Long-Term Safety and Efficacy of Ozanimod in Relapsing Multiple Sclerosis: Results From the DAYBREAK Open-Label Extension Study

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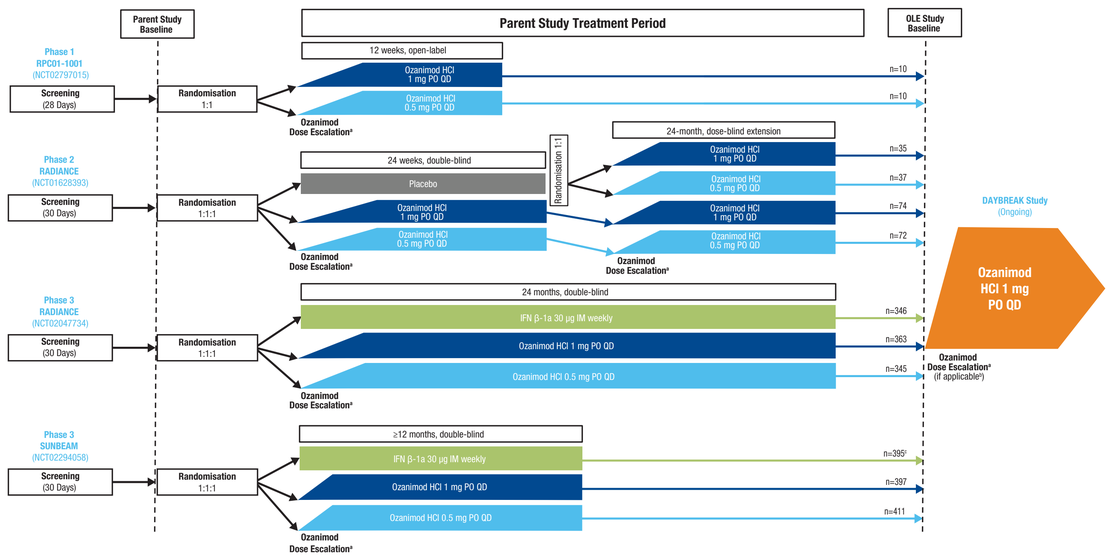
INTRODUCTION AND PURPOSE

- Ozanimod, a sphingosine 1-phosphate receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5,[1] has been evaluated for treatment of relapsing multiple sclerosis (RMS) in phase 1 clinical pharmacology and in phase 2 and 3 efficacy and safety studies[2-4]
  - In phase 3 trials, oral ozanimod HCl 0.5 or 1 mg daily for up to 24 months was superior to intramuscular interferon (IFN) β-1a 30 µg weekly with regard to annualised relapse rate (ARR), number of gadolinium-enhancing (GdE) lesions, and new or enlarging T2 lesions on magnetic resonance imaging (MRI), and was generally well tolerated[3,4]
- Participants with RMS who completed earlier ozanimod clinical trials were eligible to enrol in an ongoing, multicentre, open-label extension (OLE) study (DAYBREAK) aimed at characterising the long-term safety and efficacy of ozanimod HCl 1 mg in RMS
  - Herein, we report a prespecified analysis of the DAYBREAK study

METHODS

- Participants with RMS who completed 1 of 4 parent trials[2-4] were eligible to enrol into DAYBREAK (NCT02576717) in which they received ozanimod HCl 1 mg/d (**Figure 1**)

Figure 1. Parent Studies and OLE Study Design



[a]In all trials, upon initiation of ozanimod HCl, participants received 0.25 mg (equivalent to ozanimod 0.23 mg) on days 1 to 4, 0.5 mg (equivalent to ozanimod 0.46 mg) on days 5 to 7, and then their assigned dose of 0.5 or 1 mg (equivalent to ozanimod 0.92 mg) on day 8 and thereafter. All participants entering the phase 2 dose-blinded extension underwent dose escalation, even if treated with ozanimod in the parent trial, to maintain the blind. [b]In DAYBREAK, dose escalation was performed for all participants entering from one of the phase 3 trials, irrespective of prior treatment assignment (to maintain the blind); dose escalation was not performed for those entering from the phase 1 or 2 trials unless the last dose of ozanimod was >14 days before entering DAYBREAK. [c]One IFN-treated participant did not receive open-label ozanimod and was therefore excluded from the OLE intent-to-treat (ITT) population.
HCl, hydrochloride; IFN, interferon; IM, intramuscular; OLE, open-label extension; PO, per os (oral); QD, once daily.

- DAYBREAK primary objective: to evaluate long-term safety and tolerability of ozanimod, which included treatment-emergent adverse event (TEAE) monitoring
- DAYBREAK secondary objective: to evaluate long-term efficacy of ozanimod
  - ARR was calculated via negative binomial regression, with adjustments for parent trial treatment group, region (Eastern Europe vs rest of world), age at parent trial baseline, and parent trial baseline number of GdE lesions, with time on treatment used as an offset term
  - Number of new or enlarging T2 lesions and number of GdE lesions on MRI were analysed using descriptive statistics in the subgroup who entered DAYBREAK from a phase 3 parent trial
  - Efficacy data were summarised for the overall OLE population and by pooled parent trial treatment groups

RESULTS

Analysis Population

- 2,639 participants completed the parent trials; 2,495 (84.6%) consented to DAYBREAK
- This interim analysis (data cutoff 30 June 2018) includes 2,494 participants in the ITT population of whom 2,323 (93.1%) were ongoing at the time of data cutoff. The ITT population mean exposure to ozanimod HCl 1 mg during the OLE was 19.0 (0.03–32.5) months, and 3959.1 person-years
- On average, participants were 37.7 years of age at OLE baseline, with a mean of 6.8 years since MS symptom onset at the parent study baseline; the majority were female (66.9%), white (99.2%), and from Eastern Europe (90.1%)
  - Demographics and OLE baseline disease characteristics were generally similar across parent study treatment groups

Safety

- TEAEs during the OLE are summarized in **Table 1**
  - The only serious TEAEs (SAEs) to occur in >2 participants were acute pyelonephritis (n=5), uterine leiomyoma (n=5), appendicitis (n=4), and pneumonia (n=3)
  - Similar rates of TEAEs and SAEs occurred when assessed by parent trial treatment group (data not shown)
  - Findings were generally consistent with the phase 3 studies (**Table 1**)

Table 1. Summary of TEAEs During Ozanimod HCl 1 mg in the OLE and in the Pooled Phase 3 Parent Trials, Safety Population

Safety Parameter	OLE Total (N=2,494)	Ozanimod HCl 1 mg During Phase 3 Trials (Pooled) (n=882)[a]
Any TEAE, n (%)	1,704 (68.3)	592 (67.1)
SAEs, n (%)	144 (5.8)	41 (4.6)
Severe TEAEs, n (%)	76 (3.0)	22 (2.5)
Treatment-related TEAE, n (%)	138 (5.5)	26 (2.9)
TEAE leading to permanent discontinuation of ozanimod, n (%)	30 (1.2)	26 (2.9)
TEAEs in ≥5% of participants in OLE total, by preferred term,[b] n (%)		
Nasopharyngitis	291 (11.7)	98 (11.1)
Headache	222 (8.9)	78 (8.8)
Lymphopenia[c]	206 (8.3)	--
Upper respiratory tract infection	169 (6.8)	52 (5.9)
Lymphocyte count decreased[c]	165 (6.6)	--
Alanine aminotransferase increased	56 (2.2)	47 (5.3)

[a]Pooled safety population from phase 3 trials, irrespective of OLE enrolment.
[b]Coded using MedDRA, version 18.1. Participants who had more than 1 event were counted only once per TEAE.
[c]Reduction in lymphocyte count is an expected effect of ozanimod's mode of action; TEAE reporting was based on investigator discretion and not based on any specific level of ALC decline. Investigators were blinded to results of ALC and hematology labs in the phase 3 parent studies and at OLE baseline and received these lab reports for the first time at month 3 in the OLE. If ALC counts <200 cells/µL were found and confirmed on repeat testing, treatment was temporarily stopped until lymphocyte counts reached >500 cells/µL.
ALC, absolute lymphocyte count; HCl, hydrochloride; IFN, interferon; OLE, open-label extension; SAE, serious treatment-emergent adverse event; TEAE, treatment-emergent adverse event.

- Treatment-related TEAEs occurred in 138 participants (5.5%)
  - The only treatment-related TEAEs that occurred in >2 participants were lymphopenia (n=74 [3.0%]), lymphocyte count decreased [n=30 [1.2%], leukopenia (n=17 [0.7%]), urinary tract infection (n=4 [0.2%]), alanine aminotransferase increased (n=4 [0.2%]), gamma-glutamyltransferase increased (n=4 [0.2%]), neutrophil count decreased (n=3 [0.1%]), and respiratory tract infection (n=3 [0.1%])
    - Investigators were blinded to ALC and hematology results in the phase 3 parent studies and at OLE baseline; they received reports of these labs for the first time at month 3 in the OLE
- Transient increases in hepatic enzyme levels were consistent with the parent trial experience
  - Such increases, reported as TEAEs, were more common among those who switched from IFN than among those who received ozanimod HCl 1 mg continuously (alanine aminotransferase increase: 3.3% vs 1.1%; gamma-glutamyl transferase increase: 6.0% vs 3.4%; aspartate aminotransferase increase: 1.5% vs 0.4%)
- Among participants who switched from IFN during the parent trials to ozanimod HCl 1 mg during the OLE, first-dose cardiac monitoring results were similar to those observed during the phase 3 studies
  - Maximum reduction in mean heart rate (HR) of 1.2 bpm was observed at hour 5 following the initial dose of ozanimod HCl 0.25 mg
- QT prolongation was reported on OLE day 1 at hour 6 (QTcF 472 ms; OLE baseline: 448 ms) in a 46-year-old woman who had received ozanimod HCl 0.5 mg in the parent study; this TEAE led to permanent discontinuation of ozanimod on day 15
- Nonserious herpes zoster infections were more frequent in the OLE than in the parent studies (0.7% vs 0.3%)
- There were 8 (0.5%) treatment-emergent malignancies (4 nonmelanoma skin cancers, 4 noncutaneous malignancies) in ozanimod-treated participants in the phase 3 parent studies and 13 (0.5%) during the OLE (5 nonmelanoma skin cancers, 1 malignant melanoma, 7 noncutaneous malignancies), with comparable exposure time of approximately 4000 person-years in the parent and OLE studies

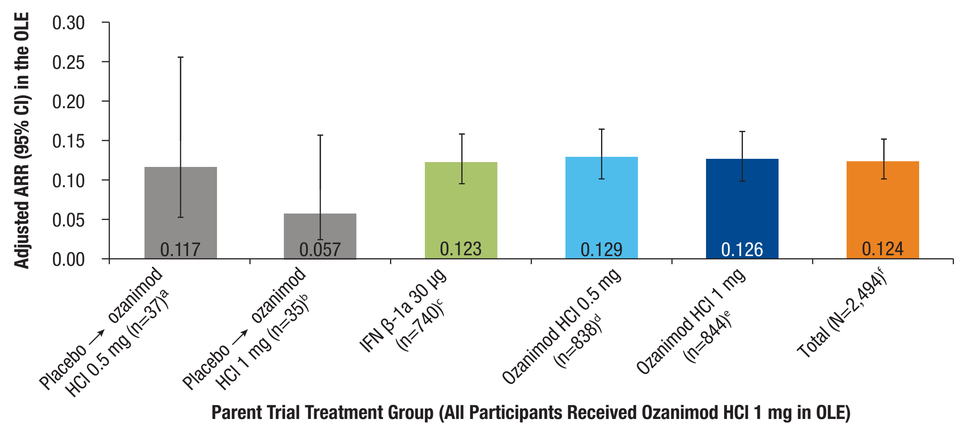
RESULTS (cont'd)

- There were 3 (0.1%) confirmed cases of macular oedema during the OLE, consistent with the 0.2% incidence among phase 3 trial participants treated with ozanimod
- There were 2 deaths in the OLE, both considered unlikely to be treatment related: 1 participant died from injuries after being struck by a train (no evidence of suicidal intent) and 1 died from pulmonary embolism following surgery on a lower limb fracture
  - Two other participants died after permanently discontinuing study drug; both deaths were considered unlikely to be treatment related. One participant died due to metastatic pancreatic cancer and one due to glioblastoma

Relapse Rates in the Overall OLE Population

- The overall ARR during the OLE was 0.124 (95% CI, 0.101–0.152)
  - As a point of reference, adjusted ARRs during the phase 3 parent trials were 0.246, 0.184, and 0.153 among participants treated with IFN β-1a and ozanimod HCl 0.5 and 1 mg, respectively, who went on to enrol in DAYBREAK
- Participants who continued ozanimod HCl 1 mg from any of the parent trials through the OLE had a sustained low ARR during the additional average 19.2 months of exposure (**Figure 2**)
- Participants who switched from ozanimod HCl 0.5 mg in the parent trials to ozanimod HCl 1 mg in the OLE had a slightly lower ARR during the additional average 18.9 months of exposure (**Figure 2**)
- Among those who received IFN in 1 of the phase 3 parent trials, ARR was markedly lower after switching to ozanimod HCl 1 mg in the OLE (average 18.3 months of exposure) (**Figure 2**)

Figure 2. ARR in the OLE, in Which All Participants Received Ozanimod HCl 1 mg

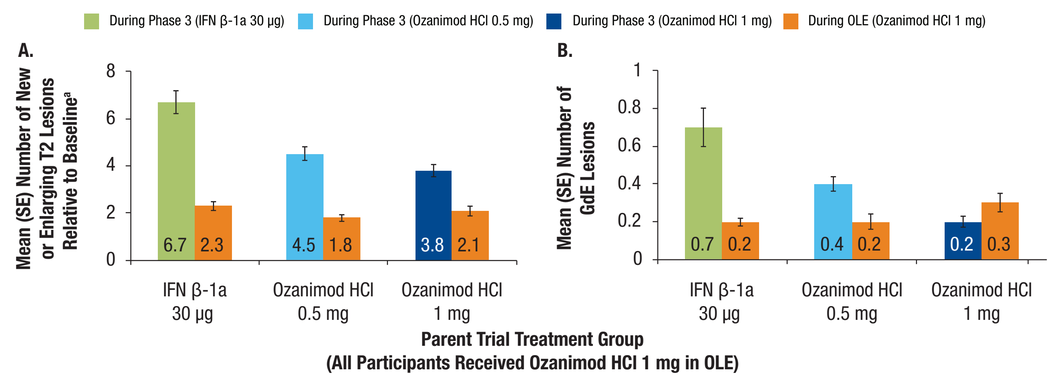


[a]Participants from the phase 2 RADIANCE trial who received placebo for 24 weeks during the double-blind study and were then randomised to ozanimod HCl 0.5 mg for 24 months in the phase 2 extension before entering the OLE. [b]Participants from the phase 2 RADIANCE trial who received placebo for 24 weeks during the double-blind study and were then randomised to ozanimod HCl 1 mg for 24 months in the phase 2 extension before entering the OLE. [c]Participants who received IFN β-1a during either of the phase 3 trials. [d]Participants initially allocated to ozanimod HCl 0.5 in any of the 4 parent trials. [e]Participants initially allocated to ozanimod HCl 1 mg in any of the 4 parent trials. [f]Total of all OLE participants.
ARR, annualised relapse rate; CI, confidence interval; HCl, hydrochloride; IFN, interferon; OLE, open-label extension.

MRI Outcomes in the Phase 3 Parent Trial Subgroup

- Over the first 12 months in the phase 3 parent studies, participants had an average of 6.7, 4.5, and 3.8 new or enlarging T2 lesions with IFN β-1a, ozanimod HCl 0.5 mg, or ozanimod HCl 1 mg treatment, respectively
  - During the first 12 months of the OLE study, these same participants all had a similar average of 1.8 to 2.3 new or enlarging T2 lesions (**Figure 3A**)
  - The phase 3 SUNBEAM trial included MRIs at months 6 and 12, which both contributed to cumulative new/enlarging T2 lesion counts over the 12 months; in phase 3 RADIANCE and the OLE, these lesion counts were based on a single MRI at month 12 relative to their respective baselines
- Participants originally treated with ozanimod HCl 1 mg had similar GdE lesion counts at month 12 in the phase 3 parent study and OLE (**Figure 3B**)
  - Those treated with IFN β-1a and ozanimod HCl 0.5 mg in the phase 3 parent trials had lower GdE lesion counts at month 12 of the OLE, during which they received ozanimod HCl 1 mg, compared with month 12 in the parent trials (**Figure 3B**)

Figure 3. MRI Lesion Counts in the Phase 3 Parent Trials vs OLE. (A) New or Enlarging T2 Lesions During First 12 Months of Phase 3 Parent Trials vs First 12 Months of OLE. (B) GdE Lesions at Phase 3 Month 12 vs OLE Month 12



[a]Baseline refers to parent trial baseline in the parent trial, and OLE baseline in the OLE study.
GdE, gadolinium-enhancing; HCl, hydrochloride; IFN, interferon; OLE, open-label extension; SE, standard error.

CONCLUSIONS

- Ozanimod was generally well tolerated in the DAYBREAK OLE; no new safety concerns were raised with either continued ozanimod HCl 1 mg use, increasing ozanimod HCl dose from 0.5 to 1 mg, or when switching from IFN β-1a to ozanimod HCl 1 mg
- Treatment with ozanimod HCl 1 mg during DAYBREAK (mean 19.0 months) was associated with a low ARR and low average number of new or enlarging T2 lesions and GdE lesions on MRI
- ARR and average number of GdE lesions were lower after switching from IFN β-1a or ozanimod HCl 0.5 mg to ozanimod HCl 1 mg in the OLE
- Changes from OLE baseline in new or enlarging T2 lesions were similar among those who switched to ozanimod HCl 1 mg in the OLE and in those continuously treated with ozanimod HCl 1 mg from the parent studies
- These data provide additional support for ozanimod as a potential safe and effective oral therapy option for patients with RMS

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