9$/L). The study drug was discontinued on Study Day 10, and the subject was started on methylprednisolone. His platelet count improved to $79x10^9$/L on Study Day 18, worsened to $44x10^9$/L on Study Day 55, and again increased to $61x10^9$/L on Study Day 120.

  Reviewer Comment: Although the identification of thrombocytopenia soon after starting the long term extension (Study AC-058B303) may suggest a temporal correlation with the study drug, the subject was randomized to ponesimod in Study AC058B301. Although his thrombocytopenia worsened well after

ponesimod was withdrawn, immune-mediated thrombocytopenia can persist after its precipitant. Given this, and the recent inclusion of thrombocytopenia as a possible adverse reaction in Section 6 of the labelling for another S1P receptor modulator (Gilenya), it is possible that the development of this SAE is related to ponesimod.

Syncope

- At enrollment, Subject (b) (6) was a 46 yo man with a history of hypertension who was randomized to ponesimod 40 mg in Study AC-058B201, remained on this dose in Treatment Period 1 of Study AC-058B202, and transitioned to ponesimod 20 mg in Treatment Period 2 of this extension study. On Day 1159 of Study AC-058B202, the subject's wife reported the following:

  "he was not joining conversation, looked still and did not respond to his name being called. At 21:00, the subject experienced syncope with unknown cause; he slumped forward and was then put in a recovery position. After 2-3 minutes, his words were slurred at first, but he was able to recognize his wife. He also desperately needed to urinate."

  The work-up of this event appears unremarkable, but the subject discontinued the study drug. Further information is not given.

  Reviewer Comment: The lack of details regarding this case hinders its interpretation.

Hepatosplenomegaly

- At enrollment, Subject (b) (6) was a 26 yo woman who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 20 mg for the three Treatment Periods of its AC-058B202 extension. On Day 2654 of Study AC-058B202, she experienced a fever and was diagnosed with right pyelonephritis and was treated with ceftriaxone. A CT of her abdomen on Study Day 2671 revealed hepatosplenomegaly and "multiple small focal infection on inflammatory lesions," and the study drug was interrupted. Her hepatic transaminases and bilirubin were reportedly normal, and subsequent imaging showed improvement in the hepatosplenomegaly. She eventually defervesced, and the SAE was considered resolved without sequelae on Study Day 2691.

  Reviewer Comment: With the reported fever and initial diagnosis of "pyelonephritis," this reviewer suspects that this SAE was infectious in etiology, so a drug like ponesimod that sequesters circulating lymphocytes could be at least partially causative.

- At enrollment, subject (b) (6) was a 36 yo woman who was randomized to placebo in Study AC-058B201, transitioned to ponesimod 10 mg for Treatment Periods 1 and 2 of its AC-058B202 extension, and transitioned to ponesimod 20 mg in Treatment Period 3 of this extension study. She developed abdominal discomfort on Study Day 3065 and was found to have an adrenal tumor, which was eventually shown to be a pheochromocytoma, for which further workup was planned.

The 120-day safety update included one SAE in the section on TEAEs leading to discontinuation, but this case is described here. A review of the other 24 SAE's that were reported in Study AC-058B303 between the cut-off date for the initial NDA submission and that for the 120-day safety update reveals two serious urinary tract infections, a case of community-acquired pneumonia, two spontaneous abortions, and the following other cases of interest:

- At enrollment, Subject (b) (6) was a 44 yo woman who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. On Study Day 28 of the extension, she was hospitalized for a severe relapse (left face, hand, and leg weakness) that caused her EDSS to increase from 5.5 to 8.0. A brain MRI showed three new typical and one atypical MS lesions. Although progressive multifocal leukoencephalopathy was initially suspected, a CSF JC virus PCR (and other serologies) was negative. The study medication was discontinued for this severe MS relapse, which was treated with seven days of intravenous methylprednisolone. Her hospital course was complicated by metrorrhagia, cervicitis, and a UTI. On Study Day 71, her EDSS had improved to 6.5

- At enrollment, Subject (b) (6) was a 43 yo man with a history of hypertension, dyslipidemia, and tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301 and continued on this in Study AC-058B303. On Study Day 253 of this extension, he developed acute pain in his leg foot and calf (suggestive of intermittent claudication) and was found to have thromboembolism of his left iliac artery, which was treated with a peripheral artery bypass and anticoagulation.

  Reviewer Comment: Although this subject had risk factors for peripheral arterial disease, a causal contribution of ponesimod cannot be ruled out.

- At enrollment, Subject (b) (6) was a 47 yo woman with a history of a uterine fibroma who was randomized to ponesimod 20 mg in Study AC-058B301 and continued on this in Study AC-058B303. On Study Day 584 of this extension, she had an abnormal mammogram and was later diagnosed with invasive breast carcinoma. The subject did not have a family history of breast or ovarian cancer and was reportedly not screened for BRCA1/2 mutations.

- At enrollment, Subject (b) (6) was a 52 yo woman who was randomized to

ponesimod 20 mg in Study AC-058B301 and continued it in Study AC-058B303. On Study Day 263 of this extension, she developed post-menopausal bleeding and was hospitalized for this and a uterine cervical abrasion one week later. Work-up revealed cervical dysplasia (CIN grade 3), for which a total hysterectomy was performed on Study Day 399.

Reviewer Comment: Several cases of malignancy, especially breast cancer, have already been discussed in this review, so this adverse event of special interest will be explored further in Section 8.5.3 of this review.

- At enrollment, Subject (b) (6) was a 44 yo woman who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. On Study Day 455 of this extension, she woke up screaming in a confusional state and experienced motor automatism, for which she was hospitalized and had an electroencephalogram (EEG) which reportedly showed a focal epileptic seizure with secondary generalization, so she was started on topiramate. No action was taken with the study drug.

- At enrollment, Subject (b) (6) was a 44 yo woman who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. On Study Day 632 of this extension, she was hospitalized with a seizure and started on carbamazepine despite not having a history of seizures or risk factors for seizures, likely because her EEG reportedly showed epileptiform activity and her MRI showed 6 enhancing lesions of MS. She was re-hospitalized one week later with quadriparesis and cerebellar ataxia; since she had a pyloric ulcer, she was not treated with steroids, but her neurologic deficits did improve. She was switched from carbamazepine to valproic acid on Study Day 643 after an EEG showed generalized seizure activity.

  Reviewer Comment: Although seizures occur somewhat more commonly in people with MS than they do in the general population, it is possible that ponesimod played a role in these SAEs, especially as seizures have been described with the use of other S1P receptor modulators.

- At enrollment, Subject (b) (6) was a 29 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on this study medication in Study AC-058B303. On Study Day 714 of this extension, she was hospitalized with acute bronchitis and treated with antibiotics and corticosteroids. She was readmitted on Study Day 724 with a fever, cough, and a sensation of suffocation and was found to have a respiratory syncytial virus infection, for which she was treated with ceftriaxone and corticosteroids.

- At enrollment, Subject (b) (6) was a 43 yo woman who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. On Study Day 666 of this extension, she developed herpes zoster (site unspecified) and was treated with oral and then intravenous acyclovir. No action was taken with the study drug, and she remained hospitalized at the time of the data cut-off for this 120-day safety update.

  Reviewer Comment: Since S1P receptor modulators like ponesimod are thought to sequester circulating lymphocytes in secondary lymphoid tissue, it is not surprising that they may increase the risk of infections.

A review of the eight new SAE's that were reported in Study AC-058B202 between the cut-off date for the initial NDA submission and that for the 120-day safety update reveals the following case of interest:

- At enrollment, subject (b) (6) was a 39 yo man who had a blood pressure of 160/90 at baseline and was randomized to ponesimod 10 mg in Study AC-058B201, continued this dose in Treatment Periods 1 and 2 of its AC-058B202 extension, and transitioned to ponesimod 20 mg in Treatment Period 3 of this extension study. After stopping his antihypertensive agent (enalapril) in the setting of food poisoning, the subject was hospitalized with a headache and a blood pressure of 230/100 mm Hg on Study Day 2967. An echocardiogram showed left ventricular hypertrophy and atherosclerosis of his brachiocephalic trunk. No action was taken with the study drug, and the event was considered resolved on Study Day 2972.

  Reviewer Comment: Although this subject reportedly discontinued his antihypertensive medication, hypertension, including episodes suggestive of accelerated hypertension and posterior reversible encephalopathy syndrome (PRES), have been reported with S1P receptor modulators.

SAE, Plaque Psoriasis

The NDA includes data from two placebo-controlled studies exploring the use of ponesimod for the treatment of plaque psoriasis: 66 subjects were randomized in the 6-week study (AC-058A200), and 326 subjects were randomized in Study AC-058A201, the duration of which was up to 28 weeks. Other than psoriasis and disease progression, no SAE was reported more than once in the pooled plaque psoriasis population. The following SAEs are of interest:

- Subject (b) (6) was a 58 yo woman who was randomized to ponesimod 20 mg in the induction period of Study AC-058A201. At screening, frequent ventricular extrasystoles and short episodes of non-sustained supraventricular tachycardia were recorded, and second-degree Mobitz I atrioventricular block with a heart rate of 50 bpm was noted two hours after the first dose of ponesimod was administered. A

24-hour Holter monitor on Study Day 1 recorded "Mobitz I (Wenckebach) second-degree AV block (more than 20 episodes) and 2:1 AV block (4 episodes)." The study medication was discontinued, and the subject was discharged from hospital observation on Study Day 2.

Reviewer Comment: Although this narrative suggests that this subject may have baseline cardiac rhythm issues, bradyarrhythmia and AV block have been reported after administration of the first dose of S1P receptor modulators, including ponesimod.

- Subject (b) (6) was a 37 yo man who was randomized to ponesimod 40 mg in the induction period of Study AC-058A201. He reported "bad vision" of Study Day 32, and a diagnosis of cystoid macular edema of the right eye was made by OCT on Study Day 34, so the study drug was discontinued. Since his OCT was reportedly normal on Study Day 41, the event was considered resolved on that day.

  Reviewer Comment: Macular edema has been reported with S1P receptor modulators, including ponesimod; however, this reviewer is surprised by the seemingly rapid (one week) resolution of the OCT abnormalities.

- Subject (b) (6) was a 60 yo woman with a history of hypertension and "vascular encephalopathy" who was randomized to ponesimod 40 mg in the induction period of Study AC-058A201. Her blood pressure was 152/91 mmHg at screening and 160/80 mm Hg when she received the first dose of the study drug. On Study Day 107, she was hospitalized with a blood pressure of 200/120 mmHg, and she was diagnosed with hypertensive crisis, cardiac failure, transient ischemic attack, and aphasia. The study drug was not interrupted, and the events were considered resolved without sequelae on Study Day 130.

  Reviewer Comment: Increased blood pressure (and posterior reversible encephalopathy syndrome [PRES], which is often associated with accelerated hypertension) has been reported with other S1P receptor modulators. It is unclear if the "aphasia" was a stroke / TIA or hypertensive encephalopathy.

- Subject (b) (6) was a 50yo man with a history of hypertension and hepatitis B and a family history of leukemia who was randomized to ponesimod 40 mg in the induction period and remained on this dose for the maintenance period of Study AC-058A201. Although he noted a lymph node in his right axilla 1-2 months after starting the study drug, he did not inform the investigator of the node (which had become painful and swollen) until three months after completion of the study (and two months after starting adalimumab). The lymph node was extracted, and a diagnosis of Hodgkin's lymphoma was made; a PET-CT scan showed supra- and infra-

diaphragmatic involvement. The event was unresolved at the time of the last report.

Reviewer Comment: Although this case is confounded by a family history of leukemia, it is possible that ponesimod played a role in the development of this SAE; however, this seems less likely since the axillary lymph node was reportedly noticed 1-2 months after starting the study drug.

- Subject (b) (6) was a 40 yo woman who was randomized to ponesimod 40 mg in the induction period of Study AC-058A201. On Study Day 36, she experienced an unspecified "viral infection," which was followed by an elevated body temperature and difficulty breathing. She saw a pneumologist on Study Day 51 and was diagnosed with pneumonia, for which she was hospitalized, and the study medication was discontinued. This SAE was considered resolved on Study Day 80.

  Reviewer Comment: Although details about this case of pneumonia are limited, the presumed mechanism of ponesimod suggests that it may have played a role in the development or severity of this event.

SAE, Healthy Volunteers

In addition to the previously described death of Subject (b) (6) in Study AC-058-112, five subjects reported a total of seven SAEs in the Phase 1 studies of ponesimod:

- Subject (b) (6) was a 22 yo woman in Study AC-058-111 who developed bradycardia (HR < 40 bpm) 40 minutes after administration of a single dose of ponesimod 10 mg. Almost an hour later, she reported a feeling of tightness in her chest and was found to have episodes of second degree (type 1 and 2) and third degree AV block on ECG. She was hospitalized, and the bradycardia and AV block had resolved the next morning. This subject discontinued the study after this event.

- Subject (b) (6) was a 56 yo woman who was randomized to diltiazem 240 mg in Study AC-058-111. After taking six daily doses of diltiazem, a single dose of ponesimod 10 mg was administered, after which she developed episodes of second degree AV block (Mobitz 1 and 2), for which she was hospitalized. She was discharged the next morning in normal sinus rhythm. This subject discontinued the study after this SAE.

- Subject (b) (6) was a 54 yo woman who was randomized to atenolol 50 mg in Study AC-058-111. After taking six daily doses of atenolol, a single dose of ponesimod 10 mg was administered. Three hours later, she developed bradycardia with a heart rate between 27 and 37 bpm. While on the way to lunch, she experienced circulatory collapse and was incontinent of urine – her cardiac monitor showed asystole followed by a second degree AV-block type Mobitz 2. She was hospitalized

overnight for observation. The study was terminated after this event.

- Subject (b) (6) was a 56 yo man who participated in Study AC-058-115 and experienced dizziness and palpitations and was diagnosed with atrial fibrillation six hours after his eighth dose of ponesimod 20 mg. The study medication was stopped, and the event resolved.

- Subject (b) (6) was a 49 yo woman who was diagnosed with a benign breast tumor (fibroma) on Day 30 of Study AC-058-117, 11 days after she received the last dose of the study drug.

Reviewer Comment: Although the breast fibroma is almost certainly not related to the study medication, the cardiac dysrhythmias (with the possible exception of the case of atrial fibrillation) are probably related to the study medication.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

If subjects wished to discontinue the study medication, they were encouraged to continue to be followed in the study but obviously were free to discontinue from the study. Multiple protocol-specified discontinuation criteria were implemented in the ponesimod studies, including the following in Study AC-058B301:

- Any HR < 30 bpm or symptomatic HR < 40 bpm for one hour
- QTcF > 500 ms
- Prolonged (>24 hours) of bradyarrhythmia or AV-block after first dose of ponesimod
- Need to receive chronic treatment with β-blockers, diltiazem, verapamil, digoxin, or other anti-arrhythmics
- Confirmed total lymphocyte count < 0.2 x 10^9/L, neutrophil count < 1.0 x 10^9/L, or platelet count < 50 x 10^9/L
- Confirmed 30% decreased in FEV_1 or FVC
- Pregnancy
- Any ALT/AST ≥ 8x ULN, confirmed ALT/AST ≥ 5x ULN, or confirmed ALT/AST ≥ 3x ULN and (TB ≥ 2x ULN or INR > 1.5)
- Confirmed macular edema
- Rapid serum creatinine increase to > 150 µmol/L or rapid decrease in calculated creatinine clearance to < 30 mL/min / 1.73 m^2 (Cockroft-Gault)
- Stevens-Johnson syndrome or toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms

<u>TEAEs leading to study drug withdrawal, active-controlled RMS population (Study AC-058B301)</u>
Eighty-three subjects in Study AC-058B301 experienced 103 TEAEs leading to discontinuation of the study drug. Table 40 delineates those TEAEs leading to discontinuation that occurred more

than once in subjects randomized to ponesimod in this study.

Table 40. Reviewer Table. AE's leading to study drug withdrawal, Study AC-058B301

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Dyspnea	7[1]	0
ALT increased	5	6
Macular edema	5	0
AST increased	3	5
Pregnancy	3	3
Hepatic enzyme increased	3	2
Pregnancy of partner	2	1
Hypertension	2	0
Lymphocyte count decreased	2	0
Nausea	2	0

Source: AC-058B301 ADAE where SAFFL and TRTEMF ='Y' and AEACN='DRUG WITHDRAWN' by AEDECOD and TRT01A. [1] One of the cases of dyspnea was coded as dyspnea at rest.

Reviewer Comment: Percentages are not calculated in Table 40 because of the very low incidence of TEAEs leading to discontinuation in Study AC-058B301. The cases of dyspnea, macular edema, increased transaminases, hypertension, and decreased lymphocytes are of interest; pregnancies are discussed in Section 8.2.2 of this review.

Dyspnea

- At enrollment, Subject (b) (6) was a 51 yo man with a history of hypertension and left ventricular hypertrophy who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 17, the subject reported dyspnea and cough, and on Day 29, his "FEV1 was 2.69 L (77.1% of baseline), FVC was 4.28 L (86.5% of baseline)." The study medication was discontinued, and the events resolved.

- At enrollment, Subject (b) (6) was a 34 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. The subject reported dyspnea on Study Day 15, and the study drug was discontinued on Day 24. Further information about this AE is not provided by the narrative.

- At enrollment, Subject (b) (6) was a 42 yo man with a previous history of tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 16, the subject reported dyspnea that was considered moderate in intensity, so the study drug was temporarily interrupted. After restarting the study drug on Study Day 42, the subject again noted dyspnea, so the study medication was discontinued.

- At enrollment, Subject (b) (6) was a 41 yo woman with a previous history of tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301. She experienced bronchitis on Study Day 9 and was treated with amoxicillin. On Study Day 30, she reported symptoms of bronchospasm, chest discomfort, and dyspnea, and follow-up pulmonary function tests showed "FEV1 was 2.33 L, FEV1% predicted 106%, FVC 3.17 L, FVC% predicted 123% and FEV1/FVC 73%.". The subject experienced dyspnea during a cardiac examination on Study Day 134 and "obstructive airways disorder" on Study Day 140, so the study medication was stopped. She was reported to have chronic obstructive pulmonary disease (COPD) on Study Day 266.

- At enrollment, Subject (b) (6) was a 36 yo woman with a previous history of tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301. She had nasopharyngitis on Study Day -1 and then reported dyspnea at rest and with action after starting the study drug on Day 1. The subject received salbutamol from Day 22 to 26 for breathing difficulties, and the study drug was discontinued on Study Day 26. The event was reported not resolved on Study Day 751.

- At enrollment, Subject (b) (6) was a 41 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. He reported dyspnea that was deemed to be mild in intensity on Study Day 38 and again on Study Day 424. On Study Day 422, his "FEV1 was 4.59 L (96.2% of baseline) and FVC was 5.94 L (104.0% of baseline)," and a chest X-ray was reportedly normal. The study drug was discontinued on Study Day 426, and the event was ongoing at the last study visit.

  Reviewer Comment: Although some of these TEAEs had confounding factors (including a history of tobacco use), it appears that respiratory effects / dyspnea can be associated with the use ponesimod, as has been noted with other S1P receptor modulators.

Transaminase Elevations

- At enrollment, Subject (b) (6) was a 47 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 340, he was found to have elevated transaminases (ALT 169 U/L and AST 511 U/L) with a normal bilirubin, so the study drug was stopped. His transaminases normalized, and this AE was considered resolved on Study Day 373.

- At enrollment, Subject (b) (6) was a 36 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 71, she was found to have asymptomatically elevated transaminases (ALT 120 U/L and AST 75 U/L) with a normal bilirubin, so the study drug was stopped on Study Day 140. Her transaminases were normal on Study Day 177.

- At enrollment, Subject (b) (6) was a 26 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 16, she was found to have asymptomatically elevated transaminases (ALT 198 U/L and AST 100 U/L) with a normal bilirubin, so the study drug was discontinued on Study Day 31. Her transaminases were normal on Study Day 106.

- At enrollment, Subject (b) (6) was a 39 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 173, he was found to have an asymptomatic increase in his transaminases (ALT 158 U/L, AST 64 U/L) with a normal total bilirubin. Even though his transaminases continued to increase, the study drug was not discontinued until Study Day 434, when his ALT was 470 U/L, his AST was 204 U/L, and his ALP was 542 U/L. His bilirubin remained normal throughout the study. His liver parameters were normal on Study Day 526.

- At enrollment, Subject (b) (6) was a 47 yo woman with a history of hepatitis A who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 27, her hepatic transaminases were mildly elevated (ALT 100 U/L, AST 69 U/L). On Study Day 89, she noted reported abdominal pain, and she experienced dyspepsia on Study Day 107; therefore, the study medication was discontinued on Study Day 111. Her bilirubin remained normal. On Study Day 167, her liver labs were normal.

- At enrollment, Subject (b) (6) was a 46 yo woman with a history of obesity, vitamin B12 deficiency, and Hashimoto's thyroiditis who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 28, her hepatic transaminases were elevated (ALT 160 U/L, AST 69 U/L); however, she was asymptomatic, and her total bilirubin was normal. Since these values were higher on Study Day 32 (ALT 222 U/L, AST 103 U/L), the study medication was discontinued, after which her ALT/AST slowly improved.

- At enrollment, Subject (b) (6) was a 44 yo man with a history of obesity, tobacco and alcohol use, and chronic gastritis who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 253, he was found to have an asymptomatic increase in his transaminases (ALT 164 U/L, AST 67 U/L), but his TB and ALP remained normal; since his ALT/AST remained elevated on Study Day 258, the study drug was discontinued. On Study Day 267, he was diagnosed with gallbladder polyps, biliary dyskinesias, and chronic gastritis associated with Helicobacter pylori. His elevated transaminases were considered resolved on Study Day 290.

- At enrollment, Subject (b) (6) was a 34yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 14, she was found to have asymptomatic mild hepatic transaminase elevations (ALT 72 U/L, AST 55 U/L) with a

normal TB and ALP, so the study drug was temporarily interrupted on Study Day 30. After resolution of her transaminase elevations, the study drug was restarted on Study Day 79; however, her hepatic transaminases again became abnormal (ALT 120 U/L, AST 63 U/L) on Study Day 103, so the study medication was discontinued. The event was considered resolved on Study Day 140.

- At enrollment, Subject (b) (6) was a 24 yo man who had a mild elevated ALT (65 U/L) at baseline who was randomized to ponesimod 20 mg in Study AC-058B301. He had intermittent asymptomatic transaminase elevations during the study (peak ALT and AST 98 U/L, respectively, on Study Day 436) but only had one slightly elevated bilirubin (22.2 µmol/L, 1.1xULN); nevertheless, the study drug was discontinued on Study Day 451.

  Reviewer Comment: Although none of these cases meet Hy's law criteria for drug-induced liver injury (DILI), several of these AEs occurred shortly after starting ponesimod, and one had a positive re-challenge; therefore, it appears likely that ponesimod may have played a role in the development of these events.

- At enrollment, Subject (b) (6) was a 44 yo woman with a history of cholecystectomy and sphincter of Oddi dysfunction who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 55, she was found to have mild transaminase elevations (ALT 75 U/L, AST 72 U/L); however, these rapidly worsened, so the study drug was discontinued on Study Day 79. On Study Day 99, her AST and ALT peaked to 871 U/L and 1147 U/L, respectively, and her TB (40.5 µmol/L) and ALP (216 U/L) were also elevated. Initial relevant serologies and an abdominal ultrasound were reportedly unremarkable, and she was diagnosed with "toxic hepatitis" and hospitalized on Study Day 112. Other than scleral icterus and jaundice, she was reportedly asymptomatic, and her liver parameters improved; therefore, she was discharged from the hospital on Study Day 125. On Study Day 126, she was diagnosed with acute hepatitis E. The events of hepatitis E and toxic hepatitis were considered resolved on Study Day 254.

  Reviewer Comment: Although a component of drug-induced liver injury (DILI) associated with ponesimod cannot be ruled out, it appears that this AE is attributable to acute hepatis E.

- At enrollment, Subject (b) (6) was a 24 yo man with a history of chronic gastritis / duodenitis and alcohol and tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 100, he was found to have transaminase elevations (ALT U/L 159, AST U/L 70), albeit with a normal bilirubin and alkaline phosphatase, so the study drug was discontinued on Study Day 108. On Study Day 149, he was found to have ALT, AST, and CRP elevations, and an ultrasound revealed

hepatomegaly; therefore, a diagnosis of non-alcoholic steatohepatitis (NASH) was made. His transaminases remained elevated, but his TB and ALP remained normal. He was eventually diagnosed with ascariasis and treated with ademetionine.

Reviewer Comment: Although it is rare, ascariasis can involve the liver; it is more common for this parasitic roundworm to affect the biliary tract, but this subject's ALP remained normal. Although this LFT elevation is being attributed to NASH, the narrative suggests that he frequently drank alcohol, further confounding an analysis of a causative role for ponesimod.

- At enrollment, Subject (b) (6) was a 47 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 despite having an elevated total bilirubin of 28 µmol/L (1.4 x ULN) at screening. On Study Day 29, her liver parameters were elevated (ALT 92 U/L, AST 66 U/L, TB 26.4 µmol/L, and ALP 168 U/L), so the study medication was discontinued on Study Day 132. Her liver parameters improved but remained slightly elevated on Study Day 176.

  Reviewer Comment: The role of ponesimod in this event is unclear, since she had a mild bilirubin elevation at screening and experienced an increase in her alkaline phosphatase when her transaminases and bilirubin increased.

- At enrollment, Subject (b) (6) was a 44 yo man who had an elevated ALT and AST at his initial baseline (159 U/L and 69 U/L, respectively) but had subsequent normalization of his transaminases at Study Day -10 who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 79, he was found to have an elevation in his hepatic transaminases (137 U/L and 51 U/L), and his TB was elevated at 42.8 µmol/L (2.1x ULN). The study drug was discontinued on Study Day 83, and his hepatic transaminases and TB were essentially normal on Study Day 92.

  Reviewer Comment: Although this AE could be construed as a Hy's law case of DILI, the baseline transaminase abnormalities and the rapid resolution of this event are reassuring.

<u>Macular Edema</u>

- At enrollment, Subject (b) (6) was a 35 yo man with a history of uveitis of his left eye who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 85, he was diagnosed with macular edema by ophthalmologic exam and OCT. The study drug was discontinued on Study Day 86, and the event was considered resolved on Day 141. The Ophthalmic Safety Board considered this event more likely to be related to a macular hole and posterior vitreous detachment than to ponesimod.

- At enrollment, Subject (b) (6) was a 54 yo man with a history of (reportedly uncontrolled) diabetes mellitus who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 426, ophthalmologic examination and OCT showed evidence of "mild" macular edema in his left eye, but no action was taken with the study drug. On Study Day 504, ophthalmologic examination and OCT showed evidence of macular edema in his right eye, so the study medication was discontinued. The events of left and right macular edema were considered resolved on Study Days 441 and 554, respectively.

- At enrollment, Subject (b) (6) was a 46 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 despite displaying evidence of chorioretinal inflammation on her baseline ophthalmologic examination and OCT. On Study Day 174, she experienced "acute macular edema and uveitis," so the study drug was immediately stopped. She was treated with topical diclofenac and dexamethasone, and the event was considered resolved on Study Day 286.

  Reviewer Comment: Although macular edema is a known risk with S1P receptor modulators, interpretation of the role of ponesimod in these three cases of macular edema is confounded by independent risk factors for this adverse event (uveitis, diabetes mellitus, and chorioretinitis, respectively).

- At enrollment, Subject (b) (6) was a 23 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 6, she reportedly experienced macular edema in her left eye, so the study was discontinued on Day 8. After treatment with two weeks of intraocular indomethacin, the event was considered resolved on Study Day 22; however, it reportedly recurred on Study Day 28, so she was again treated with a course of intraocular indomethacin.

  Reviewer Comment: This reviewer agrees with the Ophthalmic Safety Board that the rapid appearance of macular edema after starting ponesimod and its recurrence after stopping ponesimod suggests that this AE may not be entirely attributable to ponesimod.

- At enrollment, Subject (b) (6) was a 37 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 87, he was found to have bilateral macular edema by ophthalmologic exam and OCT. The study drug was discontinued on Study Day 87, and the event was considered resolved on Day 191. The Ophthalmic Safety Board confirmed the diagnosis of macular edema but opined "based on a history of optic neuritis and abnormal findings at baseline the relationship to treatment remains unsure in the expert view."

  Reviewer Comment: This reviewer does not agree that a history of optic neuritis

is a risk factor for macular edema and suspects that ponesimod may have played a role in the development of this TEAE.

Hypertension

The case of hypertensive crisis in Subject (b) (6) has been previously described in this review.

- At enrollment, Subject (b) (6) was a 49 yo woman with a history of hypertension who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 6, she experienced dyspnea and was subsequently found to have worsening hypertension. The study medication was discontinued on Study Day 33, and her blood pressure was 136/84 the next day.

- At enrollment, Subject (b) (6) was a 49 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Days 90 and 174, her blood pressures were 140/96 and 137/93 mm Hg, respectively, so she was started on lisinopril Day 216 and the study drug was discontinued on Day 222.

Reviewer Comment: Blood pressure increases have been reported with other S1P receptor modulators. Although the previously reported case of hypertensive crisis is very concerning, the blood pressure elevations in the two individuals described here seem relatively mildly. Blood pressure changes with ponesimod will be explored in subsequent analyses of vital signs.

Lymphopenia

In addition to the two cases of lymphocyte count decreased listed in Table 40, there was a single case coded as lymphopenia.

- At enrollment, Subject (b) (6) was a 42 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 30, she was found to be markedly lymphopenic (0.16 x 10^9/L); although this later improved somewhat, her lymphocyte count on Study Day 114 was 0.17 x 10^9/L. After a third occurrence of very low lymphocytes (0.18 x 10^9/L) on Study Day 429, the study drug was discontinued with subsequent improvement in her lymphocyte counts.

- At enrollment, Subject (b) (6) was a 27 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 672, she was found to be markedly lymphopenic (0.15 x 10^9/L), so the study drug with discontinued with subsequent improvement in her lymphocyte count.

- At enrollment, Subject (b) (6) was a 32 yo woman with a history of epilepsy who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 32, she

was found to be markedly lymphopenic (0.18 x 10^9/L), so the study drug with discontinued with subsequent improvement in her lymphocyte count; interestingly, she had a generalized tonic clonic seizure on Study Day 33.

Reviewer Comment: Since S1P receptors are thought to act by sequestering circulating lymphocytes in secondary lymph tissue, it is not surprising that cases of lymphopenia occurred with ponesimod.

A review of those TEAEs leading to study discontinuation in those subjects randomized to ponesimod in Study AC-058B301 is notable for include single reports of neutropenia, cardiomyopathy, and acute pancreatitis.

- At screening, Subject (b) (6) was a 33 yo woman with a history of hypertension who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 335, she was diagnosed with acute pancreatitis, for which she was admitted to an intensive care unit on Study Day 339. A relevant potential cause for pancreatitis was not found, and she denied the use of herbal remedies or dietary supplements at the time of the event. The study drug was discontinued on Study Day 339, and the event was considered resolved with sequelae on Day 346.

  Reviewer Comment: Since an alternative etiology of her pancreatitis was not discovered, it is certainly possible that ponesimod played a role in the development of this event.

- At screening, Subject (b) (6) was a 19 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. While being treated with intravenous methylprednisolone for an MS relapse, she was diagnosed with autoimmune thyroiditis on Study Day 472. While being treated with methylprednisolone for another MS relapse, she was found to have an abnormal ECG and laboratory abnormalities (troponin and NT-proBNP elevations), leading to a diagnosis of cardiomyopathy and discontinuation of the study drug on Study Day 738.

  Reviewer Comment: Although analysis of this case of cardiomyopathy is limited by a paucity of details, this reviewer wonders if the use of methylprednisolone at the time of the event played a role in its development.

- At screening, Subject (b) (6) was a 19 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. Her neutrophil count was mildly abnormal (1.5x10^9/L, normal range 1.8-7.7x10^9/L) at baseline and remained low throughout much of the study until the study drug was discontinued as per protocol after she had a neutrophil count of 1.5x10^9/L on Study Days 503 and 509.

Reviewer Comment: Since this subject had neutropenia at baseline, the role in ponesimod in the TEAE is unclear.

AEs leading to study drug withdrawal, placebo-controlled RMS population (Study AC-058B201)

Fifty-two TEAE leading to discontinuation of the study drug were reported by 38 subjects in Study AC-058B201. Only six of these were reported in subjects randomized to ponesimod 20 mg; however, subjects randomized to ponesimod 10 and 40 mg reported 20 and 22 TEAEs, respectively. An analysis of those TEAEs leading to discontinuation of the study drug that occurred more than once in Study AC-058B201 follows in Table 41.

Table 41. Reviewer Table. AE's leading to study drug withdrawal, Study AC-058B201

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
MACULAR EDEMA	2	0	0	0
ALT INCREASED	1	0	1	1
ATRIOVENTRICULAR BLOCK 2nd DEGREE	1	0	2	0
BRADYCARDIA	1	0	0	1
DYSPNEA	0	0	1	4
DYSPNEA EXERTIONAL	0	0	0	2
PALPITATIONS	0	0	1	1

Source: AC-058B201 ADAE where ITTFL and AETREMFL='Y' and AEACN='Permanently discontinued' by AEDECOD and TRT01P.

Reviewer Comment: Percentages are not calculated in Table 41 because of the very low incidence of SAEs in the placebo-controlled RMS population. Those AEs leading to discontinuation of the proposed marketing dose of ponesimod (20 mg) are discussed below.

Macular Edema

The cases of macular edema listed in Table 41 occurred in Subjects (b) (6) and (b) (6) and have already been described in this review.

Bradyarrhythmia and Atrioventricular Block

The case of second degree heart block listed in Table 41 occurred in Subject (b) (6) and has already been described in this review. A description of the case of bradycardia follows.

- Subject (b) (6) was a 30 yo woman when she was randomized to ponesimod 20 mg in Study AC-058B201. Three hours after her first dose of ponesimod (10 mg) was administered, she developed dizziness, weakness, fatigue, and marked bradycardia with a HR of 43 bpm, but she remained on the study drug. She reported continued symptoms and had a HR of 49 bpm on Study Day 8, so the study drug was discontinued. Her pulse was 59 bpm four days after the study drug was stopped and 61 on Study Day 36.

  Reviewer Comment: Bradyarrhythmia and AV block have been previously noted with ponesimod and are known to occur with other S1P receptor modulators.

Elevated Transaminases

- Subject (b) (6) was a 31 yo man when he was randomized to ponesimod 20 mg in Study AC-058B201. Reportedly, he had a history of liver disease ("hepathopatia"), but his liver parameters were reportedly normal at baseline; however, his ALT and AST started to increase soon after he started the study drug. Since his ALT was 3.5 x ULN and his AST was 1.8 x ULN on Study Day 57, the study drug was discontinued, and his AST/ALT improved. Reportedly, his bilirubin remained normal during the time.

  Reviewer Comment: Given a reported history of liver disease, the role of ponesimod in this event is somewhat unclear, even with the temporal correlation between starting the study drug and the increase in his ALT/AST. Since his total bilirubin was normal, this case does not meet criteria for a Hy's law case of DILI.

TEAEs leading to study drug withdrawal, uncontrolled RMS population

Forty-five TEAEs leading to study drug withdrawal were reported by 44 subjects in the long term extensions of Studies AC-058B201 and AC-058B301. Those TEAEs leading to study drug withdrawal occurring more than once with ponesimod 20 mg in the uncontrolled RMS population are shown in Table 42.

Table 42. Reviewer Table. AEs leading to study drug withdrawal, uncontrolled RMS population

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Macular edema	4	0	1
Dyspnea	3	0	2
Unintended pregnancy	3	1	0
Multiple sclerosis	2	1	1
Angioedema	2	1	0

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Invasive ductal breast carcinoma	2	0	1
Abdominal pain	2	0	0
Hepatocellular injury	2	0	0
Nausea	2	0	0
Edema peripheral	2	0	0

Source: ISS LT ADAE where SAFFL, TRTEMFL ='Y,' ACAT1='Starts in Extension,' and AEACN='DRUG WITHDRAWN' by AEDECOD and TRT01A.

Reviewer Comment: Percentages are not calculated in Table 42 because of the low incidence of TEAEs leading to study drug withdrawal in the uncontrolled RMS population. The "Multiple sclerosis" TEAEs relate to a lack of efficacy, and the pregnancy TEAEs are discussed in Section 8.8.2 of this review. TEAEs of interest that occurred with ponesimod 20 mg and led to discontinuation of the study drug during the extension studies are reviewed below.

Macular Edema

- At enrollment, Subject (b) (6) was a 49 yo man who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 726 of Study AC-058B301, the subject reported blurred vision, and on Day 85 of Study AC-058B303, he was diagnosed with bilateral macular edema; therefore, the study medication was discontinued. Ophthalmological examination and OCT were reportedly normal on Study Day 127, so this TEAE was considered resolved.

- At enrollment, Subject (b) (6) was a 51 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on this dose of the study drug in its AC-058B303 extension. On Day 84 of Study AC-058B303, he was diagnosed with asymptomatic left macular edema by ophthalmological examination and OCT, so the study medication was discontinued. This event was considered resolved after a normal OCT on Study Day 113.

- At enrollment, Subject (b) (6) was a 26 yo man with a history of retinal angiopathy who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 81 of Study AC-058B303, he was diagnosed with left macular edema, and the study drug was discontinued. The event was considered resolved on Study Day 131.

- At enrollment, Subject (b) (6) was a 48 yo woman with a history of diabetes mellitus who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 169 of Study AC-058B303, she was diagnosed with macular edema and diabetic retinopathy by ophthalmological examination and OCT, so the study medication was discontinued.

  Reviewer Comment: Although the case of macular edema in Subject (b) (6) is confounded by diabetes mellitus and that in Subject (b) (6) is possible confounded by "retinal angiopathy," the other two cases of macular edema may be attributable to ponesimod since macular edema is known to occur with other S1P receptor modulators.

Dyspnea

In addition to the three subjects reporting dyspnea with ponesimod 20 mg, a subject with "Pulmonary function test decrease" is also discussed here.

- At enrollment, Subject (b) (6) was a 49 yo woman with a history of diabetes mellitus who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. She had never smoked. On Day 88 of Study AC-058B303, the subject experienced dyspnea and was diagnosed with asthma on Study Day 171 (FEV1 1.56 L [-31.9% from baseline], FVC 2.55 L [-15.6% from baseline]); therefore, the study drug was discontinued on Study Day 197.

- At enrollment, Subject (b) (6) was a 27 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on this dose of the study drug in its AC-058B303 extension. On Day 20 of Study AC-058B303, she experienced dyspnea; even though her pulmonary function tests were not much worse than baseline (FEV1 3.07 L [89.8% of baseline], FVC 4.16 L [97.7% of baseline), the study medication was discontinued.

- At enrollment, Subject (b) (6) was a 21 yo woman with a history of diabetes mellitus who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 14 of Study AC-058B303, the subject reported dyspnea that was deemed moderate in severity, so she discontinued the study medication on Day 19. On Study Day 21, her FEV1 was 3.76 L (94.2% of baseline), and her FVC was 4.76 L (99.2% of baseline). After treatment with salbutamol, the event was considered resolved on Study Day 24.

- At enrollment, Subject (b) (6) was a 34 yo man who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on this dose of ponesimod in Treatment Periods 1 and 2 of its AC-058B202 extension. Although the subject's pulmonary function tests were consistently well below baseline during the study, his FEV1 was 3.39L (56.3 % of baseline; 83.2% of the predicted normal), and his FVC was 4.74L (71.8 % from baseline; 96.0% of the predicted normal) on Day 907 of AC-058B202, so the study drug was discontinued. His PFTs improved, and this TEAE was considered resolved on Study Day 921.

  Reviewer Comment: Respiratory effects and decreases in pulmonary function tests are known to occur with other S1P receptor modulators, so it is likely that these events are at least partially attributable to ponesimod.

Angioedema

In addition to the three cases of angioedema noted in Table 42, a case of skin rash and peripheral edema are also discussed in this section.

- At enrollment, Subject (b) (6) was a 36 yo woman with a history of seasonal allergies and hypersensitivity to sulfa drugs and glatiramer acetate who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 10 mg in its AC-058B202 extension. On Day 1138 of Study AC-058B202, she developed hives that were deemed moderate in severity and were treated with ranitidine, hydroxyzine, ipratropium with salbutamol, epinephrine, and cetirizine. She again developed moderate hives on Study Day 1442, so the medicine was temporarily interrupted. Two days after restarting the study drug, she again developed hives that were assessed as severe in intensity and treated with methylprednisolone and prednisone, so the study drug was discontinued.

- At enrollment, Subject (b) (6) was a 39 yo man who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-059B303 extension. On Day 16 of the extension, he developed angioedema which was deemed moderate in intensity and treated with chloropyramine. The study drug was discontinued on Study Day 18.

- At enrollment, Subject (b) (6) was a 39 yo woman who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 12 of Study AC-058B303, she developed swelling of her eyelids and lips and was started on desloratadine; after also developing dyspnea on Study Day 19, the study drug was

temporarily discontinued. The study drug was reinitiated on Study Day 56, and she developed angioedema on Study Day 59. She was treated with cetirizine with good effect, and the study drug was discontinued.

- At enrollment, Subject (b) (6) was a 39 yo man who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 20 of Study AC-058B303, he developed a skin rash and lower extremity edema; therefore, the study drug was stopped, and he was treated with loratadine. Both events were considered resolved on Study Day 22.

  Reviewer Comment: Three of these four reactions started soon after starting ponesimod, and two had a positive rechallenge, strongly suggesting a causative role for the study drug.

Malignancy

One of the cases of invasive ductal breast carcinoma (Subject (b) (6)) was previously described in this review.

- At enrollment, Subject (b) (6) was a 54yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on this dose in its AC-058B303 extension. After a mammogram, she was diagnosed with invasive ductal breast carcinoma with lymph node metastasis on Day 159 of Study AC-058B303, so she had a mastectomy on Study Day 200. The study drug was discontinued on Study Day 227, and she started chemotherapy on Day 231.

  Reviewer Comment: Malignancies, including breast cancer, have been noted previously in this review of ponesimod and with other S1P receptor modulators. As these agents sequester circulating lymphocytes in secondary lymphoid tissue, it is biologically plausible that they may increase the risk of malignancy.

Hepatocellular injury

One of the cases of hepatocellular injury (Subject (b) (6)) was previously described in this review.

- At enrollment, Subject (b) (6) was a 19 yo man who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 163 of Study AC-058B301, he experienced a "non-serious" transaminase elevation which was considered resolved on Day 257. On Day 34 of Study AC-058B303, he experienced another transaminase elevation (ALT 147 U/L, AST 61 U/L), so the study

medication was discontinued. His bilirubin remained normal, and the event of "hepatocellular injury" was considered resolved on Study Day 79.

Reviewer Comment: With a relatively minor transaminase elevation and a normal total bilirubin, it is unclear why the study drug was discontinued in this subject and why the TEAE was not coded as transaminase elevation.

Abdominal pain

- At enrollment, Subject (b) (6) was a 26 yo woman who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 213 of Study AC-058B303, the subject experienced abdominal pain (especially after eating), diarrhea, and fever, which led to a diagnosis of cholangitis. Imaging showed evidence of gallbladder inflammation, so the study drug was discontinued on Study Day 225. These AEs were considered resolved on Study Day 238.

  Reviewer Comment: Since S1P receptor modulators like ponesimod sequester circulating lymphocytes in secondary lymphoid tissue, it is biologically plausible that they may increase the risk of infection.

Excluding the one SAE leading to discontinuation that was described in the SAE section of this review (Subject (b) (6)), a review of the seven new TEAE's leading to study drug withdrawal that were reported in Study AC-058B202 between the cut-off date for the initial NDA submission and that for the 120-day safety update reveals the following cases of interest:

- At enrollment, Subject (b) (6) was a 47 yo woman who had not been vaccinated against the varicella zoster virus and who was randomized to ponesimod 10 mg in Study AC-058B201 and remained on that dose in its AC-058B202 extension until transitioning to ponesimod 20 mg in Treatment Period 3. On Study Day 3201, she developed zoster on her left forehead (herpes zoster ophthalmicus), so the study drug was discontinued, and she was treated with valacyclovir and amitriptyline. This TEAE was considered resolved without sequelae on Study Day 3280.

- At enrollment, Subject (b) (6) was a 42 yo woman who was randomized to ponesimod 10 mg in Study AC-058B201 and remained on that dose of ponesimod in its AC-058B202 extension until transitioning to ponesimod 20 mg in Treatment Period 3. On Study Day 3276, she developed herpes zoster (site not specified) and discontinued the study medication. This TEAE was considered resolved with sequelae (post-herpetic neuralgia) on Study Day 3288.

Reviewer Comment: Since S1P receptor modulators like ponesimod are felt to work by sequestering circulating lymphocytes in secondary lymphoid tissue, infections, including herpetic infections, are an identified and expected risk with this class of medication.

- At enrollment, Subject (b) (6) was a 23 yo man who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on that dose of ponesimod in its AC-058B202 extension. He experienced transaminase elevations on Day 117 of Study AC-058B201 (ALT 95 U/L, AST 52 U/L), Day 1039 of Study AC-058B202 (ALT 287 U/L, AST 127 U/L, normal TB), and Day 1445 of Study AC-058B202 (ALT 193 U/L, AST 91 U/L, normal TB). Although these prior transaminase elevations had resolved, the study drug was discontinued on Day 2990 after an addition transaminase elevation (AST 415 U/L, AST 267 U/L) associated with a TB of 26.7 umol/L (normal range reported as 5.0-26.0 umol/L). Hepatitis B/C testing was reportedly negative, but other details on the work-up of these transaminase elevations are not provided. His transaminases were further elevated at the end of the study (ALT 571 U/L, AST 237 U/L), but his TB had normalized.

  Reviewer Comment: Although transaminase elevations and liver injury are known risks of S1P receptor modulators, the continued increase in his transaminases after cessation of the study drug is unsettling, although the TB < 1.5 x ULN (and subsequent normalization) is somewhat reassuring. An Information Request was sent to request further information about this case. The Applicant's 24JUL2020 states that the subject refused further work-up of his elevated transaminases but suggests that his transaminases and TB were normal (ALT 9 U/L, AST 3 U/L, TB 13.2 µmol/L, but reference ranges were not provided) when he was hospitalized for hypertensive crisis approximately one year after cessation of the study drug.

- At enrollment, Subject (b) (6) was a 40 yo man without a history of tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on that dose of ponesimod in its AC-058B303 extension. On Day 29 of Study AC-058B301, he was diagnosed with obstructive pulmonary disease, and this event was considered resolved with sequelae on Study Day 440. On Day 337 of Study AC-058B303, his FEV1 was 1.99 L (59.9% of baseline) and his FVC was 4.01 L (82.9% of baseline), and he was diagnosed with pulmonary obstructive disorder. On Study Day 345, his FEV1 was 1.88 L (59.9% of baseline) and his FVC was 3.33 L (68.8% of baseline), so the study drug was discontinued. Although his pulmonary test was improving, the event had not resolved at the time of the data cut-off for this safety update.

- At enrollment, Subject (b) (6) was a 51 yo man with an ongoing history of tobacco use who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 27 of AC-058B303, the subject reported dyspnea, and his FEV1 and FVC were 2.60 L (85.5% of baseline) and 4.19 L

(94.6% of baseline), respectively. The study drug was temporarily interrupted and then discontinued. This TEAE was considered resolved on Study Day 88.

- At enrollment, Subject (b) (6) was a 28 yo man with an ongoing history of tobacco use who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in its AC-058B303 extension. On Day 333 of Study AC-058B303, he experienced a feeling of suffocation while sleeping, and on Day 395, his FEV1 was 2.72 L (68.2% of baseline), and his FVC was 3.17 L (70.6% of baseline); therefore, the study drug was discontinued. On Study Day 444, his FEV1 was 3.43 L (86.0% of baseline), and his FVC was 4.08 L (90.9% of baseline), so the TEAE was considered resolved.

  Reviewer Comment: Although the narrative for Subject (b) (6) is suggestive of chronic obstructive pulmonary disease (COPD) and two of the other cases were confounded by tobacco use, respiratory effects, including a decrease in pulmonary function testing, has been reported with other S1P receptor modulators and has been previously noted in this review of ponesimod.

AEs leading to study drug withdrawal, Healthy Volunteers

Eleven subjects reported an TEAE that lead to study drug withdrawal in the Phase 1 studies of ponesimod; interestingly, eight of these occurred in Study AC-058-110. Four of these 11 were for dyspnea, and three were for cardiac conduction abnormalities. The single cases of lymphopenia, transaminase elevation, and creatine phosphokinase are also of interest.

Dyspnea

Per the CSR for Study AC-058-110, "The 4 subjects discontinued due to dyspnea were withdrawn as a result of their FEV1 and or FVC meeting the criteria for withdrawal specified in the protocol (≥ 50% decrease from baseline FEV1 and/or FVC). This occurred for one subject during dosing at the 60 mg dose level and one subject at the 80 mg dose level, and for 2 subjects at the 100 mg dose level."

Reviewer Comment: These discontinuations for dyspnea occurred with much higher doses of ponesimod than that proposed in this NDA.

Bradyarrhythmia and Atrioventricular Block

Per the CSR for Study AC-058-110, "The second-degree AV block and prolongation of PR interval which led to discontinuation of Subjects (b) (6) and (b) (6), respectively, started on Day 2 at the start of multiple dosing with 10 mg ponesimod;" of note, Subject (b) (6) also was noted to have second-degree AV block type I despite being randomized to placebo.

- Two and a half hours after receiving the first dose of ponesimod (10 mg), Subject (b) (6) developed dizziness, bradycardia (HR of 35 bpm), and second degree AV block (Mobitz I). The subject's HR normalized four hours after the administration of

ponesimod, and the AV block had resolved at 24 hours.

- Two and a half hours after receiving the first dose of ponesimod (10 mg) on Study Day 2, Subject (b) (6) experienced first-degree AV block; at four hours, the subject's PR interval had increased to 286 ms, so the study drug was discontinued. The subject's PR interval was initially 290 ms on Study Day 3, but it normalized later that day. The subject inadvertently received second dose of ponesimod on Study Day 4 but did not exhibit PR interval abnormalities.

Six subjects were withdrawn from Study AC-058-117 for meeting protocol-mandated discontinuation requirements, but these events were not classified as TEAEs.

Reviewer Comment: Bradycardia and AV block is a known adverse event with other S1P receptor modulators and has been described previously in this safety review. In its 25JUN2020 response to an Information Request asking why the protocol-mandated discontinuations from Study AC-058-117 were not reported as TEAEs, the Applicant clarified that events were only classified as TEAEs if they were considered clinically significant.

Lymphopenia

Subject (b) (6) in Study AC-058-104 developed lymphopenia (120 cells/µL) on ponesimod and triggered a predefined study drug discontinuation criterion (lymphocyte count below 200 cells/µL).

Transaminase Elevation

Subject (b) (6) in Study AC-058-110 developed transaminase elevations soon after starting ponesimod (ALT 209 U/L, AST 121 U/L on Study Day 12). The subject's bilirubin remained normal, and the transaminase elevations had resolved after three days.

Creatine Phosphokinase Elevation

Subject (b) (6) in Study AC-058-110 was found to have a creatine phosphokinase (CPK) elevation (2372 U/L) on Study Day 8 after receiving ponesimod 10 mg from Days 2-4 and ponesimod 20 mg from Days 5-7. The study drug was discontinued, and the CPK elevation had resolved four days later.

Reviewer Comment: Lymphopenia and transaminase elevations are a known adverse event with other S1P receptor modulators and have been described previously in this safety review of ponesimod. The CPK elevation in Subject (b) (6) is notable in magnitude but is of unclear significance since it resolved very rapidly and appears to be the only case leading to study drug discontinuation in the ponesimod clinical trials.

AEs leading to study drug interruption, active-controlled RMS population (Study AC-058B301)

Twenty-five subjects in Study AC-058B301 experienced 29 TEAEs leading to interruption of the study drug. Table 43 delineates those adverse events leading to study drug interruption that occurred more than once in the ponesimod arm of Study AC-058B301.

Table 43. Reviewer Table. AE's leading to treatment interruption, Study AC-058B301

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Dyspnea	3	0
Lymphocyte count decreased	2	0
Lymphopenia	2	0

Source: AC-058B301 ADAE where SAFFL and TRTEMFL='Y' and AEACN='DRUG INTERRUPTED' by AEDECOD and TRT01A.

Reviewer Comment: Percentages are not calculated in Table 43 because of the low incidence of these AEs in Study AC-058B301 and because the same AE could be reported more than once by the same subject. Cases of interest, including those of dyspnea and lymphopenia, are described below.

Dyspnea

- At enrollment, Subject (b) (6) was a 24 yo man with a former history of tobacco use who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 42, the subject experienced dyspnea, and on Day 43, his FEV1 was 3.44 L (84.5% of baseline) and his FVC was 4.85 L (92.7% of baseline). The study medication was temporarily interrupted, and his dyspnea resolved on Study Day 46; however, the subject subsequently decided to discontinue the study medication, reportedly for efficacy reasons.

- At enrollment, Subject (b) (6) was a 26 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 17, she experienced dyspnea and then experienced dyspnea and vomiting the next day. The study drug was temporarily discontinued on Study Day 18, after which her symptoms resolved; therefore, the study drug was resumed on Day 20.

  Reviewer Comment: The narrative for Subject (b) (6) suggests that the discontinuation of the study drug may have been partially due to efficacy. The co-occurrence of dyspnea and vomiting in Subject (b) (6) is more suggestive of a GI process than dyspnea, especially with the rapid resolution of symptoms and a negative rechallenge.

Lymphopenia

The "lymphocyte count decreased" and the "lymphopenia" categories are combined here.

- At enrollment, Subject (b) (6) was a 44 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and who was noted to have a very low lymphocyte count ($0.18x10^9$/L) on Study Day 589. The study drug was temporarily interrupted, after which her lymphocyte count improved, so the study drug was restarted on Study Day 624.

- At enrollment, Subject (b) (6) was a 41 yo woman with a history of autoimmune thyroiditis and recurrent sinus infections who was randomized to ponesimod 20 mg in Study AC-058B301. She was noted to have a very low lymphocyte count ($0.16x10^9$/L) on Study Day 162. The study drug was temporarily interrupted, after which her lymphocyte count improved, so the study drug was restarted on Study Day 205. Of note, she also developed a lymphocyte count ($0.17x10^9$/L) on Day 162 of Study AC-058B303, for which the study medication was again temporarily interrupted with normalization of her lymphocyte count.

- At enrollment, Subject (b) (6) was a 33 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and was noted to have a lymphocyte count of $0.16x10^9$/L on Study Day 500. The study drug was temporarily interrupted on Study Day 503; since the event was considered resolved on Day 505, she resumed the study drug on Day 506. The study drug was again temporarily interrupted for lymphopenia on Study Day 667 ($0.16x10^9$/L).

  Reviewer Comment: Since S1P receptor modulators like ponesimod lead to sequestration of circulating lymphocytes into secondary lymphoid tissue, it is not surprising that lymphopenia is a known adverse effect with this class of medication.

The single cases of herpes zoster, ALT elevation, neutropenia, and rash that lead to temporary interruption of ponesimod are also of interest.

- At enrollment, Subject (b) (6) was a 45 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and developed thoracic herpes zoster on Study Day 28. The study drug was interrupted on Study Day 29, after which the event resolved; the study drug was resumed on Day 54.

- At enrollment, Subject (b) (6) was a 32 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 42, the study drug was interrupted since his AST, ALT, and ALP were mildly elevated at 150 U/L, 55 U/L, and 135 U/L, respectively; however, his bilirubin remained normal. The event was

considered resolved on Study Day 49, and the study drug was resumed on Day 70 He again had a mild ALT increase on Study Day 420, but no action was taken with the study drug.

- At enrollment, Subject (b) (6) was a 29 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and in whom the study drug was interrupted for Grade 2 neutropenia (0.9 x 10^9/L) on Study Day 35. The event was considered resolved on Study Day 36, and the study drug was resumed on Day 59. Most of her neutrophil counts after that time were normal, although she did have mildly decreased neutrophil counts of 1.4 and 1.7 x 10^9/L on Study Days 330 and 500, respectively.

- At enrollment, Subject (b) (6) was a 48 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and developed a rash on the medial aspect of her left arm on Study Day 1. She was treated with diphenhydramine and resumed the study drug on Study Day 7, seemingly without issue.

Reviewer Comment: It is not clear that these single adverse events leading to temporary discontinuation of the study drug offer much to this safety analysis. As the rash in Subject 8 (b) (6) was localized and presumably occurred during the first dose observation, this reviewer suspects that this may represent a contact dermatitis.

AEs leading to study drug interruption, placebo-controlled RMS population (AC-058B201)
A query of TEAE's leading to temporary study drug interruption in the safety population of Study AC-058B201 did not reveal any events reported more than once. Only one such TEAE (acute tonsillitis) occurred with ponesimod 20 mg.

AEs leading to study drug interruption, uncontrolled RMS population
Fifty-one TEAEs led to temporary interruption of the study drug in 38 subjects, but only hepatic transaminase elevations and lymphopenia (or TEAE coding related to these) occurred more than once in subjects taking the 20 mg dose of ponesimod. There were also single cases of infectious colitis, which is described below, and herpes zoster (Subject (b) (6)).

Transaminase Elevations

- At enrollment, Subject (b) (6) was a 42 yo woman with a history of pancreatitis who was randomized to ponesimod 10 mg in Study AC-058B201 and transitioned to ponesimod 20 mg for the three treatment periods of the AC-058B202 extension. On Day 922 of Study AC-058B202, her ALT and AST were found to be elevated at 229 and 188 U/L, respectively; the investigator thought that these laboratory abnormalities were representative of pancreatitis and temporarily interrupted the study drug. The hepatic transaminase elevations were considered resolved on Study Day 944; the study drug

was resumed on Day 958, and the pancreatitis was considered resolved on Day 999. Interestingly, the subject experienced a second episode of pancreatitis on Study Day 1576, and her ALT and ALP was elevated at 84 and 531 U/L, respectively on Study Day 1583. The study drug was temporarily interrupted on Study Day 1590, after which the pancreatitis and ALT/ALP elevations resolved. The study drug was again resumed on Study Day 1658.

Reviewer Comment: The seeming co-occurrence of these two episodes of transaminase elevations and pancreatitis in a subject with a history of pancreatitis before starting the study suggests that these events may not be related to the study drug, but this review will remain vigilant for other cases of pancreatitis with ponesimod.

- At enrollment, Subject (b) (6) was a 23 yo man who was randomized to ponesimod 40 mg in Study AC-058B201 and remained on this dose for Treatment Period 1 of its AC-058B202 extension before transitioning to ponesimod 20 mg for Treatment Periods 2 and 3 of the extension. On Day 1870 of Study AC-058B202, his AST was 643 U/L, his ALT was increased at 627 U/L, and his LDH was increased at 627 U/L; therefore, the study drug was interrupted on Day 1875. These laboratory abnormalities had resolved on Study Day 1877, so the study drug was resumed.

  Reviewer Comment: Although the magnitude of these laboratory abnormalities is notable, their very rapid resolution suggests the possibility of a laboratory error.

- At enrollment, Subject (b) (6) was a 22 yo man who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 20 mg for the three Treatment Periods of its AC-058B202 extension. This subject had TEAEs for hepatic transaminase elevations several times during the extension, and the study drug was interrupted on Study Day 688, when his ALT was 662 U/L and his AST was 82 U/L. This particular event was considered resolved on Study Day 741, so the study medication was resumed. His TB remained normal during these episodes.

- At enrollment, Subject (b) (6) was a 26 yo man who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 40 mg for Treatment Period 1 of its AC-058B202 extension. On Day 15 of Study AC-058B202, he experienced hepatic transaminase elevations (ALT 140 U/L, AST 72 U/L) with a normal bilirubin. Since his transaminases were higher on Day 29 (ALT 205, AST 121), the study drug was interrupted on Day 36 and resumed on Day 58. Since his ALT and AST elevations recurred after resuming the study drug (146 U/L and 68 U/L, respectively), the study drug was discontinued with subsequent normalization of his AST and ALT.

- At enrollment, Subject (b) (6) was a 34 yo man who was randomized to ponesimod 20 mg in Study AC-058B201 and remained on this dose of ponesimod for Treatment Periods 1 and 2 of its AC-058B202 extension. He had multiple TEAEs for mild ALT elevations during the study, including one on Day 1227 of Study AC-058B303 that led to a brief interruption in the study drug and another on Day 1334 (ALT 153 U/L and AST 58 U/L) that lead to discontinuation of the study drug. His hepatic transaminases were normal on Study Day 1403.

- At enrollment, Subject (b) (6) was a 31 yo man who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 20 mg for the three Treatment Periods of its AC-058B202 extension. On Day 1394 of Study AC-058B202, the study drug was temporarily interrupted for "liver function test increase," but the narrative does not define the degree of abnormality; however, his transaminases normalized, and the study drug was resumed on Study Day 1443.

- At enrollment, Subject (b) (6) was a 36 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on ponesimod 20 mg in the AC-058B303 extension. He had two non-serious events of transaminase elevations in Study AC-058B301; on Day 61 of Study AC-058B303, he had another episode of transaminase elevation (ALT 149 U/L, AST 75 U/L, ALP 161 U/L but normal bilirubin) for which the study drug was temporarily interrupted on Day 69. The study drug was re-initiated on Study Day 75, and the event was considered resolved on Day 79.

- At enrollment, Subject (b) (6) was a 30 yo man who was randomized to teriflunomide 14 mg in Study AC-058B301 (despite a mild elevation of total bilirubin at 21.1 µmol/l) and transitioned to ponesimod 20 mg in the AC-058B303 extension. On Day 78 of Study AC-058B303, he was found to have ALT (386 U/L) and AST (126 U/L) elevations with a normal total bilirubin. The study drug was temporarily interrupted on Study Day 81; the transaminase elevations rapidly resolved, so the study drug was reinitiated on Day 169.

- At enrollment, Subject (b) (6) was a 42 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on ponesimod 20 mg in the AC-058B303 extension. During Study AC-058B301, she had several episodes of mild transaminase elevations; on Day 5 of Study AC-058B303, she was reportedly diagnosed with drug-induced liver injury (ALT 144 U/L, AST 70 U/L with normal bilirubin), for which the study drug was temporarily interrupted. The transaminase elevations rapidly improved, and the study drug was resumed on Study Day 60.

  Reviewer Comment: The relatively rapid resolution of these cases, most of which reported a concomitant normal total bilirubin, is reassuring; however, it is

already clear that ponesimod, like other S1P receptor modulators, is associated with a risk of transaminase elevations and liver injury.

Lymphopenia

In Subject (b) (6) (discussed above), the study drug (ponesimod 20 mg) was temporarily interrupted for lymphopenia (lymphocytes below $0.16x10^9$/L) in both Study AC-058B301 and its AC-058B303 extension.

- At enrollment, Subject (b) (6) was a 41 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on ponesimod 20 mg in the AC-058B303 extension. During both studies, she had multiple episodes of low lymphocyte counts (most considered mild); however, the study drug was temporarily discontinued on Day 44 of Study AC-058B303 and later discontinued on Day 161 due to a lymphocyte count of $0.16x10^9$/L.

Reviewer Comment: Given the purported mechanism of S1P receptor modulators, it is not surprising to have cases of lymphopenia with ponesimod.

The case of infectious colitis in Subject (b) (6) is of interest. At enrollment, the subject was a 34 yo man with a history of irritable bowel syndrome who was randomized to teriflunomide 14 mg in Study AC-058B301 and transitioned to ponesimod 20 mg in Study AC-058B303. On Day 23 of Study AC-058B303, he was hospitalized to receive three days of intravenous methylprednisolone for an MS relapse. On Study Day 26, he developed fatigue, fever / chills, vomiting, and severe diarrhea. The subject was diagnosed with infectious colitis and gastroenteritis, so the study drug was temporarily discontinued. The study drug was resumed on Study Day 30, and the subject was discharged from the hospital on Day 32.

Reviewer Comment: Although ponesimod could have played a role in this event, the onset of infectious colitis / gastroenteritis during this subject's hospitalization for intravenous steroids suggests another causative factor for this AE.

The 120-day safety update includes six additional TEAEs leading to study drug interruption, including three cases of lymphopenia (0.15, 0.35, and 0.1 x 10^9/L), one case of transaminase elevation (AST 244 U/L and AST 366 U/L with normal TB), and one case of blood pressure, transaminase, and ALP elevation (BP 144/90 mm Hg, ALT 209, AST 99, ALP 258, normal TB).

Reviewer Comment: Lymphopenia, transaminase elevation, and increased blood pressure are known risks with other S1P receptor modulators and have been previously described with ponesimod in this review.

AEs leading to study drug interruption, placebo-controlled plaque psoriasis population
Study drug interruptions were not allowed in Study AC-058A200. The study drug was temporarily discontinued in four subjects in Study AC-058A201 for transaminase elevations.

8.4.4. Significant Adverse Events

As per Section 8.3.2, the severity of AEs was graded as mild, moderate, or severe.

Severe TEAEs, active-controlled RMS population (Study AC-058B301)
Sixty-five subjects in Study AC-058B301 reported 84 TEAEs that were classified as "Severe." Those that were reported more than once with ponesimod are delineated in Table 44.

Table 44. Reviewer Table. TEAEs classified as "severe," Study AC-058B301

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Headache	6	0
Lymphopenia	5	0
Drug-induced liver injury	2	0
Fatigue	2	0
Hepatic enzyme increased	2	0
Hysterectomy	2	0
Intervertebral disc protrusion	2	0
Pain in extremity	2	0

Source: AC-058B301 ADAE where SAFFL and TRTEMF ='Y' and AESEV='SEVERE' by AEDECOD and TRT01A.

Reviewer Comment: Although the lack of TEAEs classified as 'Severe' with teriflunomide is notable, the numbers of each TEAE listed in Table 44 are quite low and do not suggest a new obvious or concerning safety signal. Headaches are common events (probably more so in individuals with RMS), and transaminase elevations and lymphopenia have been described with other S1P receptor modulators and are discussed elsewhere in this review.

Severe TEAEs, placebo-controlled RMS population (Study AC-058B301)
Similarly, 36 TEAEs that were graded as 'Severe' (AESEV='SEVERE') were reported by 29 subjects in Study AC-058B201. Those occurring with ponesimod 20 mg are delineated in Table 45.

Table 45. Reviewer Table. TEAEs classified as "severe," Study AC-058B201

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
ABDOMINAL PAIN UPPER	1	0	0	0
APPENDICECTOMY	1	0	0	0
APPENDICITIS	1	0	0	0
BRADYCARDIA	1	0	0	0
CHEST PAIN	1	0	0	0
DYSPNEA	1	0	0	0
HEADACHE	1	2	1	2
MACULAR EDEMA	1	0	0	0

Source: AC-058B201 ADAE where ITTFL and AETREMFL='Y' and AESEV='SEVERE' by AEDECOD and TRT01P

Reviewer Comment: The results of Table 45 do not show an obvious or concerning signal for TEAEs graded as severe. Bradycardia, dyspnea, and macular edema have been previously reported with ponesimod and other S1P receptor modulators.

Severe TEAEs, uncontrolled RMS population

There were 143 adverse events (reported by 89 subjects) that were graded as severe in the uncontrolled RMS population. Those occurring more than once with ponesimod 20 mg are delineated in Table 46.

Table 46. Reviewer Table. TEAEs classified as "severe," uncontrolled RMS population

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Lymphopenia	4	0	0
Lymphocyte count decreased	3	0	0
ALT increased	2	0	0
Hypoesthesia	2	0	0
Invasive ductal breast carcinoma	2	0	1
Metrorrhagia	2	0	0
Nausea	2	0	1

Source: ISS LT ADAE where SAFFL, TRTEMFL ='Y,' ACAT1='Starts in Extension,' and AESEV='SEVERE' by AEDECOD and TRT01A.

Reviewer Comment: The results of Table 46 do not show an obvious new or concerning signal for TEAEs graded as severe. Lymphopenia and transaminase elevations have

already been reported with ponesimod and other S1P receptor modulators, and the cases of breast cancer have already been discussed.

Severe TEAE, plaque psoriasis population

An analysis of TEAEs that were graded as severe and occurred in the ponesimod 20 mg arm of the plaque psoriasis population include single cases of ALT increased, Gilbert's syndrome, increased hepatic enzymes, disease progression, hyperkalemia, intervertebral disc protrusion, and viral infection.

Reviewer Comment: An analysis of TEAEs graded as severe in the plaque psoriasis population does not appear to add any new insights into the safety of ponesimod.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAE, active-controlled RMS population

In Study AC-058B301, 502 (88.8%) of subjects randomized to ponesimod 20 mg and 499 (88.2%) of subjects randomized to teriflunomide 14 mg reported one or more TEAEs. The numbers of subjects reporting a TEAE in particular System Organ Classes (SOCs) are delineated in Table 47, and those TEAEs reported by more than 2% of subjects randomized to ponesimod in Study AC-058B301 are delineated in Table 48.

Table 47. Reviewer Table. TEAEs stratified by SOC , Study AC-058B301

AEBODSYS	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Infections and infestations	306 (54.2%)	295 (52.1%)
Investigations	187 (33.1%)	134 (23.7%)
Nervous system disorders	173 (30.6%)	149 (26.3%)
Gastrointestinal disorders	142 (25.1%)	174 (30.7%)
Musculoskeletal and connective tissue disorders	112 (19.8%)	101 (17.8%)
General disorders and administration conditions	85 (15.0%)	92 (16.3%)
Respiratory, thoracic and mediastinal disorders	76 (13.5%)	60 (10.6%)
Skin and subcutaneous tissue disorders	72 (12.7%)	145 (25.6%)
Psychiatric disorders	65 (11.5%)	81 (14.3%)
Eye disorders	64 (11.3%)	57 (10.1%)
Vascular disorders	60 (10.6%)	58 (10.2%)
Injury, poisoning and procedural complications	55 (9.7%)	50 (8.8%)

AEBODSYS	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Metabolism and nutrition disorders	47 (8.3%)	40 (7.1%)
Cardiac disorders	36 (6.4%)	28 (4.9%)
Blood and lymphatic system disorders	32 (5.7%)	34 (6.0%)
Renal and urinary disorders	28 (5.0%)	30 (5.3%)
Reproductive system and breast disorders	28 (5.0%)	34 (6.0%)
Surgical and medical procedures	25 (4.4%)	12 (2.1%)
Neoplasms benign, malignant and unspecified	23 (4.1%)	24 (4.2%)
Ear and labyrinth disorders	22 (3.9%)	14 (2.5%)
Hepatobiliary disorders	14 (2.5%)	20 (3.5%)
Endocrine disorders	10 (1.8%)	6 (1.1%)
Congenital, familial and genetic disorders	4 (0.7%)	4 (0.7%)
Pregnancy, puerperium and perinatal conditions	4 (0.7%)	3 (0.5%)
Immune system disorders	3 (0.5%)	9 (1.6%)
Social circumstances	2 (0.4%)	1 (0.2%)

Source: N Categories (SUBJID) of AC-058B301 ADAE where SAFFL and TRTEMF ='Y' by AEBODSYS and TRT01A.

Reviewer Comment: The safety of the active comparator (teriflunomide) needs to be considered in this analysis of TEAEs with ponesimod by body system, especially for those TEAEs that are common to both. Even though both ponesimod and teriflunomide can lead to transaminase elevations and lymphopenia, the percentage of subjects reporting a TEAE of the "Investigations" system is almost 10% higher with ponesimod than teriflunomide; therefore, subsequent laboratory analyses of this study will be of interest. Although respiratory effects can occur with both agents, the percentage of subjects reporting a TEAE in this body system is almost 3% higher with ponesimod.

Table 48. Reviewer Table. Common TEAEs, Study AC-058B301

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
ALT increased	110 (19.5%)	53 (9.4%)
Nasopharyngitis	109 (19.3%)	95 (16.8%)
Headache	65 (11.5%)	72 (12.7%)
Upper respiratory tract infection	60 (10.6%)	59 (10.4%)

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Hypertension	45 (8.0%)	44 (7.8%)
Nausea	43 (7.6%)	47 (8.3%)
AST increased	36 (6.4%)	20 (3.5%)
Fatigue	34 (6.0%)	37 (6.5%)
Back pain	33 (5.8%)	38 (6.7%)
Urinary tract infection	32 (5.7%)	29 (5.1%)
Dyspnea	30 (5.3%)	7 (1.2%)
Dizziness	28 (5.0%)	15 (2.7%)
Bronchitis	26 (4.6%)	25 (4.4%)
Influenza	24 (4.2%)	23 (4.1%)
Depression	21 (3.7%)	29 (5.1%)
Cough	20 (3.5%)	14 (2.5%)
Diarrhea	20 (3.5%)	44 (7.8%)
Pain in extremity	20 (3.5%)	17 (3.0%)
Abdominal pain upper	19 (3.4%)	24 (4.2%)
Alopecia	18 (3.2%)	72 (12.7%)
Anxiety	18 (3.2%)	16 (2.8%)
Respiratory tract infection viral	18 (3.2%)	10 (1.8%)
Somnolence	18 (3.2%)	9 (1.6%)
Arthralgia	17 (3.0%)	16 (2.8%)
Constipation	17 (3.0%)	21 (3.7%)
Oral herpes	17 (3.0%)	21 (3.7%)
Paresthesia	17 (3.0%)	28 (4.9%)
Respiratory tract infection	17 (3.0%)	16 (2.8%)
Hypoesthesia	14 (2.5%)	14 (2.5%)
Pharyngitis	14 (2.5%)	14 (2.5%)
Dyspepsia	13 (2.3%)	14 (2.5%)
Hepatic enzyme increased	13 (2.3%)	8 (1.4%)
Hypercholesterolemia	13 (2.3%)	3 (0.5%)
Vertigo	13 (2.3%)	7 (1.2%)
Abdominal pain	12 (2.1%)	18 (3.2%)
C-reactive protein increased	12 (2.1%)	7 (1.2%)
Gastroenteritis	12 (2.1%)	18 (3.2%)
Pyrexia	12 (2.1%)	7 (1.2%)
Rhinitis	12 (2.1%)	17 (3.0%)

Source: N Categories (SUBJID) of AC-058B301 ADAE where SAFFL and TRTEMF ='Y' by AEDECOD and TRT01A.

Reviewer Comment: The rates of infections, transaminase elevations, and dyspnea are higher in subjects randomized to ponesimod even though these are also known risks with

teriflunomide. Although the rates of hypertension with ponesimod and teriflunomide are almost equal, teriflunomide has a known risk of hypertension. The rates of dizziness and hypercholesterolemia are also somewhat higher in the ponesimod group.

A TEAE summary in which related TEAEs are grouped together may give a clearer picture of the safety of a medication, so the results of a safety grouping tool for TEAEs reported by at least 2% of subjects in Study AC-058B301 follow in Table 49.

Table 49. Reviewer Table. Safety grouping analysis of TEAEs, Study AC-058B301

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
infection, all	304 (53.8%)	296 (52.3%)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	211 (37.3%)	212 (37.5%)
GOT, GPT, GGTP, LFTs	141 (25.0%)	77 (13.6%)
infection, viral	89 (15.8%)	73 (12.9%)
Headache	74 (13.1%)	82 (14.5%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenal	62 (11.0%)	84 (14.8%)
abdominal pain, distension, bloating, spasm, IBS, megacolon	57 (10.1%)	67 (11.8%)
hypertension, BP increased	57 (10.1%)	51 (9.0%)
asthenia, fatigue, malaise, weakness, narcolepsy	49 (8.7%)	63 (11.1%)
somnolence, fatigue, sedation	47 (8.3%)	45 (8.0%)
Nausea, vomiting	46 (8.1%)	60 (10.6%)
fall, dizziness, balance disorder	40 (7.1%)	27 (4.8%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	40 (7.1%)	27 (4.8%)
UTI	39 (6.9%)	36 (6.4%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	38 (6.7%)	72 (12.7%)
dyspnea, SOB, respiratory distress	35 (6.2%)	7 (1.2%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	33 (5.8%)	29 (5.1%)
eye other	32 (5.7%)	24 (4.2%)
dizziness, light-headedness	28 (5.0%)	16 (2.8%)
Depression	26 (4.6%)	34 (6.0%)
herpes virus	26 (4.6%)	26 (4.6%)
anxiety, nervousness, panic attacks	24 (4.2%)	19 (3.4%)
arthralgia, arthritis, arthrosis	24 (4.2%)	24 (4.2%)

AEDECOD	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Influenza	24 (4.2%)	23 (4.1%)
infection, fungal	21 (3.7%)	22 (3.9%)
Anemia	20 (3.5%)	19 (3.4%)
confusion, delirium, altered mental status, disorientation, coma	20 (3.5%)	15 (2.7%)
Cough	20 (3.5%)	15 (2.7%)
insomnia, sleep disturbance, abnormal dreams	19 (3.4%)	23 (4.1%)
leukopenia (neutropenia and/or lymphopenia)	19 (3.4%)	24 (4.2%)
neuralgia, neuritis, neuropathy	19 (3.4%)	20 (3.5%)
Arrhythmia	18 (3.2%)	9 (1.6%)
Constipation	17 (3.0%)	21 (3.7%)
paresthesia, hypoesthesia	17 (3.0%)	28 (4.9%)
vertigo; vestibular dysfunction	17 (3.0%)	11 (1.9%)
edema, non-pulm, fluid retention, overload	15 (2.7%)	11 (1.9%)
Insomnia	14 (2.5%)	16 (2.8%)
solid neoplasia, ALL (benign, malignant, unknown)	14 (2.5%)	8 (1.4%)
Hyperbilirubinemia, alk phosphatase, jaundice	13 (2.3%)	9 (1.6%)
conduction disturbance	13 (2.3%)	9 (1.6%)
chest pain (non-cardiac or unknown)	12 (2.1%)	8 (1.4%)
fever, rigors	12 (2.1%)	7 (1.2%)
Fracture	12 (2.1%)	8 (1.4%)
Lymphopenia	12 (2.1%)	0
visual disturbance	12 (2.1%)	21 (3.7%)

Reviewer Comment: This grouped safety analysis of Study AC-058B301 again suggests higher risks of infections, transaminase elevation, hypertension, dizziness, dyspnea, eye disorders, arrhythmia, lymphopenia, and perhaps neoplasia with ponesimod.

TEAEs, placebo-controlled RMS population (Study AC-058B201)

The numbers (and percentages) of subjects who experienced TEAEs in Study AC-058B201 are stratified by primary System Organ Class (SOC) and shown in Table 50. Those TEAEs reported by more than 2% of subjects randomized to ponesimod are delineated in Table 51.

Table 50. Reviewer Table. TEAEs stratified by SOC, Study AC-058B201

AEBODSYS	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
INFECTIONS AND INFESTATIONS	61 (53.5%)	90 (74.4%)	70 (64.8%)	69 (58.0%)
GENERAL DISORDERS AND ADMINISTRATION CONDITIONS	46 (40.4%)	33 (27.3%)	31 (28.7%)	56 (47.1%)
NERVOUS SYSTEM DISORDERS	45 (39.5%)	39 (32.2%)	62 (57.4%)	61 (51.3%)
INVESTIGATIONS	25 (21.9%)	16 (12.3%)	30 (27.8%)	38 (31.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	25 (21.9%)	19 (15.7%)	17 (15.7%)	53 (44.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	24 (21.1%)	39 (32.2%)	16 (14.8%)	25 (21.0%)
GASTROINTESTINAL DISORDERS	23 (20.2%)	32 (26.4%)	17 (15.7%)	24 (20.2%)
PSYCHIATRIC DISORDERS	18 (15.8%)	9 (7.4%)	18 (16.7%)	13 (10.9%)
EYE DISORDERS	12 (10.5%)	13 (10.7%)	13 (12.0%)	6 (5.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12 (10.5%)	15 (12.4%)	7 (6.5%)	9 (7.6%)
CARDIAC DISORDERS	9 (7.9%)	6 (5.0%)	13 (12.0%)	6 (5.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8 (7.0%)	13 (10.7%)	14 (13.0%)	5 (4.2%)
METABOLISM AND NUTRITION DISORDERS	6 (5.3%)	4 (3.3%)	3 (2.8%)	7 (5.9%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	6 (5.3%)	7 (5.8%)	3 (2.8%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5 (4.4%)	4 (3.3%)	2 (1.9%)	2 (1.7%)
RENAL AND URINARY DISORDERS	5 (4.4%)	2 (1.7%)	1 (0.9%)	1 (0.8%)
SURGICAL AND MEDICAL PROCEDURES	5 (4.4%)	5 (4.1%)	1 (0.9%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (3.5%)	1 (0.8%)	6 (5.6%)	0
VASCULAR DISORDERS	4 (3.5%)	0	2 (1.9%)	4 (3.4%)
EAR AND LABYRINTH DISORDERS	3 (2.6%)	12 (9.9%)	4 (3.7%)	2 (1.7%)
ENDOCRINE DISORDERS	1 (0.9%)	0	0	0
IMMUNE SYSTEM DISORDERS	1 (0.9%)	3 (2.5%)	1 (0.9%)	3 (2.5%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	1 (0.9%)	0

AEBODSYS	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	1 (0.8%)	0	0

Source: N Categories (USUBJID) of AC-058B201 ADAE where ITTFL and AETREMFL='Y' by AEBODSYS and TRT01P

Reviewer Comment: Although Study AC-058B201 enrolled a smaller number of subjects and followed them for a shorter period of time than did Study AC-058B301, this reviewer is surprised that the ponesimod 20 mg arm had a much lower rate of TEAEs in the "Infections" body system than the placebo (and other ponesimod) arms. The rates of TEAEs in the "General disorders," "Nervous system disorders," "Investigations," "Respiratory Disorders," "Psychiatric Disorders," and "Cardiac Disorders" and notably higher in the ponesimod 20 mg arm than the placebo arm; although most of these are not surprising given the known safety signals with other S1P receptor modulators. The inclusion of "Psychiatric Disorders" in this list is note-worthy.

Table 51. Reviewer Table. Common TEAEs, Study AC-058B201

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
HEADACHE	21 (18.4%)	20 (16.5%)	24 (22.2%)	21 (17.6%)
NASOPHARYNGITIS	14 (12.3%)	23 (19.0%)	22 (20.4%)	14 (11.8%)
DYSPNEA	10 (8.8%)	5 (4.1%)	5 (4.6%)	20 (16.8%)
UPPER RESPIRATORY TRACT INFECTION	9 (7.9%)	16 (13.2%)	6 (5.6%)	15 (12.6%)
FATIGUE	9 (7.9%)	7 (5.8%)	8 (7.4%)	9 (7.6%)
DIZZINESS	7 (6.1%)	3 (2.5%)	8 (7.4%)	14 (11.8%)
ALT INCREASED	7 (6.1%)	1 (0.8%)	7 (6.5%)	7 (5.9%)
BACK PAIN	6 (5.3%)	6 (5.0%)	2 (1.9%)	7 (5.9%)
SINUSITIS	5 (4.4%)	5 (4.1%)	5 (4.6%)	6 (5.0%)
CHEST DISCOMFORT	5 (4.4%)	4 (3.3%)	0	4 (3.4%)
BRONCHITIS	5 (4.4%)	3 (2.5%)	4 (3.7%)	6 (5.0%)
BRADYCARDIA	5 (4.4%)	0	0	2 (1.7%)
RHINITIS	4 (4.4%)	1 (0.8%)	3 (2.8%)	0
PAIN IN EXTREMITY	4 (4.4%)	1 (0.8%)	0	2 (1.7%)
NAUSEA	4 (4.4%)	8 (6.6%)	2 (1.9%)	4 (3.4%)
JOINT SWELLING	4 (4.4%)	0	0	1 (0.8%)
INSOMNIA	4 (4.4%)	1 (0.8%)	4 (3.7%)	2 (1.7%)
GASTROENTERITIS	4 (4.4%)	4 (3.3%)	6 (5.6%)	2 (1.7%)
EDEMA PERIPHERAL	3 (2.6%)	2 (1.9%)	2 (1.9%)	14 (11.8%)

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
MIGRAINE	3 (2.6%)	0	1 (0.9%)	6 (5.0%)
MACULAR EDEMA	3 (2.6%)	1 (0.8%)	0	0
LYMPHOPENIA	3 (2.6%)	0	1 (0.9%)	1 (0.8%)
INFLUENZA	3 (2.6%)	2 (2.8%)	3 (2.8%)	5 (4.2%)
HYPERCHOLESTEROLEMIA	3 (2.6%)	2 (1.9%)	2 (1.9%)	3 (2.5%)
HEAD INJURY	3 (2.6%)	0	1 (0.9%)	0
DYSPEPSIA	3 (2.6%)	2 (1.9%)	0	1 (0.8%)
DRY MOUTH	3 (2.6%)	1 (0.8%)	0	0
DIARRHEA	3 (2.6%)	9 (7.4%)	3 (2.8%)	3 (2.5%)
DEPRESSION	3 (2.6%)	1 (0.8%)	1 (0.9%)	4 (3.4%)
COUGH	3 (2.6%)	3 (2.5%)	1 (0.9%)	8 (6.7%)
CHOLESTEROL INCREASED	3 (2.6%)	1 (0.8%)	3 (2.8%)	3 (2.5%)
ANXIETY	3 (2.6%)	0	5 (4.6%)	5 (4.2%)

Source: N Categories (USUBJID) of AC-058B201 ADAE where ITTFL and AETREMFL='Y' by AEDECOD and TRT01P

Reviewer Comment: As noted in the analysis of the TEAEs in Study AC-058B201 by body system, it is surprising that the rates of nasopharyngitis and upper respiratory tract infections are lower with ponesimod 20 mg than with placebo. Dyspnea, fatigue, dizziness, transaminase elevations, bradycardia, rhinitis, lymphopenia, macular edema, and insomnia occurred more often with ponesimod than placebo.

As before, a TEAE summary in which related TEAEs are grouped together and only counted once per subject may give a clearer picture of the safety of a medication, so the results of a grouped safety analysis for TEAEs reported by at least 2% of subjects in the placebo-controlled RMS population follow in Table 52.

Table 52. Reviewer Table. Grouped safety analysis of TEAEs, Study AC-058B201

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
infection, all	37 (32.5%)	54 (44.6%)	43 (39.8%)	42 (35.3%)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	27 (23.7%)	36 (29.8%)	30 (27.8%)	28 (23.5%)
Headache	20 (17.5%)	18 (14.9%)	18 (16.7%)	19 (16.0%)
somnolence, fatigue, sedation	12 (10.5%)	7 (5.8%)	9 (8.3%)	7 (.9%)

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
asthenia, fatigue, malaise, weakness, narcolepsy	10 (8.8%)	13 (10.7%)	9 (8.3%)	9 (7.6%)
dyspnea, SOB, respiratory distress	8 (7.0%)	4 (3.3%)	5 (4.6%)	19 (16.0%)
fall, dizziness, balance disorder	8 (7.0%)	5 (4.1%)	11 (10.2%)	14 (11.8%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	8 (7.0%)	5 (4.1%)	11 (10.2%)	14 (11.8%)
GOT, GPT, GGTP, LFTs	7 (6.1%)	1 (0.8%)	9 (8.3%)	11 (9.2%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	7 (6.1%)	11 (9.1%)	7 (6.5%)	6 (5.0%)
dizziness, light-headedness	7 (6.1%)	3 (2.5%)	8 (7.4%)	11 (9.2%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	7 (6.1%)	8 (6.6%)	6 (5.6%)	6 (5.0%)
insomnia, sleep disturbance, abnormal dreams	7 (6.1%)	3 (2.5%)	5 (4.6%)	2 (1.7%)
Arrhythmia	6 (5.3%)	3 (2.5%)	3 (2.8%)	3 (2.5%)
chest pain (non-cardiac or unknown)	6 (5.3%)	5 (4.1%)	3 (2.8%)	6 (5.0%)
Bradycardia	5 (4.4%)	0	0	2 (1.7%)
Dry mouth, dry lips, thirst	4 (3.5%)	1 (0.8%)	0	0
Nausea, vomiting	4 (3.5%)	7 (5.8%)	4 (3.7%)	5 (4.2%)
anxiety, nervousness, panic attacks	4 (3.5%)	1 (0.8%)	5 (4.6%)	4 (3.4%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	4 (3.5%)	4 (3.3%)	4 (3.7%)	5 (4.2%)
edema, non-pulm, fluid retention, overload	4 (3.5%)	2 (1.7%)	2 (1.9%)	16 (13.4%)
infection, viral	4 (3.5%)	13 (10.7%)	8 (7.4%)	10 (8.4%)
Insomnia	4 (3.5%)	1 (0.8%)	3 (2.8%)	2 (1.7%)
rash, eruption, dermatitis	4 (3.5%)	2 (1.7%)	1 (0.9%)	0

AEDECOD	Ponesimod 20 mg (n=114)	Placebo (n=121)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
abdominal pain, distension, bloating, spasm, IBS, megacolon	3 (2.6%)	5 (4.1%)	2 (1.9%)	5 (4.2%)
Cough	3 (2.6%)	2 (1.7%)	1 (0.9%)	8 (6.7%)
Depression	3 (2.6%)	1 (0.8%)	1 (0.9%)	4 (3.4%)
eye other	3 (2.6%)	5 (4.1%)	6 (5.6%)	2 (1.7%)
Influenza	3 (2.6%)	2 (1.7%)	3 (2.8%)	5 (4.2%)
leukopenia (neutropenia and/or lymphopenia)	3 (2.6%)	0	3 (2.8%)	2 (1.7%)
Lymphopenia	3 (2.6%)	0	1 (0.9%)	2 (1.7%)
macular degeneration, maculopathy	3 (2.6%)	1 (0.8%)	1 (0.9%)	0
Migraine	3 (2.6%)	0	1 (0.9%)	5 (4.2%)

Reviewer Comment: As noted in the analysis of the TEAEs in Study AC-058B201 by AEBODSYS and AEDECOD, it is surprising that the rates of infection were lower with ponesimod 20 mg than with placebo in Study AC-058B201. Once again, dyspnea, transaminase elevations, fatigue, dizziness, bradyarrhythmia, macular edema, and lymphopenia occurred more commonly with ponesimod 20 mg; there is also a suggestion of a signal for anxiety, depression, and headaches with ponesimod.

TEAE, uncontrolled RMS population

The numbers (and percentages) of subjects who experienced a TEAE in the uncontrolled RMS population (Studies AC-058B202 and AC-058B303) are stratified by primary System Organ Class (SOC) in Table 53. TEAEs reported by more than 2% of subjects in this population are delineated in Table 54.

Table 53. TEAEs stratified by SOC, uncontrolled RMS population

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Infections and infestations	327 (28.5%)	87 (62.6%)	93 (61.6%)
Investigations	189 (16.5%)	41 (29.5%)	49 (32.5%)
Nervous system disorders	142 (12.4%)	63 (45.3%)	53 (35.1%)
Musculoskeletal and connective tissue disorders	120 (10.5%)	47 (33.8%)	39 (25.8%)
Blood and lymphatic system disorders	119 (10.4%)	15 (10.8%)	18 (11.9%)

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Gastrointestinal disorders	112 (9.8%)	36 (25.9%)	44 (29.1%)
Respiratory, thoracic and mediastinal disorders	90 (7.8%)	38 (27.3%)	45 (29.8%)
General disorders and administration site conditions	84 (7.3%)	20 (14.4%)	30 (19.9%)
Psychiatric disorders	71 (6.2%)	22 (15.8%)	23 (15.2%)
Skin and subcutaneous tissue disorders	66 (5.7%)	33 (23.7%)	27 (17.9%)
Eye disorders	65 (5.7%)	27 (19.4%)	28 (18.5%)
Injury, poisoning and procedural complications	65 (5.7%)	40 (28.8%)	28 (18.5%)
Metabolism and nutrition disorders	59 (5.1%)	23 (16.5%)	15 (9.9%)
Vascular disorders	44 (3.8%)	20 (14.4%)	20 (13.2%)
Reproductive system and breast disorders	41 (3.6%)	22 (15.8%)	17 (11.3%)
Neoplasms benign, malignant and unspecified	34 (3.0%)	16 (11.5%)	21 (13.9%)
Cardiac disorders	26 (2.3%)	14 (10.1%)	7 (4.6%)
Renal and urinary disorders	21 (1.8%)	11 (7.9%)	6 (4.0%)
Ear and labyrinth disorders	20 (1.7%)	10 (7.2%)	8 (5.3%)
Hepatobiliary disorders	18 (1.6%)	4 (2.9%)	4 (2.6%)
Surgical and medical procedures	13 (1.1%)	4 (2.9%)	2 (1.3%)
Endocrine disorders	7 (0.6%)	3 (2.2%)	1 (0.7%)
Immune system disorders	6 (0.5%)	3 (2.2%)	1 (0.7%)
Pregnancy, puerperium and perinatal conditions	4 (0.3%)	1 (0.7%)	2 (1.3%)
Congenital, familial and genetic disorders	3 (0.3%)	0	1 (0.7%)

Source: N Categories of ISS ADAE (supplement) where SAFFL and TRTEMFL ='Y,' and ACAT1='Starts in Extension' by AEBODSYS and TRT01A

Reviewer Comment: Although less information can be gleaned from a safety analysis of an uncontrolled population, Table 53 suggests that TEAEs in the "Infections," "Investigations," and "Nervous system disorders" body systems are common in the long-term extensions of Studies AC-058B201 and AC-058B301. Since Study AC-058B201 started much earlier than Study AC058B301, subjects could remain in the AC-058B202

extension for a longer period of time, likely explaining the higher rates of some TEAEs in the ponesimod 10 and 40 mg arms of this uncontrolled RMS pool.

Table 54.Common TEAEs, uncontrolled RMS population

AEDECOD	Ponesimod 20 mg N=1148	Ponesimod 10 mg N=139	Ponesimod 40 mg N=151
Nasopharyngitis	105 (9.1%)	38 (27.3%)	37 (24.5%)
ALT increased	89 (7.8%)	13 (9.4%)	14 (9.3%)
Lymphopenia	82 (7.1%)	0	6 (4.0%)
Upper respiratory infection	57 (5.0%)	25 (18.0%)	32 (21.2%)
Headache	54 (4.7%)	25 (18.0%)	26 (17.2%)
Back pain	40 (3.5%)	14 (10.1%)	15 (9.9%)
Lymphocyte count decreased	37 (3.2%)	1 (0.7%)	2 (1.3%)
Hypertension	36 (3.1%)	12 (8.6%)	14 (9.3%)
Urinary tract infection	36 (3.1%)	18 (12.9%)	19 (12.6%)
Fatigue	35 (3.0%)	6 (4.3%)	9 (6.0%)
Bronchitis	28 (2.4%)	18 (12.9%)	17 (11.3%)
Influenza	28 (2.4%)	17 (12.2%)	16 (10.6%)
Anemia	25 (2.2%)	6 (4.3%)	6 (4.0%)
Arthralgia	25 (2.2%)	13 (9.4%)	9 (6.0%)
Rhinitis	25 (2.2%)	12 (8.6%)	2 (1.3%)
Hypercholesterolemia	24 (2.1%)	11 (7.9%)	7 (4.6%)
Insomnia	24 (2.1%)	6 (4.3%)	8 (5.3%)

Source: N Categories of ISS ADAE (supplement) where SAFFL, TRTEMFL ='Y,' and ACAT1='Starts in Extension' by AEDECOD and TRT01A.

Reviewer Comment: With the caveats previously noted, this analysis of TEAEs in the uncontrolled RMS pool further suggest that lymphopenia is a risk with ponesimod, which is not surprisingly given its purported mechanism of action.

As before, a TEAE summary in which related TEAEs are grouped together and only counted once per subject may give a clearer picture of the safety of a medication, so a grouped safety analysis for TEAEs reported by at least 2% of subjects in the uncontrolled RMS population follows in Table 55.

Table 55. Reviewer Table. Grouped safety analysis of TEAEs, uncontrolled RMS population

AEDECOD	Ponesimod 20 mg (n=1148)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
infection, all	326 (28.4%)	87 (62.6%)	94 (62.3%)

AEDECOD	Ponesimod 20 mg (n=1148)	Ponesimod 10 mg (n=108)	Ponesimod 40 mg (n=119)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	228 (19.9%)	75 (54.0%)	72 (47.7%)
leukopenia (neutropenia and/or lymphopenia)	130 (11.3%)	6 (4.3%)	11 (7.3%)
Lymphopenia	118 (10.3%)	1 (0.7%)	8 (5.3%)
GOT, GPT, GGTP, LFTs	114 (9.9%)	14 (10.1%)	19 (12.6%)
infection, viral	100 (8.7%)	36 (25.9%)	38 (25.2%)
Headache	65 (5.7%)	30 (21.6%)	31 (20.5%)
UTI	55 (4.8%)	21 (15.1%)	27 (17.9%)
asthenia, fatigue, malaise, weakness, narcolepsy	52 (4.5%)	9 (6.5%)	14 (9.3%)
diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	46 (4.0%)	22 (15.8%)	17 (11.3%)
hypertension, BP increased	40 (3.5%)	14 (10.1%)	18 (11.9%)
somnolence, fatigue, sedation	40 (3.5%)	6 (4.3%)	11 (7.3%)
abdominal pain, distension, bloating, spasm, IBS, megacolon	36 (3.1%)	13 (9.4%)	15 (9.9%)
arthralgia, arthritis, arthrosis	35 (3.0%)	18 (12.9%)	13 (8.6%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	35 (3.0%)	21 (15.1%)	18 (11.9%)
Anemia	33 (2.9%)	11 (7.9%)	8 (5.3%)
insomnia, sleep disturbance, abnormal dreams	32 (2.8%)	11 (7.9%)	9 (6.0%)
eye other	31 (2.7%)	18 (12.9%)	14 (9.3%)
fall, dizziness, balance disorder	31 (2.7%)	16 (11.5%)	16 (10.6%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	31 (2.7%)	16 (11.5%)	16 (10.6%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duoden	28 (2.4%)	13 (9.4%)	15 (9.9%)
Influenza	28 (2.4%)	17 (12.2%)	16 (10.6%)
herpes virus	26 (2.3%)	10 (7.2%)	13 (8.6%)
infection, fungal	26 (2.3%)	10 (7.2%)	13 (8.6%)
anxiety, nervousness, panic attacks	25 (2.2%)	3 (2.2%)	5 (3.3%)
Insomnia	24 (2.1%)	6 (4.3%)	8 (5.3%)

Reviewer Comment: Given the safety profile of ponesimod and other S1P receptor modulators, it is not surprising that infections, lymphopenia, transaminase elevations, and hypertension are among the most common TEAEs in Table 55.

TEAEs, plaque psoriasis population

The numbers (and percentages) of subjects who experienced a TEAE in the plaque psoriasis population (Studies AC-058A200 and AC-058A201) are stratified by primary System Organ Class (SOC) in Table 56, and TEAEs reported by more than 2% of subjects in this population are delineated in Table 57.

Table 56. Reviewer Table. TEAEs stratified by SOC, plaque psoriasis population

AEBODSYS	Ponesimod 20 mg n=171	Placebo N=88	Ponesimod 40 mg n=133
Infections and infestations	35 (20.5%)	18 (20.5%)	23 (17.3%)
Investigations	29 (17.0%)	10 (11.4%)	27 (20.3%)
Nervous system disorders	27 (15.8%)	10 (11.4%)	18 (13.5%)
General disorders and administration site conditions	26 (15.2%)	9 (10.2%)	25 (18.8%)
Respiratory, thoracic and mediastinal disorders	20 (11.7%)	6 (6.8%)	43 (32.3%)
Cardiac disorders	16 (9.4%)	6 (6.8%)	22 (16.5%)
Gastrointestinal disorders	13 (7.6%)	8 (9.1%)	8 (6.0%)
Musculoskeletal and connective tissue disorders	10 (5.8%)	7 (8.0%)	8 (6.0%)
Skin and subcutaneous tissue disorders	9 (5.3%)	9 (10.2%)	9 (6.8%)
Ear and labyrinth disorders	7 (4.1%)	2 (2.3%)	2 (1.5%)
Eye disorders	6 (3.5%)	2 (2.3%)	8 (6.0%)
Vascular disorders	6 (3.5%)	1 (1.1%)	7 (5.3%)
Metabolism and nutrition disorders	5 (2.9%)	1 (1.1%)	7 (5.3%)

Source: N Categories AES_POOL where SAFETY and TRTEM7 =1 by AEBODSYS and P_ANAGC

Reviewer Comment: Since this safety analysis is of a different disease state (plaque psoriasis), its applicability to an RMS population may be reduced somewhat; however, it again shows that TEAEs referable to the "Investigations," "Nervous system disorders," "General disorders," "Respiratory disorders," and "Cardiac disorders" body systems are more common with ponesimod. Although this population is smaller than that of the RMS pools, this reviewer is surprised that the rate of TEAEs referable to the "Infections" body system is not higher for ponesimod 20 mg than it is for placebo.

Table 57. Reviewer Table. Common TEAEs, plaque psoriasis population

AEDECOD	Ponesimod 20 mg n=171	Placebo n=88	Ponesimod 40 mg n=171
ALT Increased	18 (10.5%)	2 (2.3%)	14 (10.5%)
Headache	17 (9.9%)	8 (9.1%)	8 (6.0%)
Disease Progression	14 (8.2%)	3 (3.4%)	16 (12.0%)
Dyspnea	14 (8.2%)	1 (1.1%)	35 (26.3%)
Nasopharyngitis	11 (6.4%)	6 (6.8%)	6 (4.5%)
Dizziness	10 (5.8%)	1 (1.1%)	6 (4.5%)
AST Increased	7 (4.1%)	2 (2.3%)	9 (6.8%)
Vertigo	7 (4.1%)	0	2 (1.5%)
Bradycardia	6 (3.5%)	1 (1.1%)	6 (4.5%)
Pruritus	6 (3.5%)	4 (4.5%)	3 (2.3%)
AV Block 2nd Degree	5 (2.9%)	1 (1.1%)	4 (3.0%)
Arthralgia	4 (2.3%)	2 (2.3%)	3 (2.3%)
Cough	4 (2.3%)	3 (3.4%)	3 (2.3%)
Enterovirus Infection	4 (2.3%)	0	0
Fatigue	4 (2.3%)	0	1 (0.8%)
Hypertension	4 (2.3%)	0	5 (3.8%)

Source: N Categories AES_POOL where SAFETY and TRTEM7 =1 by AEDECOD and P_ANAGC

Reviewer Comment: Although it is surprising that nasopharyngitis did not occur more commonly in subjects receiving ponesimod given its purported mechanism of action, ALT/AST increases, dyspnea, dizziness, vertigo, bradycardia, 2nd degree AV block, hypertension, fatigue, and enteroviral infections did occur more commonly in subjects randomized to ponesimod in the pooled plaque psoriasis population.

A TEAE summary in which similar TEAEs are grouped together may give a clearer picture of the safety of a medication, so the results of a grouped safety analysis for those TEAEs reported by at least 2% of subjects in the plaque psoriasis pool follow in Table 58.

Table 58. Reviewer Table. Grouped safety analysis of TEAEs, plaque psoriasis population

AEDECOD	Ponesimod 20 mg n=171	Placebo n=88	Ponesimod 40 mg n=171
infection, all	32 (18.7%)	18 (20.5%)	24 (18.0%)
GOT, GPT, GGTP, LFTs	23 (13.5%)	4 (4.5%)	15 (11.3%)
URI, cold, rhinitis, upper resp tract infection, flu-like illness	19 (11.1%)	12 (13.6%)	16 (12.0%)
Headache	17 (9.9%)	8 (9.1%)	8 (6.0%)

AEDECOD	Ponesimod 20 mg n=171	Placebo n=88	Ponesimod 40 mg n=171
dyspnea, SOB, respiratory distress	15 (8.8%)	1 (1.1%)	35 (26.3%)
dizziness, light-headedness	10 (5.8%)	1 (1.1%)	6 (4.5%)
fall, dizziness, balance disorder	10 (5.8%)	1 (1.1%)	7 (5.3%)
fall, dizziness, balance disorder, gait disturbance, difficulty walking	10 (5.8%)	1 (1.1%)	7 (5.3%)
AV block	9 (5.3%)	1 (1.1%)	4 (3.0%)
conduction disturbance	9 (5.3%)	1 (1.1%)	5 (3.8%)
asthenia, fatigue, malaise, weakness, narcolepsy	8 (4.7%)	2 (2.3%)	2 (1.5%)
infection, viral	8 (4.7%)	3 (3.4%)	4 (3.0%)
Arrhythmia	7 (4.1%)	4 (4.5%)	18 (13.5%)
Bradycardia	7 (4.1%)	1 (1.1%)	10 (7.5%)
vertigo; vestibular dysfunction	7 (4.1%)	2 (2.3%)	2 (1.5%)
hypertension, BP increased	6 (3.5%)	2 (2.3%)	7 (5.3%)
Pruritis	6 (3.5%)	5 (5.7%)	3 (2.3%)
somnolence, fatigue, sedation	5 (2.9%)	1 (1.1%)	3 (2.3%)
arthralgia, arthritis, arthrosis	4 (2.3%)	2 (2.3%)	3 (2.3%)
bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	4 (2.3%)	3 (3.4%)	4 (3.0%)
Cough	4 (2.3%)	3 (3.4%)	3 (2.3%)
dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenal	4 (2.3%)	2 (2.3%)	4 (3.0%)
eye other	4 (2.3%)	2 (2.3%)	2 (1.5%)

Reviewer Comment: Given the purported mechanism of ponesimod and the risk of infection associated with other S1P receptor modulators, it is again surprising that the risk of infection does not appear to be increased in subjects randomized to ponesimod in this pooled plaque psoriasis population. Conversely, this analysis further suggests that ponesimod has increased risks of transaminase elevations, dyspnea, dizziness, bradyarrhythmia and AV block, hypertension, dizziness, and fatigue.

8.4.6. **Laboratory Findings**

Although transaminase elevations and lymphopenia are known to occur with other S1P receptor modulators, care is taken to avoid focusing exclusively on these particular safety signals. In this section, descriptive statistics on laboratory analyses relevant to major organ systems (hepatobiliary, pancreatic, renal, and hematologic) are presented. Narratives of cases identified to be of special interest but that have not been previously discussed are reviewed.

Hepatobiliary

Elevated transaminases and hepatic injury are noted in the warnings and precautions section of the labeling for three other S1P receptor modulators and are thus of interest with ponesimod. Descriptive statistics (and the number of subjects with notable abnormalities) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), and alkaline phosphatase (ALP) assessments in Study AC-058B301 are shown in Table 59.

Table 59. Reviewer Table. Hepatobiliary Labs, Study AC-058B301

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Alanine Aminotransferase (ALT); reference range: 0-44 U/L[1]		
Mean (std) (IU/L)	36.5 (27.5)	29.0 (26.6)
Median (IU/L)	28	23
Min, max (IU/L)	4, 552	5, 1180
# subjects > 5x ULN	11	11
# subjects > 10x ULN	1	8
Aspartate Aminotransferase (AST); reference range: 14-39 U/L[1]		
Mean (std) (IU/L)	26.2 (14.1)	23.3 (15.8)
Median (IU/L)	23	21
Min, max (IU,L)	6, 549	3, 925
# subjects > 5x ULN	3	10
# subjects > 10x ULN	2	3
Total Bilirubin (TB); reference range: 5.1–20.5 umol/L		
Mean (std) (umol/L)	10.8 (5.5)	10.6 (4.6)
Median (umol/L)	9.6	9.7
Min, max (umol/L)	1.7, 64.8	1, 45.6
# subjects > 2x ULN	8	2
# subjects > 3x ULN	1	0
Alkaline Phosphatase (ALP); reference range: 42-129 U/L		
Mean (std) (IU/L)	66.5 (24.6)	64.4 (20.8)
Median (IU/L)	62	61
Min, max (IU,L)	2, 361	14, 278
# subjects > 2x ULN	4	1
# subjects > 3x ULN	0	0

Source: B301 ADLB where SAFFL='Y' and AVISIT contains 'Week' by TRT01A.

[1] Several normal ranges are given, so the specified range encompasses most of the given ranges.

Reviewer Comment: Not surprisingly given the risk of transaminase elevations with other S1P receptor modulators (and the risk of hepatotoxicity with teriflunomide), a few subjects in each arm of the study had notable transaminase or bilirubin elevations. Brief narratives of those subjects who had an AST/ALT > 5x ULN during Study AC-058B301 and have not previously described in this review follow:

- At enrollment, Subject (b) (6) was a 26 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and found to have asymptomatic transaminase elevations (ALT 226 U/L and AST 90 U/L) on Study Day 31. Since his TB was normal, no action was taken with the study medication, and this TEAE was considered resolved on Study Day 77.

- At enrollment, Subject (b) (6) was a 39 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and was found to have asymptomatic transaminase elevations (ALT 227 U/L and AST 134 U/L) on Study Day 57. Since his TB was normal, no action was taken with the study medication; however, his transaminases remained elevated until he completed the study drug on Day 764.

- At enrollment, Subject (b) (6) was a 20 yo man with mildly elevated transaminases (AST 86 U/L and AST 49 U/L) and TB (TB 22.3 umol/L) at baseline who was randomized to ponesimod 20 mg in Study AC-058B301 and was found to have asymptomatic transaminase elevations on Study Days 60 (ALT 192 U/L and AST 96 U/L) and 98 (ALT 230 U/L and AST 120 U/L). Although his TB was 1.5 x ULN (31.3umol/L) on Study Day 63, no action was taken with the study drug.

- At enrollment, Subject (b) (6) was a 42 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and found to have asymptomatic transaminase elevations (ALT 242 U/L and AST 118 U/L) on Study Day 31. Since his TB was normal, no action was taken with the study medication, and the AST and ALT elevations were considered resolved on Study Days 86 and 157, respectively. He also had a mild ALT elevation (111 U/L) on Study Day 335.

- At enrollment, Subject (b) (6) was a 25 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and found to have transaminase (ALT 247 U/L and AST 145 U/L) and ALP (149 U/L) elevations on Study Day 71. Since her TB was normal, no action was taken with the study medication, and the event was considered resolved on Study Day 77.

- At enrollment, Subject (b) (6) was a 35 yo woman who was randomized to ponesimod 20 mg in Study AC-058B301 and found to have transaminase elevations (ALT 149 U/L and AST 70 U/L) on Study Day 71. Since her TB was normal, no action was taken with the study medication. On Study Day 94, the subject experienced nausea and right upper quadrant abdominal discomfort, so the study drug was discontinued, after which she was found to

have transaminase elevations (ALT 430 U/L and AST 203 U/L with a normal bilirubin), cholelithiasis, and left urolithiasis.

- At enrollment, Subject (b) (6) was a 34 yo man who was randomized to ponesimod 20 mg in Study AC-058B301 despite an elevation in TB (31.3 umol/L) at baseline and who was found to have asymptomatic transaminase elevations (ALT 288 U/L and AST 95 U/L) on Study Day 113. Since his TB was normal at the time, no action was taken with the study medication, and the event was considered resolved on Study Day 120.

- At enrollment, Subject (b) (6) was a 27 yo man who was randomized to ponesimod 20 mg in Study AC-058B301. On Study Day 95, the subject experienced dyspnea and chest pain and was noted to have elevated transaminases (ALT 241 U/L and AST 80 U/L) the next day. Since his TB was normal, no action was taken with the study drug. For unclear reasons, the subject discontinued the study drug on Study Day 159 and started the accelerated elimination procedure; however, he was again noted to have transaminase elevations (ALT 295 U/L, AST 120 U/L), albeit with a normal TB, on Study Day 167. His transaminases were normal on Study Day 188.

  Reviewer Comment: These narratives further suggest that ponesimod can be associated with transaminase elevations. Although Subject (b) (6) had an ALT > 3x ULN and a TB of 1.5 x ULN, the subject's baseline transaminase and TB abnormalities suggest that this may not be a Hy's law case of drug-induced liver injury.

Narratives are either not provided for (or do not discuss) the eight subjects randomized to ponesimod who had a TB > 2x ULN during the study; however, review of the ADLB dataset shows that seven of these eight subjects had an elevated bilirubin at screening or baseline, and the SCS suggests that five had a known history of Gilbert's syndrome. The remaining subject (b) (6) has been previously described in this review and also had an ALT elevation > 3x ULN early in the study; however, his ALT and AST were elevated at baseline.

Reviewer Comment: The pre-existing ALT/AST elevations confounds the interpretation of Hy's law in Subject (b) (6) so this reviewer agrees with the SCS that there are no clear Hy's law cases of drug-induced liver injury in Study AC-058B301.

Descriptive statistics (and the number of subjects with notable abnormalities) for ALT, AST, TB, and ALP assessments during Study AC-058B201 are shown in Table 60.

Table 60. Reviewer Table. Hepatobiliary Labs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Alanine Aminotransferase (ALT); reference range: 0-55 IU/L				
Mean (std) (IU/L)	31.1 (27.0)	21.3 (15.5)	34.0 (38.4)	33.3 (31.8)
Median (IU/L)	22	17	24	24
Min, max (IU,L)	5, 250	5, 157	7, 562	4, 331
# subjects > 5x ULN	0	0	3	2
# subjects > 10x ULN	0	0	1	0
Aspartate Aminotransferase (AST); reference range: 0-45 IU/L				
Mean (std) (IU/L)	23.3 (11.3)	19.8 (8.7)	25.4 (20.2)	25.6 (13.4)
Median (IU/L)	20	18	21	21
Min, max (IU,L)	9, 103	8, 131	9, 350	10, 176
# subjects > 5x ULN	0	0	1	0
# subjects > 10x ULN	0	0	0	0
Total Bilirubin (TB); reference range: 5-26.0 umol/L				
Mean (std) (umol/L)	9.6 (5.0)	9.9 (5.4)	9.0 (3.5)	9.8 (5.1)
Median (umol/L)	8.4	8.6	8.6	8.6
Min, max (umol/L)	1.5, 36	1.7, 47.5	1.7, 26.4	2.5, 33.5
# subjects > 2x ULN	0	0	0	0
Alkaline Phosphatase (ALP); reference range: 37-147 IU/L				
Mean (std) (IU/L)	60.7 (20.3)	60.3 (17.4)	65.4 (21.3)	58.9 (24.0)
Median (IU/L)	57	60	63	55
Min, max (IU,L)	22, 197	22, 126	11, 154	25, 365
# subjects > 2x ULN	0	0	0	1

Source: B201 LAB where ITTFL='Y' and TRTEM7=1 by TRT01P

Reviewer Comment: Not surprisingly given the risk of transaminase elevations with other S1P receptor modulators, a few subjects in each arm of Study AC-058B201 had notable transaminase elevations; however, none of subjects in the study had a TB >2X ULN, and none in the ponesimod 20 mg arm had an ALT or AST above 5x ULN. Since none of the subjects in Study AC-048B201 had a TB > 2x ULN, it can be inferred that none met Hy's law criteria for DILI.

Given the apparent signal for transaminase elevations with ponesimod and the potential severity of drug-induced liver injury, the hepatobiliary labs are also explored in the uncontrolled RMS population (long-term extensions of Studies AC-058B301 and AC-058B201).

Table 61. Reviewer Table. Hepatobiliary Labs, uncontrolled RMS population

	Ponesimod 20 mg n=1148	Ponesimod 10 mg n=139	Ponesimod 40 mg n=151
Alanine Aminotransferase (ALT); reference range: 0-55 IU/L			
Mean (std) (IU/L)	38.2 (31.9)	35.1 (26.3)	36.7 (26.5)
Median (IU/L)	29	28	29
Min, max (IU,L)	4, 1388	5, 413	4, 303
# subjects > 3x ULN	76	12	12
# subjects > 5x ULN	16	3	1
# subjects > 10x ULN	2	0	0
Aspartate Aminotransferase (AST); reference range: 0-45 IU/L			
Mean (std) (IU/L)	26.8 (14.5)	25.9 (13.2)	26.3 (13.3)
Median (IU/L)	23	23	23
Min, max (IU,L)	4, 810	6, 441	9, 543
# subjects > 3x ULN	16	5	3
# subjects > 5x ULN	6	1	1
# subjects > 10x ULN	1	0	1
Total Bilirubin (TB); reference range: 5.0-20.5 umol/L[1,2]			
Mean (std) (umol/L)	10.6 (5.3)	10.1 (4.8)	11.2 (5.9)
Median (umol/L)	9.5	9.0	9.6
Min, max (umol/L)	1.4, 64.8	1.7, 47.9	1.7, 52.2
# subjects > 2x ULN	11	1	2
# subjects > 3x ULN	1	0	0
Alkaline Phosphatase (ALP); reference range: 37-147 IU/L			
Mean (std) (IU/L)	69.0 (27.6)	72.4 (27.9)	68.0 (24.8)
Median (IU/L)	63	68	63
Min, max (IU,L)	2, 423	11, 531	10, 264
# subjects > 2x ULN	7	1	0

Source: ISS ADLB (supplement) where STUDYID ='AC-058B202' or 'AC-058B303,' SAFFL='Y,' and AVISIT contains 'Week' by TRT01A.
[1] One TB value of 11,000 was deemed in error and discarded from analysis.
[2] Some TBs had a range of 5.0 – 26.0 umol/L.

Reviewer Comment: There are cases of transaminase and TB elevations in the uncontrolled RMS population. Six of the eleven cases of TB elevations with ponesimod 20 mg had a history of Gilbert's disease or TB elevations at baseline, and three did not have concomitant transaminase elevations > 3x ULN; of the other two, one (Subject (b) (6), hepatitis C) has been previously discussed, and Subject (b) (6) is discussed below. Many of the cases of subjects with transaminases above 5x ULN have been discussed previously, but those that have not are also described below.

- At enrollment, Subject (b) (6) was a 32yo man who was randomized to ponesimod 20 mg in Study AC-058B301 and remained on ponesimod 20 mg in its AC-058B303 extension. At screening and on Day 10 of Study AC-058B303, he had a mild TB elevation (1.3 and 1.6x ULN, respectively); on Study Day 280 and 420 of this extension, his ALTs were mildly elevated at 131 and 120 U/L, respectively, and his TBs were 30.7 and 30.4 umol/L (1.5x ULN). No action was taken with the study drug.

  Reviewer Comment: As a narrative for this subject appeared to be missing from the CSR for Study AC-058B303, an IR was sent to the Applicant on 23JUL200 requesting it; his baseline TB elevation and relatively mild transaminase elevations are reassuring.

- At enrollment, Subject (b) (6) was a 38 yo man who was randomized to placebo in Study AC-058B201 and transitioned to ponesimod 20 mg for the three treatment periods of its AC-058B202 extension. On Day 89 of AC-058B202, he experienced a brief, asymptomatic increase in his transaminases (ALT 275 U/L, AST 129 U/L). His TB was normal throughout the extension study.

- At enrollment, Subject (b) (6) was a 38 yo man who was randomized to ponesimod 20 mg in AC-058B201 and remained on that dose of ponesimod for the three treatment periods of its AC-058B202 extension. At multiple times during the extension, he was noted to have transaminase elevations, including Study Day 27 (ALT 147 U/L, AST 54 U/L), 267 (ALT 172 U/L), 419 (ALT 455 U/L, AST 310 U/L), 748 (ALT 140 U/L, AST 121 U/L), 1099 (ALT 231 U/L, AST 127 U/L), 1680 (ALT 171 U/L, AST 60 U/L), and 2863 (ALT 216 U/L, AST 120 U/L). Since the reference range for the lab that analyzed his TB was 5.0-26.0, he did not have a TB > 1.5x ULN.

- At enrollment, Subject (b) (6) was a 31 yo man who was randomized to teriflunomide in Study AC-058B301 and transitioned to ponesimod in its AC-058B303 extension. On Study Day 111 of the extension, he was noted to have a mild transaminase elevation (ALT 108 U/L, AST 44 U/L) with a normal TB; subsequently, on Study Day 147, he was noted to have a further transaminase elevation (AST 306 U/L, AST 109 U/L) with a mildly increase TB of 22.8 umol/L (normal 5.0-20.5 umol/L). His TB was again normal on Study Day 153, his AST was normal on Study Day 159, but his ALT remained elevated (< 3x ULN).

- At enrollment, Subject (b) (6) was a 31 yo man who was randomized to teriflunomide in Study AC-058B301 and transitioned to ponesimod in its AC-058B303 extension. On Study Day 169 of the extension, he was noted to have a transaminase elevation (ALT 307 U/L, AST 105 U/L) with a normal TB; his transaminases had normalized when rechecked on Study Day 176.

- At enrollment, Subject (b) (6) was a 23 yo man who was randomized to ponesimod 20 mg in AC-058B201 and remained on that dose of ponesimod for the three treatment periods of its AC-058B202 extension. On Study Day 3039, he was noted to have an asymptomatic transaminase elevation (AST 265 U/L, ALT 70 U/L) with a normal bilirubin; with an AST/ALT ratio > 3, this transaminase elevation may have represented an effect of alcohol, and it had essentially resolved on Study Day 3045.

- Although this reviewer could not locate a narrative for Subject (b) (6), she had an elevated ALT of 471 U/L in the ISS ADLB dataset; however, her TBs were normal.

Reviewer Comment: These remaining cases of transaminase elevations do not appear to meet Hy's law criteria for DILI.

Electrolytes

Similarly, descriptive statistics of the electrolyte data for the safety population of Studies AC-058B301 and AC-058B201 are shown in Table 62 and Table 63.

Table 62. Reviewer Table. Electrolytes, Study AC-058B301

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Sodium; reference range: 136 – 145 mmol/L		
Mean (std) (mmol/L)	141.8 (2.1)	142.1 (2.0)
Median (mmol/L)	142	142
Min, max (mmol/L)	122, 160	131, 152
# subjects <128 mmol/L	1 (0.2%)	0
# subjects > 150 mmol/L	2 (0.4%)	4 (0.7%)
Potassium; reference range: 3.5 – 5.1 mmol/L		
Mean (std) (mmol/L)	4.5 (0.4)	4.4 (0.4)
Median (mmol/L)	4.4	4.3
Min, max (mmol/L)	2.8, 6.6	3.1, 6.6
# subjects < 3.5 mmol/L	5 (0.9%)	14 (2.5%)
# subjects > 6.0 mmol/L	8 (1.4%)	16 (2.8%)
Chloride; reference range: 99-109 mmol/L		
Mean (std) (mmol/L)	106.7 (2.3)	107.5 (2.2)
Median (mmol/L)	107	108
Min, max (mmol/L)	85, 116	96, 118
Calcium; reference range: 2.15-2.55 mmol/L		
Mean (std) (mmol/L)	2.28 (0.10)	2.28 (0.11)
Median (mmol/L)	2.28	2.28
Min, max (mmol/L)	1.56, 2.70	1.44, 2.87

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
# subjects < 2.0	30 (5.3%)	29 (5.1%)
# subjects > 2.7	0	2 (0.4%)

Source: B301 ADLB where SAFFL and TRTEMFL='Y' and AVISIT contains 'Week' by TRT01A.

Table 63. Reviewer Table. Electrolytes, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Sodium; reference range: 135 – 148 mmol/L				
Mean (std) (mmol/L)	140.9 (2.2)	140.6 (2.0)	141.0 (2.0)	140.9 (2.2)
Median (mmol/L)	141	141	141	141
Min, max (mmol/L)	133, 147	135, 148	134, 148	132, 148
# subjects <128 mmol/L	0	0	0	0
# subjects > 150 mmol/L	0	0	0	0
Potassium; reference range: 3.5 – 5.3 mmol/L				
Mean (std) (mmol/L)	4.4 (0.4)	4.4 (0.3)	4.4 (0.4)	4.4 (0.4)
Median (mmol/L)	4.4	4.3	4.3	4.3
Min, max (mmol/L)	3.1, 6.0	3.7, 4.6	3.6, 5.7	3.5, 5.8
# subjects < 3.5 mmol/L	2 (1.8%)	0	0	0
# subjects > 6.0 mmol/L	0	0	0	0
Chloride; reference range: 98-109 mmol/L				
Mean (std) (mmol/L)	106.2 (2.3)	105.6 (2.4)	105.8 (2.1)	106.2 (2.5)
Median (mmol/L)	106	106	106	106
Min, max (mmol/L)	98, 113	100, 113	100, 112	96, 113
Calcium; reference range: 2.10-2.64 mmol/L				
Mean (std) (mmol/L)	2.28 (0.10)	2.31 (0.11)	2.28 (0.12)	2.27 (0.11)
Median (mmol/L)	2.28	2.31	2.29	2.27
Min, max (mmol/L)	1.98, 2.58	1.98, 2.64	1.90, 2.67	1.78, 2.57
# subjects < 2.0	1 (0.9%)	2 (1.7%)	4 (3.7%)	7 (5.9%)
# subjects > 2.7	0	0	0	0

Source: B201 LAB where ITTFL='Y' and TRTEM7=1 by TRT01P

Reviewer Comment: Since there does not appear to be a safety signal for abnormal serum electrolytes with ponesimod 20 mg in Studies AC058B301 or AC-058B201 (or with the other approved S1P receptor modulators), the utility of further analyses of the electrolyte labs in the uncontrolled RMS population seems limited.

Renal

Descriptive statistics of the renal labs for the safety population of Studies AC-058B301 and AC-058B201 are shown in Table 64 and Table 65.

Table 64. Reviewer Table. Renal Labs, Study AC-058B301

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Serum Creatinine; reference range: 44 – 115 umol/L[1]		
Mean (std) (mmol/L)	66.7 (12.5)	64.3 (12.4)
Median (mmol/L)	65	63
Min, max (mmol/L)	32, 146	25, 115
# subjects > 150 but baseline < 120 umol/L	0	0
Blood Urea Nitrogen (BUN); reference range: 3.2 – 8.2 mmol/L		
Mean (std) (mmol/L)	4.8 (1.3)	4.7 (1.3)
Median (mmol/L)	4.7	4.7
Min, max (mmol/L)	1.5, 10.8	1.5, 10.9
# subjects > 1.5x ULN	0	0
Urine Protein; reference range = {Negative, Trace}		
# subjects with (+) urine protein	33	52

Source: B301 ADLB where SAFFL='Y' and AVISIT contains 'Week' by TRT01A.
[1] Two normal ranges are given for serum creatinine in the ADLB dataset of Study AC-058B301:

Reviewer Comment: Of the 33 subjects randomized to ponesimod 20 mg who had an elevated urine protein, most (25) were '+,' four were '++,' one was '+++,' and one was '++++.'

Table 65. Reviewer Table. Renal Labs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Serum Creatinine; reference range: 53 – 115 umol/L[1]				
Mean (std) (mmol/L)	70.7 (12.3)	72.4 (13.1)	70.3 (13.9)	71.6 (13.1)
Median (mmol/L)	71	71	69	71
Min, max (mmol/L)	35, 133	44, 117	44, 129	44, 133
# subjects > 150 but baseline < 120 umol/L	0	0	0	0
Blood Urea Nitrogen (BUN); reference range: 2.1 – 8.2 mmol/L				
Mean (std) (mmol/L)	4.6 (1.2)	4.8 (1.2)	4.8 (1.3)	4.9 (1.4)

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Median (mmol/L)	4.5	4.7	4.5	4.7
Min, max (mmol/L)	2.0, 9.1	1.7, 10.2	1.9, 9.7	1.8, 10.4
# subjects > 1.5x ULN	0	0	0	0

Source: AC-058B201 LAB where ITTFL='Y' and TRTEM7=1 by TRT01P
[1] *Two normal ranges are given for serum creatinine in the LAB dataset of AC-058B201.*

Reviewer Comment: Since there does not appear to be a safety signal for abnormal serum creatinine or blood urea nitrogen (or serum electrolytes) in Studies AC058B301 or AC-058B201 (or with other S1P receptor modulators), the utility of further analyses of the renal labs in the uncontrolled RMS population seems limited.

Hematology

Descriptive statistics for leukocyte, lymphocyte, hemoglobin, and platelet data collected from Studies AC-058B301 and AC-058B201 are shown in Table 66 and Table 67. Since lymphopenia is expected with the presumed mechanism of S1P receptor modulators, the numbers of subjects with one or more lymphocyte counts below 0.5 and 0.2 x 10^9/L are listed as well.

Table 66. Reviewer Table. Hematology Labs, Study AC-058B301

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Leukocytes; reference range 4.5 – 11.0 x 10^9/L		
Mean (std) x 10^9/L	5.2 (1.7)	5.7 (1.7)
Median x 10^9/L	4.8	5.5
Min, max x 10^9/L	1.7, 26.0	1.8, 25.3
Lymphocytes; reference range: 1.0 – 3.6 x 10^9/L		
Mean (std) x 10^9/L	0.7 (0.4)	1.6 (0.5)
Median x 10^9/L	0.7	1.6
Min, max x 10^9/L	0.1, 4.5	0.25, 5.56
# subjects < 0.5 x 10^9/L	325	12
# subjects < 0.2 x 10^9/L	17	0
Hemoglobin; reference range: 115 - 160 g/L[1]		
Mean (std) g/L	138.7 (14.3)	136.8 (14.5)
Median g/L	139	136
Min, max g/L	70, 182	77, 198
Platelets; reference range: 130 - 400 x 10^9/L		
Mean (std) x 10^9/L	260.1 (59.1)	229.6 (56.8)
Median x 10^9/L	253	224
Min, max x 10^9/L	72, 626	71, 550

Source: B301 ADLB where SAFFL='Y' and AVISIT contains 'Week' by TRT01A.
[1] Two normal ranges are given for hemoglobin in the ADLB dataset of AC-058B301

Reviewer Comment: There does not appear to be a clear signal for hemoglobin or platelet abnormalities with ponesimod in Study AC-058B301; however, given the purported mechanism of action of S1P receptor modulators, it is not surprising that leukocyte and especially lymphocyte counts are decreased with ponesimod. Some of the cases with lymphocyte counts < 0.2 x 10^9/L have already been discussed in this review; the CSR for AC-058B301 does not contain narratives for the others.

Table 67. Reviewer Table. Hematology Labs, Study AC-058B201

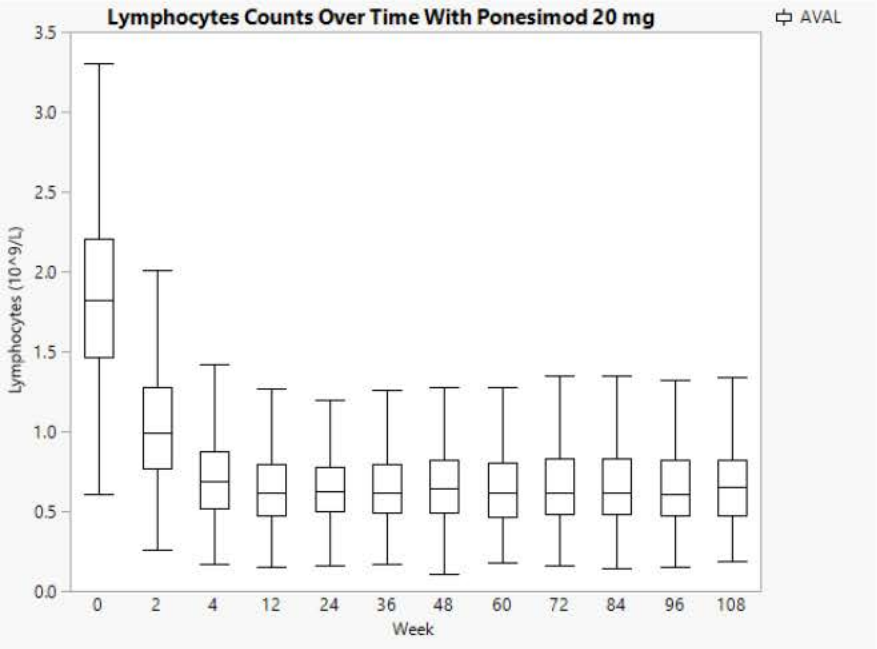
	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Leukocytes; reference range: 4.5 – 11.0 x 10^9/L				
Mean (std) x 10^9/L	5.24 (1.8)	6.9 (2.1)	5.7 (1.9)	5.3 (1.7)
Median x 10^9/L	4.9	6.6	5.4	5.1
Min, max x 10^9/L	1.6, 20.3	2.5, 18.2	2.2, 15.9	1.8, 14.8
Lymphocytes; reference range: 1.0 – 4.8 x 10^9/L				
Mean (std) x 10^9/L	0.7 (0.3)	1.9 (0.6)	1.1 (0.4)	0.7 (0.3)
Median x 10^9/L	0.7	1.8	1.0	0.6
Min, max x 10^9/L	0.1, 2.3	0.5, 5.1	0.1, 3.2	0.1, 2.2
# subjects < 0.5 x 10^9/L	62	1	21	80
# subjects < 0.2 x 10^9/L	4	0	1	6
Hemoglobin; reference range: 115 - 175 g/L[1]				
Mean (std) g/L	137.3 (14.2)	136.3 (14.7)	138.3 (14.1)	138.0 (14.6)
Median g/L	137.0	137.0	138.0	138.0
Min, max g/L	88.0, 180.0	94.0, 179.0	99.0, 176.0	86.0, 185.0
Platelets; reference range: 130 - 400 x 10^9/L				
Mean (std) x 10^9/L	279.1 (69.1)	278.4 (77.0)	286.7 (64.9)	285.5 (82.3)
Median x 10^9/L	272	267	284	277.5
Min, max x 10^9/L	134, 714	127, 561	110, 536	34, 573

Source: AC-058B201 LAB where ITTFL='Y' and TRTEM7=1 by TRT01P
[1] Two normal ranges are given for hemoglobin in the LAB dataset of AC-058B201

Reviewer Comment: There does not appear to be a clear signal for hemoglobin or platelet abnormalities with ponesimod in Study AC-058B201; however, given the purported mechanism of action of S1P receptor modulators, it is not surprising that the lymphocyte counts are decreased with ponesimod.

Given ponesimod's effect on lymphocyte counts, one might question whether the effect increases with longer durations of exposure, so a plot of mean lymphocyte counts over time in subjects who took ponesimod 20 mg in Study AC-058B301 is shown in Figure 11.

Figure 11. Reviewer Figure. Lymphocyte counts over time with ponesimod 20 mg in Study AC-058B301



Reviewer Comment: Although it appears that the drop in lymphocyte counts occurs quickly after starting ponesimod, it does not appear that lymphocyte counts continue to decrease with longer exposures to the drug.

The recovery from lymphopenia after stopping ponesimod is of interest, so descriptive statistics of the baseline, last-on-treatment, 15-day follow-up, the 30-day follow-up lymphocyte counts in Study AC-058B301 follow in Table 68.

Table 68. Reviewer Table. Lymphocyte Recovery, Study AC-058B301

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
Baseline		
N	561	558
Mean (std) x 10^9/L	1.9 (0.6)	1.9 (0.5)
Median x 10^9/L	1.8	1.8
Min, max x 10^9/L	0.6, 4.6	0.8, 4.6
End-of-Treatment		

	Ponesimod 20 mg n=565	Teriflunomide 14 mg n=566
N	560	564
Mean (std) x 10^9/L	0.7 (0.4)	1.6 (0.5)
Median x 10^9/L	0.6	1.5
Min, max x 10^9/L	0.1, 2.9	0.4, 3.8
15-Day Follow-up		
N	484	495
Mean (std) x 10^9/L	1.6 (0.5)	1.8 (0.5)
Median x 10^9/L	1.5	1.7
Min, max x 10^9/L	0.5, 4.0	0.4, 3.6
30-Day Follow-up		
N	101	100
Mean (std) x 10^9/L	1.7 (0.6)	1.8 (0.5)
Median x 10^9/L	1.7	1.9
Min, max x 10^9/L	0.6, 3.9	0.4, 3.3

Reviewer Comment: Mean lymphocyte counts essentially recovered to baseline within 15-30 days of stopping ponesimod, showing that lymphopenia with ponesimod is relatively rapidly reversible.

See further discussion about the risk of lymphopenia (and infections) with the use of ponesimod in Section 8.5.3.

8.4.7. **Vital Signs**

Vital signs are an essential component of safety monitoring for any drug but particularly one in a class of drugs with a known risk of first-dose bradyarrhythmia and AV block. Surprisingly, the ADVS dataset for Study AC-058B301 does not contain heart rates since this information was gleaned from electrocardiograms (ECGs) that were performed during the study. S1P receptor modulators also have a known risk of hypertension, so an analysis of systolic and diastolic blood pressures in Studies AC-058B301 and AC-058B201 is of interest.

Systolic Blood Pressure (SBP)

Descriptive statistics and change from baseline for systolic blood pressure (SBP) obtained at baseline, near the beginning, and near the end of Study AC-058B301 are delineated in Table 69.

Table 69. Reviewer Table. SBPs, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline SBP (mm Hg)		
N	565	566
Mean (std)	119.9 (11.6)	118.2(12.5)
Median	120	118
Min, Max	87, 164	86, 160
Week 2 SBP (mm Hg)		
N	561	566
Mean (std)	119.3 (12.3)	118.7 (12.1)
Median	120	119
Min, Max	88, 164	89, 162
Mean Chg from baseline	-0.6	0.5
# with Chg > 10	76 (13.5%)	84 (14.8%)
Week 4 SBP (mm Hg)		
N	553	562
Mean (std)	120.8 (11.9)	119.4 (11.8)
Median	120	120
Min, Max	90, 159	83, 166
Mean Chg from baseline	1.0	1.2
# with Chg > 10	87 (15.4%)	76 (13.4%)
Week 96 SBP (mm Hg)		
N	475	481
Mean (std)	122.2 (11.7)	121.1 (12.2)
Median	122	120
Min, Max	90, 176	85, 162
Mean Chg from baseline	2.8	2.7
# with Chg > 10	122 (21.6%)	106 (18.7%)
Week 108 SBP (mm Hg)		
N	470	472
Mean (std)	122.3 (12.1)	121.3 (12.5)
Median	122	120
Min, Max	90, 174	90, 160
Mean Chg from baseline	2.9	2.8
# with Chg > 10	119 (21.1%)	107 (18.9%)

Source: B301 ADVS where SAFFL and ANL01F='Y' by TRT01A

Reviewer Comment: It is clear from Table 69 that treatment with ponesimod and teriflunomide led to a small increase in SBP (2.9 and 2.8 mm Hg, respectively at week

108 of Study AC-058B301), which is not surprising since other S1P receptor modulators (and teriflunomide) have known risks of increased blood pressure.

SBP was checked hourly (for four hours) after the first dose of the study drug was administered in Study AC-058B301, and similar analyses of these "first dose" SBPs are shown in Table 70.

Table 70. Reviewer Table. First Dose SBPs, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Pre-dose SBP (mm Hg)		
N	565	566
Mean (std)	119.9 (11.6)	118.2 (12.5)
Median	120	118
Min, Max	87, 164	86, 160
Hour 1 SBP (mm Hg)		
N	565	565
Mean (std)	119.3 (11.8)	118.1 (12.6)
Median	120	118
Min, Max	90, 162	70, 159
Mean Chg from baseline	-0.5	-0.1
# with Chg > 10	37 (6.5%)	49(8.7%)
Hour 2 SBP (mm Hg)		
N	565	565
Mean (std)	119.0 (11.8)	117.6 (12.7)
Median	120	118
Min, Max	89, 160	88, 177
Mean Chg from baseline	-0.9	-0.6
# with Chg > 10	40 (7.1%)	48 (8.5%)
Hour 3 SBP (mm Hg)		
N	564	565
Mean (std)	119.5 (12.0)	117.8 (12.8)
Median)	120	117
Min, Max	88, 161	80, 160
Mean Chg from baseline	-0.3	-0.4
# with Chg > 10	45 (8.0%)	56 (9.9%)
Hour 4 SBP (mm Hg)		
N	565	564
Mean (std)	120.4 (11.9)	118.8 (12.2)
Median	120	118
Min, Max	87, 161	91.5, 160

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Mean Chg from baseline	0.6	0.6
# with Chg > 10	57 (10.1%)	54 (9.5%)

Source: B301 ADVS where SAFFL and ANL01F='Y' by TRT01A

Reviewer Comment: Although Table 69 shows that ponesimod leads to an increase in SPB over time, Table 70 does not suggest that there is a rapid or immediate increase in SBP after administration of the first dose of ponesimod.

Descriptive statistics and change from baseline for systolic blood pressure (SBP) obtained at baseline, near the beginning, and near the end of Study AC-058B201 are delineated in Table 71.

Table 71. Reviewer Table. SBPs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Baseline SBP (mm Hg)				
N	114	121	108	119
Mean (std)	119.5 (13.8)	119.7 (13.9)	122.6 (14.3)	118.0 (13.6)
Median	120	118	121	118
Min, Max	90, 153	95, 156	95, 160	90, 159
Week 2 SBP (mm Hg)				
N	109	117	99	115
Mean (std)	120.8 (13.3)	118.0 (13.8)	121.4 (14.6)	117.5 (13.2)
Median	120	118	119	116
Min, Max	90, 163	91, 162	90, 160	89, 155
Mean Chg from baseline	1.5	-1.9	-0.0	-1.2
# with Chg > 10	20	13	20	14
Week 4 SBP (mm Hg)				
N	107	117	98	112
Mean (std)	121.9 (14.0)	118.1 (13.0)	123.1 (16.4)	122.1 (13.2)
Median	121	118	120.5	122
Min, Max	90, 166	89, 152	90, 183	86, 155
Mean Chg from baseline	2.3	-1.7	1.6	2.8
# with Chg > 10	19	12	24	25
Week 20 SBP (mm Hg)				
N	99	111	92	95
Mean (std)	123.5 (13.5)	119.4 (13.1)	125.0 (13.6)	121.0 (13.4)
Median	123	119	125	120
Min, Max	90, 158	96, 169	90, 165	93, 170

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Mean Chg from baseline	4.2	-0.8	4.0	2.3
# with Chg > 10	26	16	27	22
Week 24 SBP (mm Hg)				
N	112	120	103	
Mean (std)	123.1 (14.9)	118.6 (12.6)	125.0 (16.3)	115
Median	120	118	126	121.7 (12.2)
Min, Max	90, 174	91, 151	90, 179	99, 176
Mean Chg from baseline	4.0	-1.7	3.9	3.0
# with Chg > 10	33	21	31	28

Source: B201 VIT where ITTFL='Y' by TRT01P

Reviewer Comment: Just as demonstrated in Table 69 for Study AC-058B301, Table 71 shows increased SBPs with the use of ponesimod in Study AC-058B201.

Descriptive statistics and change from baseline for systolic blood pressure (SBP) obtained at baseline and at the first four hours after the first dose of the study drug in Study AC-058B201 are delineated in Table 72.

Table 72. Reviewer Table. First Dose SBPs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Baseline SBP (mm Hg)				
N	114	121	108	119
Mean (std)	119.5 (13.8)	119.7 (13.9)	122.6 (14.3)	118.0 (13.6)
Median	120	118	121	118
Min, Max	90, 153	95, 156	95, 160	90, 159
Hour 2 SBP (mm Hg)				
N	114	120	108	119
Mean (std)	117.7 (14.6)	119.8 (15.3)	118.5 (14.5)	116.1 (13.5)
Median	118	119.5	117	115
Min, Max	85, 156	90, 163	83, 159	89, 155
Mean Chg from baseline	-1.5	-0.3	-2.6	-2.6
# with Chg > 10	10	18	10	11
Hour 4 SBP (mm Hg)				
N	114	119	108	119
Mean (std)	118.5 (13.1)	118.2 (15.3)	117.3 (13.6)	115.3 (12.8)
Median	119	117	116.5	115

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Min, Max	90, 157	90, 174	89, 161	92, 147
Mean Chg from baseline	-0.8	-1.8	-3.8	-3.x5
# with Chg > 10	12	15	12	9
Hour 6 SBP (mm Hg)				
N	114	120	107	119
Mean (std)	121.4 (14.0)	119.8 (14.0)	121.7 (15.1)	117.6 (13.3)
Median	120	119.5	121	116
Min, Max	94, 173	95, 155	92, 161	92, 152
Mean Chg from baseline	2.1	-0.3	0.6	-1.1
# with Chg > 10	19	13	18	13

Source: B201 VIT where ITTFL='Y' by TRT01P

Reviewer Comment: Although Table 71 shows that ponesimod led to an increase in SPB over time in Study AC-058B201, Table 72 does not suggest that there is a rapid or immediate increase in SBP after administration of the first dose of ponesimod.

Diastolic Blood Pressure (DBP)

Descriptive statistics and change from baseline for diastolic blood pressure (DBP) obtained at baseline and at some of the scheduled visits in Study AC-058B301 are delineated in Table 73.

Table 73. Reviewer Table. DBPs, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline DBP (mm Hg)		
N	565	566
Mean (std)	75.2 (8.3)	74.6 (8.9)
Median	75	74
Min, Max	50, 108	52, 107
Week 2 DBP (mm Hg)		
N	561	566
Mean (std)	75.9 (8.2)	75.5 (8.7)
Median	76	75
Min, Max	51, 98	50, 108
Mean Chg from baseline	0.8	0.9
# with Chg > 10	52 (9.2%)	46 (8.1%)
Week 4 DBP (mm Hg)		
N	553	562
Mean (std)	76.3 (8.5)	76.1 (8.8)

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Median	76	75
Min, Max	53, 102	50, 126
Mean Chg from baseline	1.1	1.6
# with Chg > 10	57 (10.1)	55 (9.7%)
Week 96 DBP (mm Hg)		
N	475	481
Mean (std)	77.4 (8.4)	77.8 (8.5)
Median	78	78
Min, Max	52, 112	50, 106
Mean Chg from baseline	2.4	3.3
# with Chg > 10	79 (14.0%)	90 (15.9%)
Week 108 DBP (mm Hg)		
N	470	472
Mean (std)	77.8 (8.8)	77.8 (8.7)
Median	78	78
Min, Max	52, 118	52, 101
Mean Chg from baseline	2.8	3.1
# with Chg > 10	92 (16.3%)	96 (17.0%)

Source: B301 ADVS where SAFFL and ANL01F='Y' by TRT01A

Reviewer Comment: It is clear from Table 73 that treatment with ponesimod and teriflunomide led to a small increase in DBP over time (2.8 and 3.1 mm Hg, respectively at week 108 of Study AC-058B301), which is not surprising since other S1P receptor modulators and teriflunomide have known risks of increased blood pressure.

DBPs were checked hourly (for four hours) after the first dose of the study drug was administered in Study AC-058B301, and an analyses of "first dose" DBPs are shown in Table 74.

Table 74. Reviewer Table. First Dose DBPs, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Pre-dose DBP (mm Hg)		
N	565	566
Mean (std)	75.2 (8.3)	74.6 (8.9)
Median	75	74
Min, Max	50, 108	52, 107
Hour 1 DBP (mm Hg)		
N	565	565
Mean (std)	73.9 (8.8)	73.8 (8.8)

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Median	73	74
Min, Max	48, 105	50, 99
Mean Chg from baseline	-1.2	-0.8
# with Chg > 10	17 (3.0%)	16 (2.8%)
Hour 2 DBP (mm Hg)		
N	565	565
Mean (std)	73.6 (8.7)	73.3 (8.6)
Median	74	72
Min, Max	51, 100	50, 106
Mean Chg from baseline	-1.5	-1.3
# with Chg > 10	20 (3.5%)	23 (4.1%)
Hour 3 DBP (mm Hg)		
N	564	565
Mean (std)	74.0 (8.7)	73.4 (8.5)
Median	74	73
Min, Max	49, 105	52, 104
Mean Chg from baseline	-1.2	-1.1
# with Chg > 10	22 (3.9%)	20 (3.5%)
Hour 4 DBP (mm Hg)		
N	565	564
Mean (std)	74.8 (8.6)	74.2 (8.7)
Median	75	74
Min, Max	50, 102	51, 100
Mean Chg from baseline	-0.4	-0.4
# with Chg > 10	27 (4.8%)	27 (4.8%)

Source: B301 ADVS where SAFFL and ANL01F='Y' by TRT01A

Reviewer Comment: Although ponesimod leads to an increase in DPB over time, Table 74 does not suggest that there is a rapid or immediate increase in DBP after administration of the first dose of ponesimod.

Descriptive statistics and change from baseline for DBPs obtained at baseline, near the beginning, and near the end of Study AC-058B201 are delineated in Table 75.

Table 75. Reviewer Table. DBPs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Baseline DBP (mm Hg)				
N	114	121	108	119
Mean (std)	76.1 (10.4)	75.9 (9.1)	76.1 (9.2)	75.2 (10.2)
Median	78	77	76.5	76
Min, Max	45, 103	55, 100	55, 98	52, 100
Week 2 DBP (mm Hg)				
N	109	117	99	115
Mean (std)	76.3 (9.7)	74.7 (9.4)	76.5 (10.6)	74.6 (9.2)
Median	75	75	75	73
Min, Max	60, 114	50, 96	52, 101	55, 119
Mean Chg from baseline	1.1	-0.7	0.8	-0.9
# with Chg > 10	11	7	12	10
Week 4 DBP (mm Hg)				
N	107	116	98	111
Mean (std)	77.1 (10.3)	74.7 (10.8)	77.3 (11.7)	77.4 (9.6)
Median	76	75	77.5	78
Min, Max	60, 114	45, 99	49, 125	57, 110
Mean Chg from baseline	1.7	-0.6	1.4	1.6
# with Chg > 10	10	10	11	13
Week 20 DBP (mm Hg)				
N	99	111	92	95
Mean (std)	79.4 (10.3)	75.3 (9.2)	78.2 (10.2)	77.8 (9.3)
Median	80	75	78	79
Min, Max	52, 106	50, 100	54, 106	53, 99
Mean Chg from baseline	4.4	0.1	2.2	2.4
# with Chg > 10	28	9	16	15
Week 24 DBP (mm Hg)				
N	112	120	103	115
Mean (std)	78.0 (11.6)	74.9 (9.6)	78.7 (10.4)	76.1 (9.9)
Median	80	75	79	75
Min, Max	48, 115	51, 101	58, 109	46, 105
Mean Chg from baseline	3.2	-0.7	2.8	0.7
# with Chg > 10	18	12	17	11

Source: B201 VIT where ITTFL='Y' by TRT01P

Reviewer Comment: Just as demonstrated in Table 73 for Study AC-058B301, Table 75

shows increased DBPs with the use of ponesimod in Study AC-058B201.

Descriptive statistics and change from baseline for DBPs obtained at baseline and over the first four hours after the first dose of the study drug was administered in Study AC-058B201 are delineated in Table 76.

Table 76. Reviewer Table. First Dose DBPs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Baseline DBP (mm Hg)				
N	114	121	108	119
Mean (std)	76.1 (10.4)	75.9 (9.1)	76.1 (9.2)	75.2 (10.2)
Median	78	77	76.5	76
Min, Max	45, 103	55, 100	55, 98	52, 100
Hour 2 DBP (mm Hg)				
N	114	120	108	119
Mean (std)	71.8 (10.4)	74.0 (10.6)	71.4 (10.9)	70.6 (10.7)
Median	72	72	70	70
Min, Max	49, 98	41, 101	48, 107	47, 113
Mean Chg from baseline	-3.2	-1.5	-4.3	-4.8
# with Chg > 10	4	5	6	5
Hour 4 DBP (mm Hg)				
N	114	119	108	119
Mean (std)	71.0 (9.3)	73.3 (10.7)	70.0 (10.3)	69.4 (9.2)
Median	70	73	70	69
Min, Max	52, 98	45, 110	44, 99	49, 95
Mean Chg from baseline	-3.9	-2.1	-5.7	-6.0
# with Chg > 10	7	6	6	1
Hour 6 DBP (mm Hg)				
N	114	120	107	119
Mean (std)	74.7 (9.8)	74.3 (10.5)	74.3 (10.3)	71.5 (9.8)
Median	74	75	74	70
Min, Max	55, 101	50, 105	47, 99	49, 95
Mean Chg from baseline	-0.2	-1.1	-1.5	-3.9
# with Chg > 10	7	8	9	7

Source: B201 VIT where ITTFL='Y' by TRT01P

Reviewer Comment: Although Table 75 shows that ponesimod led to an increase in DPB over time in Study AC-058B201, Table 76 does not suggest that there is a rapid or immediate increase in DBP after administration of the first dose of ponesimod and

actually may suggest an initial but minimal decrease in DBP.

8.4.8. Electrocardiograms (ECGs)

S1P receptors are expressed on atrial myocytes cells of the cardiac conduction system, so it is not surprising that bradyarrhythmia and AV block are labeled warnings for other approved S1P receptor modulators. Early literature suggests that these effects were modulated by S1P3, but later literature (and the occurrence of these adverse events with an S1P1 / S1P5 receptor modulator [siponimod]) suggests involvement of other S1P subtypes, including S1P1. Due to rapid endocytosis of the S1P receptor in the setting of treatment with an S1P receptor modulator, bradyarrhythmia and AV blocks attributable to S1P receptor modulators are felt to occur several hours after initiation of the drug. The Phase 3 study of ponesimod (AC-058B301) utilized a 14-day dose escalation in an attempt to mitigate this risk.

Unless it was deemed necessary to perform electrocardiograms (ECGs) more often (e.g., first-dose abnormalities), they were performed at a minimum at screening, at baseline, hourly for four hours after the first dose of the study drug was administered, and at scheduled visits at study weeks 2, 4, 12, 24, 36, 48, 60, 72, 84, 96, and 108.

Heart Rate (HR)

Descriptive statistics and change from baseline in ECG heart rates (HR) obtained at baseline, at week 2, and every 24 weeks throughout Study AC-058B301 are delineated in Table 77.

Table 77. Reviewer Table. ECG Heart Rates, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline HR (bpm)		
N	562	565
Mean (std)	70.5 (11.0)	70.3 (10.6)
Median	69	41, 11469
Min, Max	50, 126	45, 126
Week 2 HR (bpm)		
N	556	561
Mean (std)	67.2 (9.4)	69.2 (10.5)
Median	66	69
Min, Max	41,114	46, 108
Mean Chg from baseline	-3.3	-0.8
# with Chg < 10	115	81
Week 24 HR (bpm)		
N	525	537
Mean (std)	67.3 (9.2)	68.9 (9.7)

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Median	66	68
Min, Max	42, 126	44, 117
Mean Chg from baseline	-3.6	-1.3
# with Chg < 10	113	86
Week 48 HR (bpm)		
N	504	511
Mean (std)	68.6 (9.5)	70.6 (10.5)
Median	68	69
Min, Max	49, 117	43, 107
Mean Chg from baseline	-2.6	0.2
# with Chg < -10	90	60
Week 72 HR (bpm)		
N	488	491
Mean (std)	67.5 (8.6)	71.3 (10.4)
Median	67	71
Min, Max	46, 96	47, 113
Mean Chg from baseline	-3.7	0.8
# with Chg < -10	103	63
Week 96 HR (bpm)		
N	473	480
Mean (std)	68.3 (9.2)	71.3 (10.9)
Median	68	71
Min, Max	48, 120	44, 106
Mean Chg from baseline	-2.7	0.8
# with Chg < -10	105	60
Week 108 HR (bpm)		
N	494	499
Mean (std)	68.3 (10.6)	71.5 (11.1)
Median	67	70
Min, Max	41, 134	50, 121
Mean Chg from baseline	-2.5	1.0
# with Chg < -10	107	55

Source: B301 ADEG where SAFFL and DAY1FL='Y' and PARAMCD=' EGHRMN' by AVISIT and TRT01A

Reviewer Comment: Mild reductions in overall heart rates were seen with ponesimod throughout the duration of Study AC-058B301.

HR was checked hourly (for four hours) after the first dose of the study drug was administered in Study AC-058B301, and analyses of these "first dose" SBPs are shown in Table 78.

Table 78. Reviewer Table. First Dose HRs, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline HR (bpm)		
N	562	565
Mean (std)	70.5 (11.0)	70.3 (10.6)
Median	69	69
Min, Max	50, 126	45, 126
Hour 1 HR (bpm)		
N	561	563
Mean (std)	64.7 (9.8)	68.6 (10.9)
Median	63	68
Min, Max	44, 112	43, 115
Mean Chg from baseline	-5.9	-1.7
# with Chg < -10	153	66
Hour 2 HR (bpm)		
N	562	561
Mean (std)	61.9 (8.8)	68.5 (10.6)
Median	61	68
Min, Max	35, 97	46, 113
Mean Chg from baseline	-8.7	-1.7
# with Chg < -10	212	78
Hour 3 HR (bpm)		
N	561	562
Mean (std)	63.5 (8.8)	69.2 (9.8)
Median	62	68
Min, Max	40, 99	44, 113
Mean Chg from baseline	-7.1	-1.0
# with Chg < -10	180	72
Hour 4 HR (bpm)		
N	561	562
Mean (std)	65.1 (9.0)	69.2 (9.8)
Median	64	68
Min, Max	46, 111	46, 107
Mean Chg from baseline	-5.4	-1.0
# with Chg < -10	150	65

Source: B301 ADEG where SAFFL and DAY1FL='Y' and PARAMCD=' EGHRMN' by ATPT and TRT01A

Reviewer Comment: As expected given the risk of bradyarrhythmia after initiating other

S1P receptor modulators, administration of the first dose of ponesimod is associated with a reduction in heart rate, apparently reaching a nadir around two hours.

Descriptive statistics and change from baseline for HRs obtained at baseline and at the scheduled visits throughout Study AC-058B201 are delineated in Table 79.

Table 79. Reviewer Table. HRs, Study AC-058B201

	Ponesimod 20 mg n=114	Placebo n=121	Ponesimod 10 mg n=108	Ponesimod 40 mg n=119
Baseline HR (bpm)				
N	114	119	108	117
Mean (std)	68.2 (10.3)	68.1 (9.6)	69.0 (9.5)	68.9 (10.1)
Median	67	67	68	68
Min, Max	47, 109	48, 105	52, 102	50, 101
Week 4 HR (bpm)				
N	107	116	96	110
Mean (std)	68.4 (10.9)	68.1 (11.6)	67.8 (10.0)	67.6 (8.5)
Median	67.5	66	66	67
Min, Max	50, 133	38, 117	50, 100	49, 102
Mean Chg from baseline	-1.5	-2.5	-4.6	-2.7
# with Chg < -10	19 (17.8%)	20 (17.2%)	27 (28.1%)	18 (16.4%)
Week 12 HR (bpm)				
N	100	114	96	96
Mean (std)	68.0 (9.0)	67.7 (12.6)	68.1 (9.6)	67.6 (9.3)
Median	66	68	65.5	68
Min, Max	45, 100	47, 104	51, 112	48, 97
Mean Chg from baseline	-1.7	-2.9	-4.1	-2.7
# with Chg < -10	21 (21.0%)	26 (22.8%)	27 (28.1%)	18 (18.8%)
Week 24 HR (bpm)				
N	111	119	102	114
Mean (std)	67.4 (9.5)	68.8 (11.6)	67.7 (10.4)	67.0 (9.8)
Median	66	66	66	66
Min, Max	50, 100	47, 109	48, 114	50, 111
Mean Chg from baseline	-2.1	-1.8	-4.5	-3.0
# with Chg < -10	22 (19.8%)	25 (21.0%)	23 (21.3%)	27 (23.7%)

Source: B201 ECGA ECGNHR, ECGCHR where ITTFL='Y' by TRT01P

Reviewer Comment: There is not a clear effect of ponesimod on heart rate over time. Although the percentage of subjects with a heart rate reduction over 10 bpm seems somewhat high in all groups, the changes in HR with ponesimod 20 mg is not clearly

different from those with placebo at the time points in Table 79.

Since the dose titration was changed with Study AC-058B301, analysis of the first dose HRs with the titration used in Study AC-058B201 is deferred.

See further discussion of the risk of bradyarrhythmia and AV block after the first dose of ponesimod in Section 8.5.2.

PR Interval

Table 80 delineates the PR interval at the beginning, middle, and end of Study AC-058B301.

Table 80. Reviewer Table. PR interval, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline PR Interval (msec)		
N	563	566
Mean (std)	152.4 (20.9)	154.2 (23.6)
# subjects > 200	12	9
# subjects > 230	2	1
Hour 4 PR Interval (msec)		
N	562	564
Mean (std)	155.3 (23.0)	153.6 (23.3)
Mean Chg from baseline	3.0	-0.8
# subjects > 200	23	5
# subjects > 230	3	1
Week 2 PR Interval (msec)		
N	556	561
Mean (std)	152.9 (20.3)	151.9 (23.8)
Mean Chg from baseline	0.3	-2.1
# subjects > 200	12	8
# subjects > 230	1	1
Week 48 PR Interval (msec)		
N	504	511
Mean (std)	151.1 (20.8)	148.8 (23.6)
Mean Chg from baseline	-0.8	-5.3
# subjects > 200	7	4
# subjects > 230	1	1
Week 108 PR Interval (msec)		
N	494	499
Mean (std)	149.5 (20.7)	147.5 (20.7)
Mean Chg from baseline	-2.7	-6.4

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
# subjects > 200	6	5
# subjects > 230	0	1

Source: B301 ADEG where SAFFL and DAY1FL='Y' and PARAMCD='PRAG' by (ATPT or AVISIT) and TRT01A

Reviewer Comment: There does not appear to be a clinically meaningfully change in the PR interval associated with the use of ponesimod in Study AC-058B301.

QTcF Interval

Table 81 delineates the QTcF interval at the beginning, middle, and end of Study AC-058B301.

Table 81. Reviewer Table. QTcF, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline QTcF (msec)		
N	563	566
Mean (std)	402.7 (17.1)	403.7 (18.4)
# >430 (M) or 450 (F)	9	6
# >450 (M) or 470 (F)	0	0
# subjects > 480	0	0
Hour 4 QTcF (msec)		
N	562	564
Mean (std)	406.6 (17.8)	405.0 (18.3)
Mean Chg from baseline	3.9	1.5
# >430 (M) or 450 (F)	12	11
# >450 (M) or 470 (F)	1	1
# subjects > 480	0	0
Week 2 QTcF (msec)		
N	556	561
Mean (std)	405.7 (16.7)	406.7 (17.9)
Mean Chg from baseline	3.2	3.3
# >430 (M) or 450 (F)	11	10
# >450 (M) or 470 (F)	1	1
# subjects > 480	0	0
Week 48 QTcF (msec)		
N	504	511
Mean (std)	405.7 (16.1)	404.2 (18.2)
Mean Chg from baseline	3.0	1.0
# >430 (M) or 450 (F)	10	10
# >450 (M) or 470 (F)	0	0

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
# subjects > 480	0	0
Week 108 QTcF (msec)		
N	494	499
Mean (std)	404.8 (16.7)	403.3 (18.9)
Mean Chg from baseline	2.5	0.1
# >430 (M) or 450 (F)	11	7
# >450 (M) or 470 (F)	0	1
# subjects > 480	0	1

Source: B301 ADEG where SAFFL and DAY1FL='Y' and PARAMCD=' QTCFAG' by (ATPT or AVISIT) and TRT01A

Reviewer Comment: There does not appear to be a clinically meaningfully change in QTcF associated with the use of ponesimod in Study AC-058B301.

Table 82 delineates the commonly seen ECG abnormalities (and those of interest) in subjects in the Study AC-058B301.

Table 82. Reviewer Table. ECG abnormalities, Study AC-058B301

ECG Abnormality	Baseline	Hour 4	Week 2	Month 48	Month 108
Ponesimod 20 mg					
1ST DEGREE AV BLOCK	12	25	12	7	6
INTRAVENTRICULAR CONDUCTION DELAY, NONSPECIFIC	8	14	13	9	11
LEFT ANTERIOR FASCICULAR BLOCK	7	8	4	4	1
PREMATURE VENTRICULAR COMPLEX	2	6	1	2	0
INCOMPLETE RIGHT BUNDLE BRANCH BLOCK	3	1	1	1	3
LEFT VENTRICULAR HYPERTROPHY	1	2	1	1	3
PREMATURE ATRIAL COMPLEXES	2	1	1	2	0
ECTOPIC ATRIAL RHYTHM	2	0			
LEFT ATRIAL ABNORMALITY	1	1	1	1	2
LEFT POSTERIOR FASCICULAR BLOCK	1	1	1	0	0
RIGHT ATRIAL ABNORMALITY	1	1	0	0	1
Teriflunomide 14 mg					
1ST DEGREE AV BLOCK	9	9	8	4	5

ECG Abnormality	Baseline	Hour 4	Week 2	Month 48	Month 108
INTRAVENTRICULAR CONDUCTION DELAY, NONSPECIFIC	16	13	16	9	4
LEFT ANTERIOR FASCICULAR BLOCK	4	4	3	4	4
PREMATURE VENTRICULAR COMPLEX	2	2	3	1	3
INCOMPLETE RIGHT BUNDLE BRANCH BLOCK	5	6	4	1	1
LEFT VENTRICULAR HYPERTROPHY	0	0	0	0	1
PREMATURE ATRIAL COMPLEXES	1	8	2	2	3
ECTOPIC ATRIAL RHYTHM	3	2	2	3	1
LEFT ATRIAL ABNORMALITY	0	0	0	0	1
LEFT POSTERIOR FASCICULAR BLOCK	0	0	0	0	0
RIGHT ATRIAL ABNORMALITY	0	0	0	0	0

Source: B301 ADEG where SAFFL and DAY1FL='Y' and PARAMCD='INTP' by (ATPT or AVISIT) and TRT01A

Reviewer Comment: It is not surprising that more first-degree heart blocks were seen in subjects randomized to ponesimod, but it is reassuring that there does not appear to be cases of higher degree AV block or a clear difference in the occurrence of other ECG abnormalities between the study arms.

See further discussion of the risk of bradyarrhythmia and AV block, especially after the first dose of ponesimod, in Section 8.5.2.

8.4.9. QT

Relatively early in the development program of ponesimod (2013), the Interdisciplinary Review Team for QT Studies (QT-IRT) was consulted to comment on Study AC-058-110, a single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group, multiple-dose, up-titration study of the electrocardiographic effects of ponesimod in healthy male and female subjects. Their comments follow

- "On day 12 (40 mg) and 23 (100mg) no clinically significant changes in the mean HR were observed. In addition no subject had a HR < 45 bpm. No changes in PR or QRS were found after ponesimod on day 12 (40 mg) or on day 23 (100 mg). No subject had a PR > 200 ms.
- The safety report states that on treatment day 1 (study day 2) a decrease in 12-lead ECG HR was observed after administration of the first dose of 10 mg ponesimod. A maximum mean decrease (compared to pre-dose) of 9 bpm at 2.5 h post-dose compared to a mean increase of 4 bpm at the corresponding time point with placebo

was observed. Uptitration from 10 to 20 mg (Day 5) resulted in a mean maximum decrease of 6 bpm at 2.5 hours post-dose compared to a respective mean increase of 3 bpm at the corresponding timepoint with placebo. Following up-titration to doses of 40, 60, 80, and 100 mg, mean HR was unchanged. On treatment day 1, increases in mean QT interval were observed at the start of ponesimod dosing (doses of 10 and 20 mg). Maximum increases in mean QTcB of up to 20 ms and mean QTcF of up to 14 ms were reported. This may be explained at least in part by the decrease in HR observed on the same day.

- On treatment day 1 two subjects were withdrawn due to second-degree AV block and prolongation of PR interval on the first day of dosing with 10 mg ponesimod. The second degree AV block was associated with sinus bradycardia (35 bpm). The PR prolongation event increased gradually and lasted 24 hours.
- The safety profile of ponesimod on day 1 of dosing is a well-known (class effect) first dose effect on HR and AV conduction.
- It is recommended that in ongoing and future trials, intensive ECG monitoring be conducted on treatment day 1 and as clinically indicated thereafter."

Reviewer Comment: Refer to the consult from QT-IRT for further comments; of note, the therapeutic and supratherapeutic doses (40 and 100 mg, respectively) employed in Study AC-058-110 are higher than that of the proposed labelled dose (20 mg) of ponesimod.

8.4.10. **Pulmonary Function Tests**

S1P receptors, including S1P3, occur on the smooth muscle and the epithelium of the respiratory tract, so modulation of these receptors may lead to adverse events attributable to the respiratory system. Indeed, respiratory effects are labeled in Section 5 (Warnings and Precautions) of both a non-selective S1P receptor modulator (fingolimod) and selective S1P1/ S1P5 receptor modulators (siponimod, ozanimod) for RMS. The approval of both fingolimod and siponimod included a post market requirement (PMR) to further study the respiratory effects of these drugs. Given this, respiratory effects are an adverse event of special interest (AESI) for which pulmonary assessments were performed in the pivotal studies of ponesimod.

Pulmonary function tests, including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), were assessed in Study AC-058B301, and the results of these are shown in Table 83 and Table 84.

Table 83. Reviewer Table. FEV1, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline FEV1 (L)		
N	560	560
FEV1 mean (SD)	3.51 (0.78)	3.50 (0.80)
Week 4 FEV1 (L)		
N	536	548
FEV1 mean (SD)	3.28 (0.80)	3.45 (0.78)
FEV1 mean chg from baseline (%)	-6.44	-0.73
# with FEV1 < 80% baseline	29 (5.4%)	13 (2.4%)
Week 12 FEV1 (L)		
N	537	549
FEV1 mean (SD)	3.26 (0.79)	3.43 (0.78)
FEV1 mean chg from baseline (%)	-7.03	-1.67
# with FEV1 < 80% baseline (%)	29 (5.4%)	15 (2.7%)
Week 60 FEV1 (L)		
N	489	488
FEV1 mean (SD)	3.23 (0.77)	3.40 (0.82)
FEV1 mean % chg from baseline	-8.11	-2.25
# with FEV1 < 80% baseline (%)	38 (7.8%)	15 (3.1%)
Week 108 FEV1 (L)		
N	448	458
FEV1 mean (SD)	3.21 (0.78)	3.33 (0.79)
FEV1 mean chg from baseline (%)	-8.31	-4.39
# with FEV1 < 80% baseline (%)	42 (9.4%)	26 (5.7%)

Source: ADRE AFEV1, PCHG where SAFFL='Y,' TRTEMFL='Y,' and PARAMCD='AFEV1' by TRT01A

Reviewer Comment: Although the overall mean percent changes from baseline are small, Table 83 suggests that ponesimod has an effect on FEV1, causing a higher subset of subjects receiving ponesimod to have an FEV1 below 80% of baseline; interestingly there was a slow increase in the number of subjects with an FEV1 below 80% over time in both the ponesimod and teriflunomide arms.

Table 84. Reviewer Table. FVC, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline FVC (L)		
N	560	560
FVC mean (SD)	4.35 (0.98)	4.33 (0.99)

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Week 4 FVC (L)		
N	536	548
FVC mean (SD)	4.28 (1.00)	4.30 (0.98)
FVC mean % chg from baseline	-1.48	-0.35
# with FVC < 80% baseline (%)	8 (1.5%)	8 (1.5%)
Week 12 FVC (L)		
N	537	549
FVC mean (SD)	4.22 (0.98)	4.27 (0.98)
FVC mean % chg from baseline	-2.57	-1.26
# with FVC < 80% baseline (%)	14 (2.6%)	8 (1.5%)
Week 60 FVC (L)		
N	489	488
FVC mean (SD)	4.22 (0.98)	4.25 (1.01)
FVC mean % chg from baseline	-2.53	-1.57
# with FVC < 80% baseline (%)	10 (2.0%)	12 (2.5%)
Week 108 FVC (L)		
N	448	458
FVC mean (SD)	4.20 (0.99)	4.19 (1.01)
FVC mean % chg from baseline	-2.81	-2.95
# with FVC < 80% baseline (%)	11 (2.5%)	14 (3.1%)

Source: ADRE AFVC1, PCHG where SAFFL='Y,' TRTEMFL='Y,' and PARAMCD='AFVC' by TRT01A

Reviewer Comment: Similar to the FEV1 analysis above, Table 84 suggests that ponesimod has a small effect on FVC; however, the percentages of subjects with a FVC < 80% of baseline appears comparable between ponesimod and teriflunomide.

A subset of subjects in Study AC-058B301 participated in a substudy assessing the effect of ponesimod on diffusion capacity of the lungs for carbon monoxide (DLCO), as noted in Table 85.

Table 85. Reviewer Table. DLCO, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Baseline DLCO (mmol/min/kpa)		
N	126	125
DLCO mean (SD)	8.48 (1.97)	8.31 (2.09)
Week 4 DLCO (mmol/min/kpa)		
N	118	119
DLCO mean (SD)	7.87 (1.71)	8.43 (1.87)
DLCO mean % chg from baseline	-7.0	2.7

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
# with DLCO < 80% baseline (%)	8 (6.8%)	1 (0.8%)
Week 12 FVC (L)		
N	119	121
DLCO mean (SD)	7.64 (1.78)	8.44 (1.93)
DLCO mean % chg from baseline	-9.0	2.4
# with DLCO < 80% baseline (%)	14 (11.8%)	1 (0.8%)
Week 60 DLCO (mmol/min/kpa)		
N	113	106
DLCO mean (SD)	7.26 (1.52)	8.26 (1.96)
DLCO mean % chg from baseline	-12.8	0.9
# with DLCO < 80% baseline (%)	23 (17.7%)	2 (1.9%)
Week 108 DLCO (mmol/min/kpa)		
N	104	95
DLCO mean (SD)	7.23 (1.59)	8.31 (2.23)
DLCO mean % chg from baseline	-12.5	0.5
# with DLCO < 80% baseline (%)	28 (26.9%)	1 (1.1%)

Source: ADRE where AFVC1, PCHG where SAFFL='Y,' TRTEMFL='Y,' and PARAMCD='DLCO' by TRT01A

Reviewer Comment: Not surprisingly given the effect that ponesimod had on FEV1 and FVC (and the respiratory effects noted with other S1P receptor modulators), Table 85 shows that ponesimod 20 mg lead to a reduction in DLCO.

In brief, the presence of S1P receptors in the pulmonary smooth muscle and epithelium provides biologic plausibility that modulation of these receptors may lead to respiratory effects, and the labelling for the three S1P receptor modulators approved for RMS contain a warning for respiratory effects. This section suggests that ponesimod also adversely affect respiratory function, although the magnitude of its effects on FEV1 and FVC appears quite small, which suggests that this risk can be mitigated through appropriate labeling and patient education.

See further comments, including an integration with clinical symptoms (i.e., dyspnea) in Section 8.5.7.

8.4.11. **Immunogenicity**

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Lymphopenia / Serious Infections

It is clear from the section on hematologic laboratories that lymphopenia can occur in individuals taking ponesimod, which is not surprising since the benefit of S1P receptor modulators in RMS is likely derived from their sequestration of circulating lymphocytes in secondary lymphoid tissue such as lymph nodes.

Reviewer Comment: Because it appears that ponesimod can be associated with lymphopenia, this reviewer recommends checking a CBC with lymphocyte count before initiating ponesimod and periodically during treatment with ponesimod.

Given its association with lymphopenia, it is not surprising that ponesimod also has an increased risk of infections and that infectious SAEs, AEs leading to study discontinuation / drug withdrawal, severe AEs, and TEAEs (Sections 8.4.2 to Sections 8.2.5 occurred relatively frequently during the ponesimod clinical trials. An analysis of the Infections and Infestations SOC for PTs occurring 5 or more times in subjects randomized to ponesimod in Study AC-058B301 follows in Table 86:

Table 86. Reviewer Table. Infections and Infestations SOC, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Nasopharyngitis	170	147
Upper respiratory tract infection	92	95
Urinary tract infection	40	48
Oral herpes	37	29
Bronchitis	32	28
Respiratory tract infection viral	31	12
Influenza	27	28
Respiratory tract infection	20	17
Pharyngitis	17	15
Herpes zoster	16	3
Rhinitis	15	20
Gastroenteritis	13	22
Viral infection	13	5
Viral upper respiratory tract infection	12	9
Sinusitis	11	20
Tonsillitis	11	14
Conjunctivitis	9	12
Cystitis	8	8

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Laryngitis	8	2
Tinea versicolor	7	10
Tracheitis	7	1
Pneumonia	6	2
Acute sinusitis	5	5
Vulvovaginal candidiasis	5	1

Source: B301 ADAE where TRTEMFL and SAFFL='Y' and AEBODSYS ='INFECTIONS and INFESTATIONS' by AEDECOD and TRT01A

Reviewer Comment: As infections could occur more than once in a subject, percentages are not calculated in Table 86. The numbers of respiratory and herpes zoster infections in Study AC-058B301 are somewhat higher in subjects randomized to ponesimod compared to those randomized to teriflunomide, which also has a risk of infection; however, the numbers for many of the types of infections appear similar between the two arms of this study. Although progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis (CM) have been reported with other S1P receptor modulators, this reviewer does not appreciate cases of these opportunistic infections in the ponesimod safety population.

This reviewer agrees that a warning for infections, including a potential risk of PML and CM, should be included in Section 5 of any potential labeling for ponesimod. Because the inclusion criteria for the RMS ponesimod trials required evidence of immunity to the varicella zoster virus (VZV), a similar stipulation should be included in the ponesimod labeling.

8.5.2. Liver Injury / Increased Hepatic Transaminases

It is clear from the section on hepatobiliary laboratories that hepatic transaminase elevations may occur in individuals taking ponesimod, although there were no clear Hy's law cases of DILI in the trials of ponesimod in subjects with RMS.

Reviewer Comment: None of the narratives for liver injury / hepatic transaminase elevation are particularly concerning for a signal indicating a risk of irreversible hepatic injury; however, given the signal for transaminase elevations and potential liver injury with ponesimod, this reviewer recommends that Section 5 of any potential labeling for ponesimod include a warning for liver injury and hepatic transaminase elevations similar to that of the other approved S1P receptor modulators.

8.5.3. Malignancy

As previously noted in the safety section of this review, a few malignancies occurred during the clinical trials of ponesimod. An analysis of TEAEs in the Neoplasms Benign, Malignant, and Unspecified SOC that occurred in one or more subjects randomized to ponesimod 20 mg in Study AC-058B301 follows in Table 87.

Table 87. Reviewer Table. Malignancies, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Melanocytic nevus	4	8
Seborrheic keratosis	4	3
Uterine leiomyoma	4	3
Basal cell carcinoma	2	1
Adenoma benign	1	0
Dysplastic nevus	1	2
Eye nevus	1	0
Eyelid hemangioma	1	0
Fibrous histiocytoma	1	2
Hemangioma	1	1
Lipoma	1	1
Malignant melanoma	1	0
Pituitary tumor benign	1	0
Skin papilloma	1	1
Squamous cell carcinoma of the cervix	1	0

Source: B301 ADAE where TRTEMFL and SAFFL='Y' and AEBODSYS ='NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)' by AEDECOD and TRT01A

Reviewer Comment: Since the rate of malignancy was very low in Study AC-058B301, percentages are not calculated for the types of malignancies in Table 87; however, a longer time horizon may be required to adequately define the risk of malignancy. Since cutaneous malignancies are listed as a warning in Section 5 of the labelling for some of the S1P receptor modulators, this reviewer opines that cutaneous malignancies should be included as a warning in any potential labeling for ponesimod.

8.5.4. Bradyarrhythmia and Atrioventricular Block

The analyses in Section 8.4.8 suggests that the early doses of ponesimod can be associated with bradyarrhythmia and 1st degree AV block, similar to the experience with other S1P receptor modulators; however, this reviewer did not discover any cases of

second degree (or higher) AV block after the 14-day titration of ponesimod was implemented in Study AC-058B301.

In addition to requiring a four-hour observation after administration of the first dose of ponesimod, Study AC-058B301 implemented exclusion criteria for a resting heart rate less than 50 bpm at screening and the following cardiac conditions:

- "Myocardial infarction within 6 months prior to randomization or ongoing unstable ischemic heart disease
- Cardiac failure (New York Heart Association class III or IV) or any severe cardiac disease at the time of Visit 1 (Screening) or randomization
- 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 (e.g., 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 QTcF interval > 470 ms (females), > 450 ms (males) as measured by 12-lead ECG at Visit 1(Screening) or Visit 2 (Baseline) or by the pre-dose ECG at Visit 3 (Randomization / Day 1)
- History of syncope associated with cardiac disorders
- Systemic arterial hypertension not controlled by medication according to the investigator's judgment"

Reviewer Comment: Even though there were a small number of cases of bradyarrhythmia and first degree AV block in Study AC-058B301 of ponesimod, this reviewer opines that the aforementioned cardiac exclusions should be included in any labelling for ponesimod, as should a warning for a risk of bradyarrhythmia and AV block. This reviewer agrees that the labeling should recommend four-hour monitoring after the first dose of ponesimod is administered to individuals with sinus bradycardia [HR less than 55 beats per minute (bpm)], first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure occurring more than 6 months prior to treatment initiation.

8.5.5. **Hypertension**

The section on Vital Signs in Section 8.4.7 suggests that ponesimod is associated with increased systolic blood pressures, and hypertension was reported frequently in subjects randomized to ponesimod in Study AC-058B301.

Table 88. Reviewer Table. TEAEs of hypertension, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Hypertension	50	45

Source: B301 ADAE where TRTEMFL and SAFFL='Y' and AEDECOD='HYPERTENSION' by TRT01A

Reviewer Comment: Although a TEAE for hypertension was noted just slightly more frequently in subjects randomized to ponesimod, it should be noted that the labeling for other S1P receptor modulators for RMS have a warning for hypertension, as does teriflunomide. This reviewer recommends that any potential labeling of ponesimod should include a warning for hypertension.

8.5.6. Macular Edema

Macular edema was reported by six (1.1%) of the subjects randomized to ponesimod 20 mg in Study AC-058B301; it appears that three of these had clear confounding factors for macular edema (e.g., diabetes, mellitus, and chorioretinitis), and interestingly one (Subject 1505017) was not discontinued from the study. Similarly, three (2.6%) of the subjects randomized to ponesimod 20 mg in Study AC-058B201 developed macular edema, but this diagnosis was debatable in two, and one had confounding eye pathology. There were four cases of macular edema in subjects who were taking ponesimod 20 mg in the extension studies, but two of these were also confounded.

Reviewer Comment: Although the correlation between macular edema and ponesimod is not robust, macular edema has occurred with (and is a labeled warning for) other S1P receptor modulators. This reviewer agrees that any labeling for ponesimod should include a warning for macular edema and that an ophthalmologic evaluation should be recommended for individuals with risk factors for macular edema (e.g., a history of diabetes mellitus or uveitis) prior to (and periodically during) treatment with ponesimod.

8.5.7. Seizure

The sections on SAEs and TEAEs in Sections 8.4.2-8.4.5 suggests that ponesimod may be associated with an increased risk of seizure, although seizures are a recognized complication occurring in 3-5% of individuals with MS. As per Table 89, the rate of seizures was not clearly higher in subjects randomized to ponesimod in Study AC-058B301; however, 13 subjects in the long term extensions experienced a seizure.

Table 89. Reviewer Table. TEAEs of seizure, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Partial seizures with secondary generalization	3	0
Epilepsy	1	1
Generalized tonic-clonic seizure	1	1
Partial seizures	1	0
Seizure	1	0

Source: B301 ADAE where TRTEMFL and SAFFL='Y' and AEDECOD contains 'Seizure' or 'Epilepsy' by TRT01A

Reviewer Comment: Since the rate of seizures was very low in Study AC-058B301, percentages are not calculated in Table 89. This table suggests that there may a slightly increased risk of seizures with ponesimod, but this reviewer's confidence in this correlation is lacking.

8.5.8. Pulmonary Effects

The section on Pulmonary Function Tests in Section 8.4.10 suggests that ponesimod may be associated with decreases in pulmonary function, and respiratory effects are included as a warning in the labeling of other S1P receptor modulators. The following analysis (Table 90) shows that TEAEs relating to dyspnea and PFT abnormalities were more frequent in subjects randomized to ponesimod 20 mg in Study AC-058B301.

Table 90. Reviewer Table. Dyspnea and abnormal PFTs, Study AC-058B301

	Ponesimod 20 mg N=565	Teriflunomide 14 mg N=566
Dyspnea	35	7
Forced expiratory volume decreased	2	3
Dyspnea at rest	4	0
Pulmonary function test decreased	1	1
Carbon monoxide diffusing capacity decreased	1	0
Dyspnea exertional	1	0
Forced vital capacity decreased	0	1

Source: B301 ADAE where TRTEMFL and SAFFL='Y' and where AEDECOD={values in first column} by TRT01A

Reviewer Comment: Although the numbers of TEAEs for PFT abnormalities is relatively row in Table 90, the number of subjects with PFT abnormalities (especially in regard to DLCO) below 80% of baseline in Section 8.4.10 is notable.

Similarly, the number of TEAEs for dyspnea in subjects randomized to ponesimod is notably higher than that of subjects randomized to teriflunomide in Study AC-058B301, and as per Table 40, seven (1.2%) subjects randomized to ponesimod in Study AC-058B301 discontinued the study drug for dyspnea (one at rest).

This reviewer agrees that respiratory effects, including a decline in pulmonary function, should be included as a warning in Section 5 of any labeling for ponesimod. Since post-marketing requirements (PMR) regarding respiratory effects have been imposed on two other S1P receptor modulators, a PMR to explore this signal further with ponesimod is likely not merited.

8.6. **Safety Analyses by Demographic Subgroups**

Gender

As noted in Table 37, SAEs were relatively uncommon in Study AC-058B301. Table 91 delineates those SAEs occurring in more than one subject randomized to ponesimod 20 mg in this study, stratified by gender.

Table 91. Reviewer Table. SAEs with ponesimod 20 mg stratified by gender, Study AC-058B301

AEDECOD	Female n=363	Male N=202
Abdominal pain	3	0
Appendicitis	2	1
Lumbar radiculopathy	0	3
Abortion induced	2	0

Source: B301 ADAE where AESER, SAFFL, TRTEMFL='Y,' and TRT01A='Ponesimod 20 mg' by AEDECOD and SEX.

Reviewer Comment: The numbers of SAEs in Study AC-058B301 are too small to comment on gender differences in the occurrence of SAEs.

Similarly, TEAEs occurring 10 or more times in the ponesimod 20 mg arm of Study AC-058B301 are stratified by gender and shown in Table 92.

Table 92. Reviewer Table. Common TEAEs with ponesimod 20 mg stratified by gender, Study AC-058B301

AEDECOD	Female n=363	Male N=202
Nasopharyngitis	107	63
Alanine aminotransferase increased	91	73
Headache	75	24

AEDECOD	Female n=363	Male N=202
Upper respiratory tract infection	61	31
Nausea	45	8
Hypertension	37	13
Back pain	28	12
Urinary tract infection	37	3
Aspartate aminotransferase increased	22	16
Fatigue	28	10
Oral herpes	34	3
Dyspnea	20	15
Dizziness	27	6
Bronchitis	19	13
Respiratory tract infection viral	19	12
Influenza	12	15
Hepatic enzyme increased	11	15
Cough	14	10
Depression	14	9
Pain in extremity	17	6
Abdominal pain upper	12	10
Diarrhea	17	4
Respiratory tract infection	16	4
Alopecia	17	2
Hyperkalemia	9	10
Anxiety	14	4
Arthralgia	10	8
Somnolence	11	7
Constipation	10	7
Hypoesthesia	13	4
Paresthesia	13	4
Pharyngitis	12	5
Herpes zoster	12	4
Anemia	15	0
Hypercholesterolemia	9	6
Rhinitis	11	4
Dyspepsia	6	8
Abdominal pain	10	3
Gastroenteritis	10	3
Vertigo	12	1
Viral infection	7	6
Vomiting	10	3

AEDECOD	Female n=363	Male N=202
Asthenia	6	6
C-reactive protein increased	6	6
Pyrexia	8	4
Transaminases increased	6	6
Viral upper respiratory tract infection	7	5
Fall	7	4
Insomnia	6	5
Musculoskeletal pain	6	5
Sinusitis	9	2
Tonsillitis	6	5
Blood pressure increased	8	2
Lymphopenia	10	0

Source: B301 ADAE where SAFFL and TRTEMFL='Y,' and TRT01A='Ponesimod 20 mg' by AEDECOD and SEX.

Reviewer Comment: Since TEAEs could be reported more than once by the same subject, Table 92 does not contain percentages of subjects experiencing each TEAE, although recognizing that 2/3 of the subjects are women allows inferences to be made. Since headaches, urinary tract infections, and anemia are more common in women, it is not surprising that these TEAEs appear to have occurred more commonly in women randomized to ponesimod. Given prior analyses, it is not surprising that hypertension and the various codings for respiratory infections and transaminase elevations are common events in this analysis. Since lymphopenia and some of the infections (especially herpes zoster infections) appear to disproportionately affect women, Table 93 explores the gender differences in lymphocyte counts in subjects randomized to ponesimod in Study AC-05B301.

Table 93. Reviewer Table. Lymphocyte counts stratified by gender in subjects treated with ponesimod 20 mg, Study AC-058B301

	Female n=363	Male N=202
Mean (std) x 10^9/L	0.67 (0.31)	0.85 (0.39)
Median x 10^9/L	0.60	0.77
Min, max x 10^9/L	0.11, 3.00	0.15, 3.55
# of subjects < 0.5 x 10^9/L	259 (71.3%)	105 (52.0%)
# of subjects < 0.2 x 10^9/L	64 (17.6%)	35 (17.3%)

Source: B301 ADL where SAFFL='Y,' APHASE= 'ON-TREATMENT,' TRT01A='Ponesimod 20 mg,' and PARAMCD='LYM' by SEX

Reviewer Comment: Table 93 shows that lymphocyte counts were somewhat

lower in women randomized to ponesimod in Study AC-058B301, an observation that may explain the higher incidence of some infections in women noted in Table 92. A difference in body mass index (BMI) may be an explanation for this difference in lymphocyte counts; indeed, the average BMI was 24.4 kg/m² in the women (compared to 25.3 kg/m² in the men) who were randomized to ponesimod 20 mg in Study AC-058B301.

Age

As noted in Table 37, SAEs were relatively uncommon in the controlled RMS population. Table 94 delineates those SAEs occurring more than one subject randomized to ponesimod 20 mg in Study AC-058B301, stratified by age.

Table 94. Reviewer Table. SAEs stratified by age in subjects treated with ponesimod, Study AC-058B301

AEDECOD	Age < 40 n=349	Age ≥ 40 N=216
Abdominal pain	1	2
Appendicitis	3	0
Lumbar radiculopathy	0	3
Abortion induced	2	0

Source: B301 ADAE where AESER, SAFFL, TRTEMFL='Y,' and TRT01A='Ponesimod 20 mg' by AEDECOD and AGEGR3.

Reviewer Comment: The numbers of SAEs in the controlled RMS population who received ponesimod 20 mg are too small to comment on age differences with the occurrence of SAEs.

Similarly, TEAEs occurring commonly in subjects randomized to ponesimod 20 mg in Study AC-058B201 are stratified by age as shown in Table 95.

Table 95. Reviewer Table. Common TEAEs stratified by age in subjects treated with ponesimod 20 mg in Study AC-058B301

AEDECOD	Age < 40 n=349	Age ≥ 40 N=216
Nasopharyngitis	125	45
Alanine aminotransferase increased	122	42
Headache	50	49
Upper respiratory tract infection	51	41
Nausea	36	17
Hypertension	19	31
Back pain	22	18

AEDECOD	Age < 40 n=349	Age ≥ 40 N=216
Urinary tract infection	18	22
Aspartate aminotransferase increased	25	13
Fatigue	27	11
Oral herpes	32	5
Dyspnea	23	12
Dizziness	17	16
Bronchitis	25	7
Respiratory tract infection viral	21	10
Influenza	18	9
Hepatic enzyme increased	10	16
Cough	14	10
Depression	13	10
Pain in extremity	8	15
Abdominal pain upper	15	7
Diarrhea	6	15
Respiratory tract infection	10	10
Alopecia	13	6
Hyperkalemia	13	6
Anxiety	8	10
Arthralgia	9	9
Somnolence	14	4
Constipation	9	8
Hypoesthesia	8	9
Paresthesia	9	8
Pharyngitis	10	7
Herpes zoster	10	6
Anemia	10	5
Hypercholesterolemia	9	6
Rhinitis	13	2

Source: B301 ADAE where SAFFL and TRTEMFL='Y,' and TRT01A='Ponesimod 20 mg' by AEDECOD and AGEGR3

Reviewer Comment: Since TEAEs could be reported more than once by the same subject, Table 95 does not contain percentages of subjects experiencing each TEAE, although recognizing that over 60% of the subjects are ≤ 40yo may allow inferences to be made. It appears that headaches and TEAEs related to upper respiratory tract infections occurred more commonly in the younger subset of the population randomized to ponesimod 20 mg and that hypertension occurred more commonly in the older subset of this subpopulation.

Race
Since over 97% of the subjects randomized to ponesimod 20 mg classified their race as "white," subgroup analyses were not performed by race.

8.7. Specific Safety Studies/Clinical Trials

N/A

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See malignancy subsection of 8.5.4.

8.8.2. Human Reproduction and Pregnancy

The 120-day safety update contains a useful figure containing the pregnancies in female subjects exposed to ponesimod up to and including the 120DSU.

Study ID / Subject ID	Action taken with ponesimod	Related to study treatment?	Outcome
AC-058A201 / (b) (6)	Not applicable	No	Abortion spontaneous
AC-058B202 /	Withdrawn	No	Delivery of a normal baby
AC-058B202 /	Withdrawn	Related	Abortion induced
AC-058B202 /	Withdrawn	No	Abortion induced
AC-058B202 /	Withdrawn	No	Abortion induced
AC-058B202 /	Withdrawn	No	Delivery of a normal baby
AC-058B202 /	Withdrawn	No	Abortion spontaneous
AC-058B202 /	Not applicable	No	Delivery of a normal baby
AC-058B202 /	Not applicable	No	Delivery of a normal baby
AC-058B301 /	Withdrawn	No	Delivery of a normal baby
AC-058B303 /	Not applicable	No	Delivery of a normal baby
AC-058B303 /	Withdrawn	No	Delivery of a normal baby
AC-058B303 /	Not applicable	No	Delivery of a normal baby
AC-058B303 /	Not applicable	No	Delivery of a normal baby
AC-058B303 /	Withdrawn	No	Delivery of a normal baby
AC-058B303 /	Withdrawn	No	Abortion induced
AC-058B301 /	Withdrawn	No	Delivery of a normal baby
AC-058B301 /	Withdrawn	No	Abortion induced
AC-058B301 /	Withdrawn	No	Abortion induced
AC-058B303 /	Withdrawn	Yes	Abortion spontaneous
AC-058B303 /	Not applicable	No	Delivery of a normal baby
AC-058B303 /	Not applicable	No	Delivery of a normal baby
AC-058B303 /	Not applicable	No	Abortion spontaneous

* These subjects did not have ponesimod exposure during pregnancy (planned pregnancy)

Subject AC-(b) (6) was a 32yo woman who became pregnant while taking ponesimod 20 mg; since a transvaginal ultrasound showed a gestational sack with a double ring sign but not yolk sack, a molar pregnancy was suspected, and a therapeutic abortion was performed.

Per Section 6.2 of the 120-day safety update, five new 5-ongoing pregnancies were reported after the cut-off date for the initial NDA submission, and all five occurred in the AC-058B303: one with exposure to ponesimod resulted in a spontaneous abortion (Subject (b) (6)), three planned pregnancies without ongoing exposure to ponesimod

(normal newborns in Subjects (b) (6) and (b) (6) spontaneous abortion in Subject (b) (6), and one on-going partner pregnancy (Subject (b) (6)). In addition, the five pregnancies (two with exposure to ponesimod) that were ongoing in Study AC-058B303 at the data cutoff for the initial NDA submission resulted in normal newborns. Although not noted in Section 6.2 of the 120-day safety update, subject (b) (6) terminated an unintended pregnancy (despite having an intrauterine device) while participating in Study AC-058B303.

The ponesimod clinical trials required sexually active subjects of reproductive potential (both men and women) to use an effective form of contraception for the duration of the study. Women who became pregnant during the studies were required to discontinue the study drug, as were men whose female partners became pregnant during the studies.

Reviewer Comment: Although the data regarding the effects of exposure to ponesimod during pregnancy appear unrevealing for a safety signal, the data are limited, so the labeling for ponesimod should contain a warning for fetal risk that encourages women of child-bearing potential to use effective contraception while taking ponesimod.

The SCS states that ponesimod has not been studied in breastfeeding women but notes that a study in lactating rats showed excretion of ponesimod in breast milk. The Applicant reports that "There are no data on the presence of ponesimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production."

8.8.3. **Pediatrics and Assessment of Effects on Growth**

Because the clinical studies of ponesimod excluded subjects below 18 years of age, no clinical data were submitted to support a pediatric indication, so the indication of any ponesimod labeling should be for the treatment of adults with RMS.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Per the SCS, of the 1148 subjects who took ponesimod 20 mg daily, seven (0.6%) reported taking an extra dose of ponesimod (e.g., 40 mg in a day), but the four who were checked after taking an extra dose of ponesimod reported no symptoms of overdose. No overdoses with a magnitude greater than 40 mg/day are reported.

The SCS states "the nonclinical profile of ponesimod does not indicate any potential for abuse, based on 1) the molecular structure of ponesimod, which is not similar to known drugs of abuse, 2) the off-target receptor-binding profile of ponesimod relative to approved S1P receptor modulators and known drugs of abuse, and 3) the absence of effects on locomotor activity and adverse CNS symptoms in animals at clinically relevant

doses."

Adverse event suggestive of drug withdrawal and rebound are not reported in the SCS; however, a few cases of rebound disease activity have been reported with cessation of other S1P receptor modulators for RMS.

Although the review by the Clinical Substance Staff (CSS) is pending at this time, a potential signal for euphoria with ponesimod has been identified, for which the following enhanced pharmacovigilance is requested.

- "We request that you perform post marketing surveillance for cases of abuse or abuse-related adverse events in patients exposed to ponesimod. Submit individual reports as 15-day expedited reports to your NDA and directly to the Division of Neurology 2. Include comprehensive summaries and analyses of these events quarterly as part of your required post marketing safety reports (e.g., periodic safety update reports [PSURs]). In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the occurrence of abuse or abuse-related adverse events in patients exposed to ponesimod or the causality, along with information about dose and dose titration, duration of ponesimod therapy, time of event in relation to duration of therapy, associated signs and symptoms, concomitant therapies, treatment given for the event, and outcome of each event."

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Ponesimod is not currently marketed anywhere in the world, so there is no postmarketing safety experience available for review.

8.9.2. Expectations on Safety in the Postmarket Setting

Given the similarity of ponesimod to other approved S1P receptor modulators, vigilance for serious infections (including progressive multifocal leukoencephalopathy [PML], cryptococcal meningitis, and other opportunistic infections), cutaneous and other malignancies, posterior reversible encephalopathy syndrome (PRES), and severe increases in disability with drug cessation would be prudent with ponesimod.

8.9.3. Additional Safety Issues From Other Disciplines

This reviewer is unaware of any safety issues from other disciplines at this time.

8.10. Integrated Assessment of Safety

1. Infections / Lymphopenia

Administration of ponesimod causes a reduction in circulating lymphocytes, predominantly CD4+ and CD8+ subtypes, with relative sparing of neutrophils. Lymphopenia can increase the risk of infections, and the risk of upper respiratory tract infections and herpetic infections (e.g., herpes zoster) was increased in subjects randomized to ponesimod in its clinical trials in subjects with RMS. Although no cases of progressive multifocal leukoencephalopathy (PML) or cryptococcal meningitis were reported in the ponesimod development program, these opportunistic infections are labeled with other S1P receptor modulators and can occur in the setting of significant lymphopenia.

Lymphocyte counts should be checked before starting, and periodically during, treatment with ponesimod. Lymphopenia and the risk of infection, including the risk of herpes infections and opportunistic infections such as PML and cryptococcal meningitis, should be described in the Warnings and Precautions section of any labelling for ponesimod.

2. Liver Injury

Ponesimod can cause elevations in AST and ALT, but these elevations appear reversible with discontinuation of the drug. Most of the transaminase elevations in the ponesimod development program were asymptomatic, and there were no reported cases of fulminant hepatic failure (or clear Hy's law cases suggestive of DILI) in these studies.

Transaminases and total bilirubin should be checked before starting, and periodically during, treatment with ponesimod. Any labeling for ponesimod should include a statement regarding the risk (and symptoms) of transaminase elevation and liver injury in the Warnings and Precautions section.

3. Bradyarrhythmia / AV block

S1P receptor modulators such as ponesimod are associated with bradyarrhythmia and AV block. In the controlled RMS studies, ponesimod was initiated with a 14-day dose escalation, which appeared to reduce the rate of bradycardia and other dysrhythmias when starting the drug. Subjects with a myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months, New York Heart Association Class III / IV heart failure, cardiac conduction or rhythm disorders, risk factors for QT prolongation, severe untreated sleep apnea, or a resting heart rate less than 55 bpm at baseline, were excluded from participation in the controlled RMS studies. With these exclusions and the dose escalation, there were no reported cases with a heart rate less than 40 bpm or Type 2 (or higher) AV block in Study AC-058B301.

In order to determine whether a patient has an occult arrhythmia or to confirm an ongoing cardiac issue, all patients should have an ECG prior to initiation of ponesimod, and

ponesimod should only be initiated with the recommended dose escalation. The risk of bradyarrhythmia and AV block, and the exclusionary cardiac conditions for the controlled RMS studies, should be included in the Warnings and Precautions section of any labeling of ponesimod. The labeling should also note that the heart rate nadir after starting ponesimod should occur approximately two hours after administration of the first dose of the medication. This reviewer agrees that four hours of observation after the first dose of ponesimod is administered should be recommended for individuals with sinus bradycardia [HR less than 55 beats per minute (bpm)], first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure occurring more than 6 months prior to treatment initiation.

4. Hypertension

Similar to other S1P receptor modulators, ponesimod was associated with (usually mild) elevations in blood pressure. Blood pressure should be monitored during treatment with ponesimod, and the risk of hypertension should be included in the Warnings and Precautions section of any labeling for ponesimod.

5. Respiratory Effects

Similar to other S1P receptor modulators, ponesimod was associated with a reduction in FEV1, FVC, and DLCO, and the rate of dyspnea with ponesimod was greater than that of the study comparators. The risk of respiratory effects should be included in the Warnings and Precautions section of any labelling of ponesimod.

6. Macular edema

Macular edema was *a priori* expected to be a treatment-related adverse event due to ponesimod's effect on vascular permeability and the experience with other S1P receptor modulators; however, the rate of macular edema with ponesimod 20 mg was 1.1%, and about half of the cases had pre-existing risk factors for macular edema. Section 5 of any labelling for ponesimod should include a warning for macular edema and list the risk factors for macular edema, including a history of uveitis or diabetes mellitus.

7. Malignancy

Malignancies, especially cutaneous malignancies, are noted with other S1P receptor modulators, and it is biologically plausible that decreased immunosurveillance from sequestering lymphocytes in lymphoid tissue may increase the risk of malignancy. It appears that there may be an increased risk of cutaneous malignancies (and possibly breast cancer) in subjects taking ponesimod in its RMS studies, and an increased risk of cutaneous malignancies has been observed with other S1P receptor modulators approved for RMS. In addition to increased pharmacovigilance and timely reporting of all malignancies occurring in individuals taking ponesimod, this reviewer recommends including cutaneous malignancies in Section 5 (Warnings and Precautions) of any labelling for ponesimod.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not deemed necessary for this NDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The labeling has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

This section is not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS does not appear to be necessary to ensure the safe use of ponesimod in the indicated population.

12. Postmarketing Requirements and Commitments

At the time of completion of this review, it appears that the following postmarketing requirements (PMRs) will be imposed:

1. A two-part study of ponesimod in pediatric patients with RMS at least 10 years and less than 18 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ponesimod in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine titration and maintenance doses of ponesimod that will result in PK and PD effects that are comparable to those of the 14-day titration administered to adult patients. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ponesimod compared to an appropriate comparator.
2. A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ponesimod during pregnancy with two unexposed control populations: one

consisting of women with multiple sclerosis who have not been exposed to ponesimod before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development will be assessed through at least the first year of life.

3. A pregnancy outcomes study using a different study design than provided for the prospective pregnancy exposure study (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to ponesimod during pregnancy compared to an unexposed control population.

At the time of completion of this review, it appears that the following postmarketing commitments (PMCs) will be imposed:

1. Conduct a Drug-Drug Interaction trial to evaluate the impact of strong PXR agonists on the pharmacokinetics of Ponvory (ponesimod).

13.Appendices

13.1. References

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13.2. Kurtzke Expanded Disability Status Scale

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System (FS) score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.
Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. Each step (e.g., 3.0 to 3.5) is still part of the DSS scale equivalent (i.e., 3). Progression from 3.0 to 3.5 should be equivalent to the DSS score of 3.

0 - Normal neurological exam (all grade 0 in FS).

1.0 - No disability, minimal signs in one FS (i.e., grade 1).

1.5 - No disability, minimal signs in more than one FS (more than on FS grade 1).

2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).

4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.

4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.

5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions): (usual FS equivalents are one grade 5 alone, others 0 or 1: or combinations of lesser grades usually exceeding specifications for step 4.0).

5.5 - Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).

6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting: (usual FS equivalents are combinations with more than two FS grade 3 +).

6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3 +).

7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grad 4 +; very rarely pyramidal grade 5 alone).

7.5 - Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4 +).

8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4 + in several systems).

8.5 - Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations generally 4 + in several systems).

9.0 - Helpless bed patient: can communicate and eat; (usual FS equivalents are combinations, mostly grade 4 +).

9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4 +).

10.0 - Death due to MS.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID E JONES
03/17/2021 12:39:18 PM

PAUL R LEE
03/18/2021 09:59:37 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD, 20993

CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: NDA 213498/ref IND [redacted] (b) (4); ponesimod (ACT-128800; JNJ-67896153)

FROM: Susan Pretko, PharmD, MPH
Clinical Outcome Assessment (COA) Reviewer
Division of Clinical Outcome Assessment (DCOA)

Elektra Papadopoulos, MD, MPH
COA Associate Director
DCOA

SUBJECT: Division of Neurology 2 consult to DCOA requesting comment on the Fatigue Symptoms Impact Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS) in Study AC-058B301, the clinical meaningfulness, and appropriateness for labeling claims of the achieved results

DRUG APPLICANT: Janssen Pharmaceuticals, Inc.

COA TRACKING NUMBER: C2020184

Please check all that apply:
☒ **Rare Disease**/Orphan Designation
☐ Pediatric

Instrument type:
☒ Patient-reported outcome (PRO)
☐ Observer-reported outcome (ObsRO)
☐ Clinician-reported outcome (ClinRO)
☐ Performance outcome (PerfO)
☐ Others (e.g., passive monitoring)

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS Division of Neurology II (DN II) on April 30, 2020 (DARRTS Reference ID: 4601040) for NDA 213498 regarding ponesimod for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting MS (RRMS), and active secondary progressive MS (SPMS). This COA consult is related to the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS), a patient-reported outcome (PRO) measure.

The applicant proposed the change from baseline to week 108 in the FSIQ-RMS Symptoms domain (FSIQ-RMS-S) score as a secondary endpoint in their randomized, double-blind, active comparator-controlled, parallel-group, superiority phase 3 study (Study OPTIMUM). The NDA submission included proposed labeling claims based on the FSIQ-RMS-S describing that the (b) (4)

< ***Reviewer's Comments:*** *The FSIQ-RMS is a PRO measure comprised of 20 items assessing fatigue-related symptoms (7-items) and impacts of those symptoms (13-items) on the lives of people with RMS. This review is limited to the FSIQ-RMS-S as this is the only domain proposed to support secondary endpoints and labeling claims for NDA 213498. The FSIQ-RMS-S is in Appendix 1 and the FSIQ-RMS-S conceptual framework and FSIQ-RMS-S scoring algorithm are in Appendix 2.*

A single-item patient global impression of severity (PGI-S) anchor scale was also administered in the OPTIMUM study. The PGI-S is in Appendix 3.

Both the FSIQ-RMS and PGI-S were administered in an electronic format and were completed during the pre-randomization period, at Visits 6, 7, 10, 12, and 14 (Weeks 12, 24, 60, 84, and 108/End of Treatment, respectively), and at unscheduled visits (e.g., due to relapses). >

This review concludes that the FSIQ-RMS-S has content validity based on the evidence described in the reviewer's comments. However, insufficient information was provided to support interpretation of clinically meaningful within-patient changes in FSIQ-RMS-S scores. Refer to the reviewer's comments for more information.

Refer to previous COA reviews for the reference IND 101722:

- C2019254 dated November 1, 2019_Illoh (DARRTS Reference ID: 4513633)
- AT 2018-376 dated June 5, 2019_Pretko (DARRTS Reference ID: 4444301)
- AT 2014-111 dated October 3, 2014_Slagle (DARRTS Reference ID: 3638730)
- AT 2011-131 dated December 16, 2011_Cai (DARRTS Reference ID: 3059690)
- AT 2011-074 dated September 9, 2011_Cai (DARRTS Reference ID: 3012829)

Reviewer's Comments:
We acknowledge that fatigue is a relevant and important symptom to patients with RMS. The applicant submitted a PRO evidence dossier with data based on quantitative analyses to support

the interpretation of the FSIQ-RMS-S scores[1]. The PRO evidence dossier included cumulative distribution function (CDF) and probability density function (PDF) curves to interpret the FSIQ-RMS-S data based on the PGI-S scale. However, at the pre-NDA meeting[2], the Agency informed the sponsor, "It is important to understand what constitutes a meaningful improvement in the 11-point PGI-S scale ratings based on the patient perspective; this would aid in determining an appropriate point change in the PGI-S scale to be used as the anchor to define improvement in the FSIQ Symptoms domain score." Evidence to support interpretation of the PGI-S scale was not provided. In the absence of this information, there is insufficient evidence to support interpretation of FSIQ-RMS-S scores.

While anchor-based methods are the primary methods used by the Agency to interpret meaningful within-patient score changes in COA endpoints, the PGI-S administered in the OPTIMUM study is not an appropriate anchor scale. Anchor scales should be easier to interpret than the COA endpoint and should have distinct and non-overlapping response categories. The PGI-S uses a 0-10 numeric rating scale (NRS) which has limitations as an anchor measure given its intermediate response categories do not have verbal descriptors, and it is unclear what difference on this scale is clinically meaningful.

The magnitude of missing data in the analysis for the FSIQ-RMS-derived endpoint presents additional limitations to interpreting these data. Based on the Clinical Study Report for Study 301, approximately 20.8% (n=449) of subjects in the ponesimod group (n=567) and 19.1% (n=108) of subjects from the teriflunomide group (n=566) were missing from the analysis for change from baseline to week 108 in FSIQ-RMS-S weekly scores. There was approximately 20% missing baseline data for the FSIQ-RMS-S and an Information Request was sent to the applicant on September 11, 2020 asking for the reason for the missing data. The applicant responded[3] stating that the missing data was due to study misconduct related to the questionnaire administration procedure such that subjects failed to complete the FSIQ-RMS on at least 4 of the 7 days in the pre-randomization period, which was intended to define baseline FSIQ-RMS-S scores.

FDA has provided considerable advice on development of the FSIQ-RMS to assess fatigue symptoms and their impacts in the lives of patients with RMS. The sponsor for the reference IND used methods consistent with the FDA Guidance for Industry on the Development of Patient Reported Outcomes to Support Labeling or Promotional Claims. A literature review was conducted to inform development of a semi-structured concept elicitation (CE)/concept confirmation interview guide. Seventeen CE interviews were conducted in adult patients with relapsing-remitting MS and it was determined that concept saturation based on spontaneous reports from patients for fatigue symptoms and impacts was achieved. The FSIQ-RRMS v1 was developed containing 15 items assessing fatigue symptoms and 14 items assessing the impacts of fatigue symptoms.

Twenty patients were cognitively interviewed to assess the FSIQ-RRMS v1. Patients provided overall feedback regarding the symptom section of the instrument. The majority of subjects

[1] NDA 213498 SN0001(1) received March 18, 2020.
[2] IND 101722 Type B Pre-NDA Meeting Minutes dated September 26, 2019 (DARRTS Reference ID: 4497423)
[3] NDA 213498 SN 0018(18) received September 16, 2020.

understood the recall period as intended and did not demonstrate difficulty interpreting it. All patients interpreted the response scales as intended. All patients reported that some items in the symptom portion of the FSIQ-RRMS v1 were redundant with one another, but there was no consistency in these reports from patient to patient. Of the 15 items assessing fatigue symptoms, 7 were removed. Specifically, all of the "at rest" items (n=6) were removed due to inconsistent patient interpretations and an additional "exhausted" item was removed as it was considered by most patients to be a more severe sensation of tiredness (n=11, 55.0%). The instructions of the instrument were revised to improve clarity and the FSIQ-RRMS v2 was developed as a result of these changes.

Using quantitative data collected during patient cognitive interviews, a mixed methods analysis was performed to ensure items selected during the qualitative phase for retention in the FSIQ-RRMS v2 symptoms domain sufficiently covered the distribution of fatigue severity. This led to the inclusion of the item "worn out at rest" to further differentiate patients with more severe fatigue symptoms, resulting in the FSIQ-RRMS v3. The FSIQ-RRMS v3 was then assessed in a content confirmation study including patients with progressive relapsing MS (PRMS) and relapsing secondary progressive MS. This study found that the FSIQ-RRMS v2 was comprehensive and relevant to both populations. As such, the FSIQ-RRMS v3 was retitled the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS v1).

*The FSIQ-RMS v1 was assessed in a psychometric validation study resulting in deletion of 2 fatigue symptoms items that were found almost perfectly correlated (>0.90) with the items assessing physical and mental tiredness and thus was determined to be redundant. Based on this evidence, the previous COA review (*AT 2014-111*) concluded that the evidence submitted was sufficient to demonstrate the content validity of the FSIQ-RMS v2 which was used in the phase 3 studies of ponesimod in RMS.*

Appendix 1. FSIQ-RMS v2

Appendix 9 Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS)

INSTRUCTIONS

This questionnaire asks about your experience with your Relapsing Multiple Sclerosis (relapsing MS).

- This section of the questionnaire asks about your **fatigue-related symptoms** of relapsing MS over the **past 24 hours**.

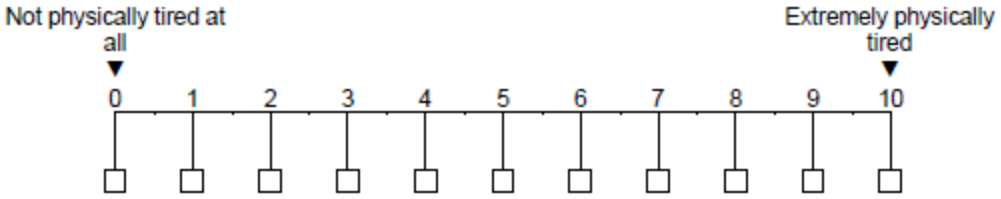
Please select the response that best describes your experience. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Section 1

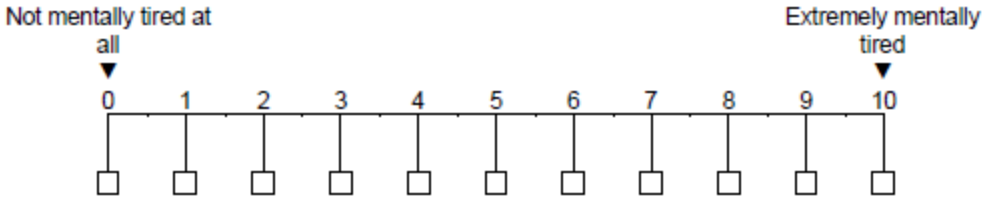
Instructions:

Please select the response that best describes your experience with **relapsing MS symptoms** in the **past 24 hours** while doing routine daily activities (e.g. housework, yard work, shopping, working).

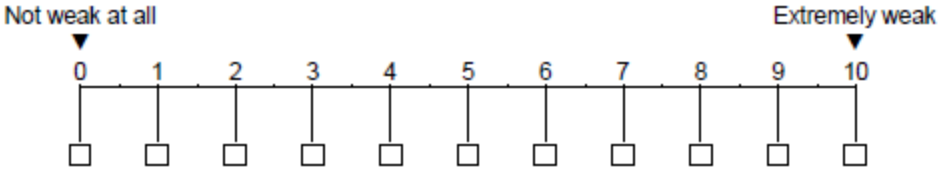
1. In the past 24 hours, while doing routine daily activities, how **physically tired did you feel**?



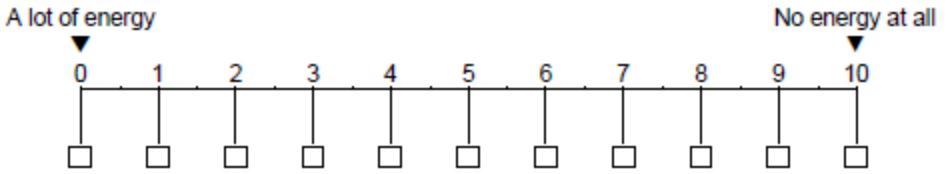
2. In the past 24 hours, while doing routine daily activities, how **mentally tired did you feel**?



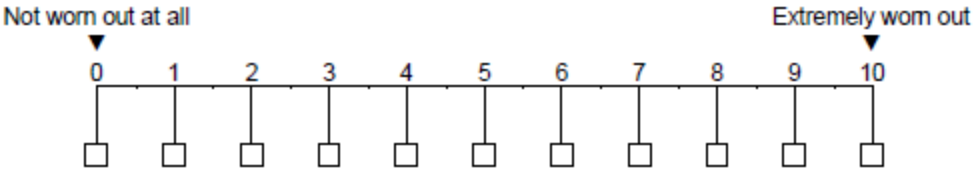
3. In the past 24 hours, while doing routine daily activities, how **physically weak did you feel**?



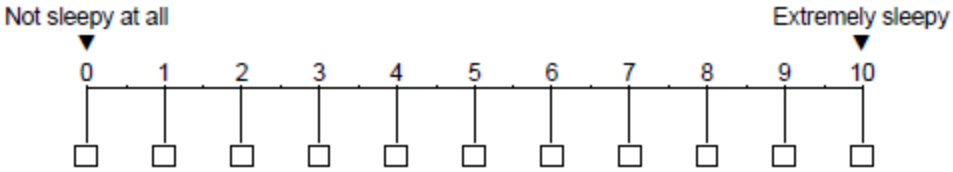
4. In the past 24 hours, how would you rate your **energy** while doing routine daily activities?



5. In the past 24 hours, while doing routine daily activities, how **worn out did you feel**?



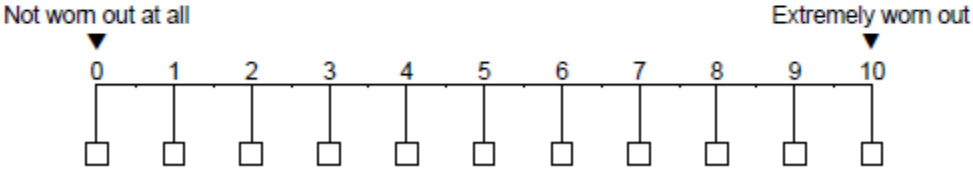
6. In the past 24 hours, while doing routine daily activities, how **sleepy did you feel**?



Instructions:

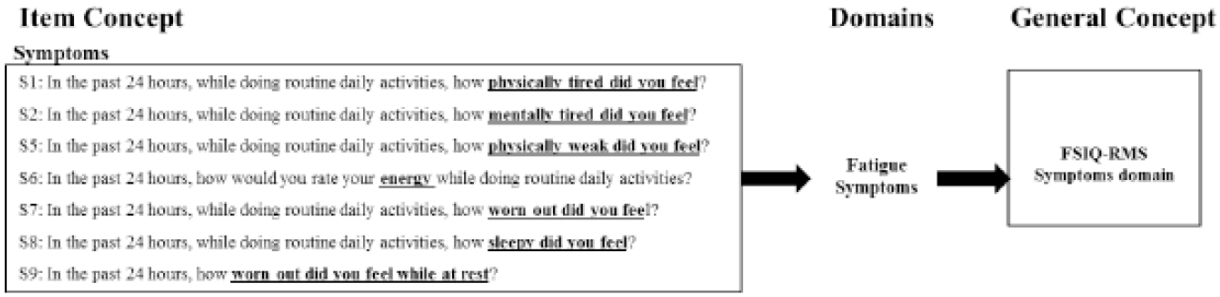
Please select the response that best describes your experience with **relapsing MS symptoms** in the **past 24 hours** **while at rest** (e.g. reading a book, watching TV).

7. In the past 24 hours, how **worn out did you feel while at rest**?



Appendix 2. FSIQ-RMS v2 Conceptual Framework and Scoring Algorithm

FSIQ-RMS v2 Conceptual Framework



FSIQ-RMS v2 Scoring Algorithm

The FSIQ-RMS symptom score can range from 0 to 100, with higher scores reflecting more severe fatigue. The scoring algorithm is:

- (Sum of individual items scores * 100)/number of items (7) * highest rating (10)

To be able to compute a daily symptoms score, at least 4 items of the symptoms diary have to be non-missing; otherwise, the score is considered "missing". For each 7-day weekly score, at least 4 reported diaries with at least 4 items completed on each diary day are need3ed to calculate the FSIQ-RMS symptom weekly score. If fewer than 4 diaries with data on at least 4 items are available within the 7-day period, then the weekly score is considered as "missing".

Appendix 3. PGI-S

Patient's Global Impression of Severity of Fatigue

Please mark an "X" in the box (☒) which best describes the severity of your fatigue **today**.

1. Overall, how severe is your fatigue today?	Not severe at all ▼ 0 1 2 3 4 5 6 7 8 9 10 ▼ Very severe ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

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/s/

SUSAN M PRETKO
11/06/2020 03:22:03 PM

ELEKTRA J PAPADOPOULOS
11/06/2020 04:02:46 PM