DMT43

Ponesimod in Relapsing Forms of Multiple Sclerosis - Long-Term Pooled Safety Results from the Clinical Development Program

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BACKGROUND

- Ponesimod is an orally active highly selective modulator of the sphingosine-1-phosphate receptor 1 (S1P1) approved in multiple countries for the treatment of relapsing forms of multiple sclerosis (RMS)[1,2]
- The Phase 2 and 3 clinical development program of ponesimod monotherapy in MS includes two completed double-blind, controlled studies (AC-058B201 and AC-058B301/OPTIMUM) and two ongoing long-term extension (LTE) studies (AC-058B202 and AC-058B303/OPTIMUM-LT)[3,4]
- This pooled analysis was designed to characterize the long-term safety of ponesimod and understand the potential adverse events (AEs) which may only occur following long-term treatment with ponesimod 20 mg in patients with RMS

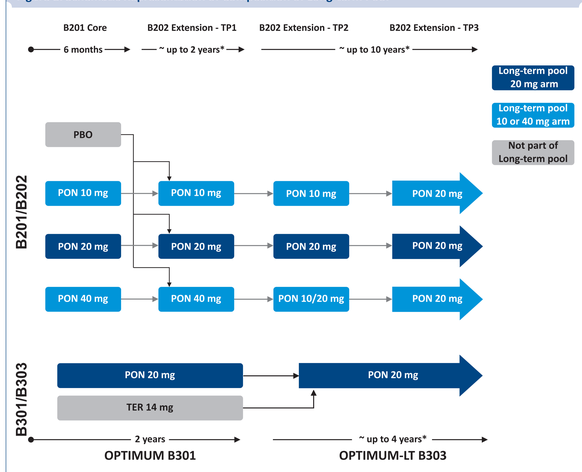
OBJECTIVE

- This safety analysis was undertaken to provide a comprehensive perspective of the safety of ponesimod in the treatment of RMS and to characterize the overall safety profile of ponesimod 20 mg in a large and robust 'long-term' pooled dataset

METHODS

- Patients from the long-term pool (i.e., all patients randomized in AC-058B201 who received at least 1 dose of ponesimod in either AC-058B201 or AC-058B202 and all patients randomized in AC-058B301 who received at least 1 dose of ponesimod in AC-058B301 or AC-058B303) were included (data collected up to and including 18 March 2020) (Figure 1)
- Analyses were performed by the first allocated dose of ponesimod (i.e., ponesimod 10 mg, 20 mg, or 40 mg), regardless of subsequent treatment assignment (Figure 1)
- As 20 mg ponesimod is the approved dose and majority of patients (79.8%) included in long-term pool received 20 mg ponesimod as their only maintenance dose, information of this poster focuses mainly on the 20 mg arm to avoid potentially misleading comparisons (Figure 1)

Figure 1: Schematic Representation of Composition of Long-term Pool



LT, long-term extension; PBO, placebo; PON, ponesimod; TER, teriflunomide; TP, treatment period
*Exposure considered from start of first ponesimod dose in the core study
Note: Box sizes are not reflective of population or study duration

RESULTS

Patients

- Patients included in ponesimod 20 mg arm were mostly White (97.6%), female (65.5%), and <40 years of age (57.3%) with mean age of 37.6 years
- In the ponesimod 20 mg arm, mean time since first MS symptoms was 8.38 years and mean time since recent documented relapse was 13.29 months
- Mean percentage of patients in ponesimod 20 mg arm with prior use of disease modifying therapies (DMTs) for MS was 63.7%, with mean Expanded Disability Status Scale (EDSS) score of 2.51 at baseline

Table 1: Baseline and Demographic Characteristics of Patients Prior to Treatment Start Date in Pool

	Ponesimod 20 mg N = 1148	Total Ponesimod N = 1438
Female, n (%)	752 (65.5)	948 (65.9)
Age (years), mean (SD)	37.6 (8.8)	37.4 (8.8)
Race, n (%)		
White	1121 (97.6)	1398 (97.2)
Time since first MS symptoms (years), mean (SD)	8.4 (6.7)	8.2 (6.7)
Time since the most recent documented relapse (months), mean (SD)[a]	13.3 (11.5)	12.1 (10.8)
EDSS at baseline, mean (SD)	2.5 (1.3)	2.5 (1.3)
Prior use of disease modifying therapies for MS[b], n (%)	731 (63.7)	827 (57.5)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis;
[a]ponesimod 20 mg, n=1134; total ponesimod, n=1420.
[b]In Study B201, disease modifying therapies received within the past 24 months prior to study entry were collected; while in Study B301 disease modifying therapies received at any time in the past were collected.
Age is re-calculated for subjects starting ponesimod treatment in B303 study. All remaining demographic data are presented as collected at entry into the core studies.

Disposition and Exposure

- The total mean exposure to ponesimod in the 20 mg arm was 2.8 years (3253.21 patient-years), of these, 855 (74.5%) patients were receiving ongoing ponesimod 20 mg treatment as of March 2020 (Tables 2 and 3)
- The treatment discontinuation rate in ponesimod 20 mg arm was 24.6%, and 11 (1.0%) patients interrupted their treatment for planned pregnancy at the time of analysis (Table 2)
- Most frequently reported reasons for discontinuation of study treatment were tolerability related or due to adverse events (AEs), reported for 79 of 282 patients (28.0%) who discontinued treatment (Table 2)

Table 2: Disposition in Ponesimod 20 mg arm of Long-term Pool

	Ponesimod 20 mg	Total Ponesimod
Randomized/allocated in the pool	1148	1438
Treated in the pool[a]	1148 (100)	1438 (100)
Ongoing treatment in the pool[a]	855 (74.5)	989 (68.8)
Restarted treatment after planned pregnancy interruption	2 (0.2)	4 (0.3)
Discontinued treatment in the pool[b]	282 (24.6)	438 (30.5)
Treatment interruption for planned pregnancy ongoing at cut-off[a]	11 (1.0)	11 (0.8)
Reason for premature discontinuation of treatment[b]		
Death	1 (0.4)	1 (0.2)
Lost to follow-up	5 (1.8)	9 (2.1)
Pre-specified study treatment discontinuation criteria	26 (9.2)	33 (7.5)
Tolerability related/adverse event	79 (28.0)	129 (29.5)
Efficacy related	36 (12.8)	61 (13.9)
Patient's decision (other/unknown)	69 (24.5)	107 (24.4)
Investigator decision (other/unknown)	13 (4.6)	20 (4.6)
Other	2 (0.7)	7 (1.6)
Completed treatment in B201 and did not enter B202	9 (3.2)	25 (5.7)
Completed treatment in B301 and did not enter B303	32 (11.3)	32 (7.3)
Completed treatment period 1 or 2 in B202 and did not enter subsequent period	4 (1.4)	8 (1.8)
Reason not provided	6 (2.1)	6 (1.4)

[a]Percentages are based on patient treated within the pool.
[b]Percentages are based on patient prematurely discontinued treatment using definition of condensed reason for discontinuation within the pool.

Table 3: Exposure in Ponesimod 20 mg arm of Long-term Pool

	Ponesimod 20 mg N = 1148	Total Ponesimod N = 1438
Exposure (years)[a]		
Mean (SD)	2.8 (2.2)	3.4 (2.9)
Exposure by category, [n (%)][a]		
≥ 3 months	1081 (94.2)	1334 (92.8)
≥ 6 months	1044 (90.9)	1270 (88.3)
≥ 1 year	977 (85.1)	1193 (83.0)
≥ 2 years	642 (55.9)	846 (58.8)
≥ 3 years	493 (42.9)	679 (47.2)
≥ 4 years	193 (16.8)	370 (25.7)
≥ 5 years	84 (7.3)	253 (17.6)
≥ 6 years	81 (7.1)	241 (16.8)
≥ 7 years	78 (6.8)	232 (16.1)
≥ 8 years	77 (6.7)	221 (15.4)
≥ 9 years	66 (5.7)	191 (13.3)
≥ 10 years	12 (1.0)	22 (1.5)
Cumulative exposure (total patient-years of exposure); sum[a]	3253.21	4934.84

[a]Treatment interruptions are excluded

Long-term Pooled Safety

- The incidence of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) in the ponesimod 20 mg arm was 87.1% and 11.1%, respectively (Tables 4 and 5)
- TEAEs classified as severe were reported in 8.8% of patients in ponesimod 20 mg arm
- TEAEs leading to discontinuation occurred in 8.9% of patients (Tables 4 and 5)
- Most frequently reported (≥ 10% of patients) TEAEs for the ponesimod 20 mg arm were: nasopharyngitis (19.7%), alanine aminotransferase increased (17.9%), headache (13.0%), and upper respiratory tract infection (11.0%) (Tables 4 and 5)

Table 4: Treatment-emergent AEs

n (%)	Ponesimod 20 mg N = 1148	Total ponesimod N = 1438
Patients with at least one event	1000 (87.1)	1280 (89.0)
Most common TEAEs (>5% of patients in 20 mg arm) by PT		
Nasopharyngitis	226 (19.7)	314 (21.8)
Alanine aminotransferase increased	205 (17.9)	240 (16.7)
Headache	149 (13.0)	223 (15.5)
Upper respiratory tract infection	126 (11.0)	191 (13.3)
Lymphopenia	109 (9.5)	116 (8.1)
Hypertension	97 (8.4)	125 (8.7)
Back pain	92 (8.0)	130 (9.0)
Fatigue	87 (7.6)	114 (7.9)
Urinary tract infection	79 (6.9)	119 (8.3)
Bronchitis	65 (5.7)	106 (7.4)
Nausea	63 (5.5)	76 (5.3)
Aspartate aminotransferase increased	62 (5.4)	75 (5.2)
Dizziness	62 (5.4)	98 (6.8)
Overview of all AEs		
Severe AE	101 (8.8)	153 (10.6)
AE leading to study drug discontinuation	102 (8.9)	158 (11.0)
SAE	127 (11.1)	179 (12.4)
Fatal AE	1 (0.1)	1 (0.1)

AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Terms; SAEs, serious AEs; TEAEs, Treatment-Emergent Adverse Events
Preferred Terms (PTs) are based on MedDRA version 21.0. PTs are sorted by descending order of frequency in the ponesimod 20 mg arm.

Table 5: Most Frequent TEAEs by System Organ Class

n (%)	Ponesimod 20 mg N = 1148	Total Ponesimod N = 1438
Patients with at least one event	1000 (87.1)	1280 (89.0)
Most common TEAEs (>10% of patients in 20 mg arm) by SOC		
Infections and infestations	618 (53.8)	824 (57.3)
Investigations	378 (32.9)	495 (34.4)
Nervous system disorders	342 (29.8)	497 (34.6)
Musculoskeletal and connective tissue disorders	274 (23.9)	380 (26.4)
Gastrointestinal disorders	272 (23.7)	370 (25.7)
General disorders and administration site conditions	201 (17.5)	288 (20.0)
Respiratory, thoracic and mediastinal disorders	197 (17.2)	320 (22.3)
Blood and lymphatic system disorders	176 (15.3)	211 (14.7)
Psychiatric disorders	166 (14.5)	228 (15.9)
Skin and subcutaneous tissue disorders	159 (13.9)	226 (15.7)
Eye disorders	145 (12.6)	206 (14.3)
Injury, poisoning and procedural complications	141 (12.3)	221 (15.4)
Vascular disorders	126 (11.0)	170 (11.8)
Metabolism and nutrition disorders	120 (10.5)	165 (11.5)

TEAEs. Treatment-Emergent Adverse Events; SOC, system organ class
System Organ Classes (SOCs) are based on MedDRA version 21.0. SOCs are sorted by descending order of frequency in the ponesimod 20 mg arm.

Table 6: Most Frequent Serious AEs by Preferred Term

n (%)	Ponesimod 20 mg N = 1148	Total Ponesimod N = 1438
Patients with at least one event	127 (11.1)	179 (12.4)
Most common serious AEs (>2 patients in 20 mg arm) by PT		
Appendicitis	6 (0.5)	7 (0.5)
Cholelithiasis	5 (0.4)	6 (0.4)
Abdominal pain	4 (0.3)	4 (0.3)
Multiple sclerosis relapse	4 (0.3)	4 (0.3)
Uterine leiomyoma	3 (0.3)	5 (0.3)
Invasive ductal breast carcinoma	3 (0.3)	4 (0.3)
Uterine polyp	3 (0.3)	3 (0.2)

AEs, adverse events, MedDRA, Medical Dictionary for Regulatory Activities
Preferred Terms (PTs) are based on MedDRA version 21.0. PTs are sorted by descending order of frequency in the ponesimod 20 mg arm.

- In the 20 mg arm, most frequent SAEs (> 1.5%) by system organ class were infections and infestations (2.2%) and nervous system disorders (1.7%) (Table 7)

Table 7: Most Frequent Serious AEs by System Organ Class

n (%)	Ponesimod 20 mg N = 1148	Total Ponesimod N = 1438
Patients with at least one event	127 (11.1)	179 (12.4)
Most common serious AEs (≥2 patients in 20 mg arm) by SOC		
Infections and infestations	25 (2.2)	35 (2.4)
Nervous system disorders	20 (1.7)	27 (1.9)
Gastrointestinal disorders	16 (1.4)	18 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (1.3)	23 (1.6)
Reproductive system and breast disorders	11 (1.0)	17 (1.2)
Hepatobiliary disorders	10 (0.9)	11 (0.8)
Injury, poisoning and procedural complications	9 (0.8)	17 (1.2)
Surgical and medical procedures	9 (0.8)	11 (0.8)
Musculoskeletal and connective tissue disorders	6 (0.5)	8 (0.6)
Renal and urinary disorders	5 (0.4)	5 (0.3)
General disorders and administration site conditions	4 (0.3)	6 (0.4)
Vascular disorders	4 (0.3)	6 (0.4)
Eye disorders	3 (0.3)	8 (0.6)
Respiratory, thoracic and mediastinal disorders	3 (0.3)	5 (0.3)
Investigations	3 (0.3)	5 (0.3)
Psychiatric disorders	3 (0.3)	3 (0.2)
Cardiac disorders	2 (0.2)	6 (0.4)
Blood and lymphatic system disorders	2 (0.2)	2 (0.1)
Metabolism and nutrition disorders	2 (0.2)	2 (0.1)
Pregnancy, puerperium and perinatal conditions	2 (0.2)	2 (0.1)

AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class
System Organ Classes (SOCs) are based on MedDRA version 21.0. SOCs are sorted by descending order of frequency in the ponesimod 20 mg arm.

- Overall, the incidence of malignancies was low with 0.3% of patients in the ponesimod 20 mg arm reporting basal cell carcinoma and one patient with malignant melanoma
- There were no cases of progressive multifocal leukoencephalopathy, cryptococcal meningitis infection or any other opportunistic infections with fatal outcome

LIMITATIONS

- There were differences in the up-titration regimens meaning that effects on heart rate and Atrioventricular conduction cannot be meaningfully evaluated in a pooled analysis
- There were differences in laboratory reference ranges for liver tests between the phase 2 and phase 3 studies, and therefore, results were not pooled

CONCLUSIONS

- **The safety profile of ponesimod 20 mg, including the pattern and nature of TEAEs, was consistent with TEAEs reported from the individual clinical trials as reflected within the product labelling.**
- **No unexpected safety findings were identified in this analysis**

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