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

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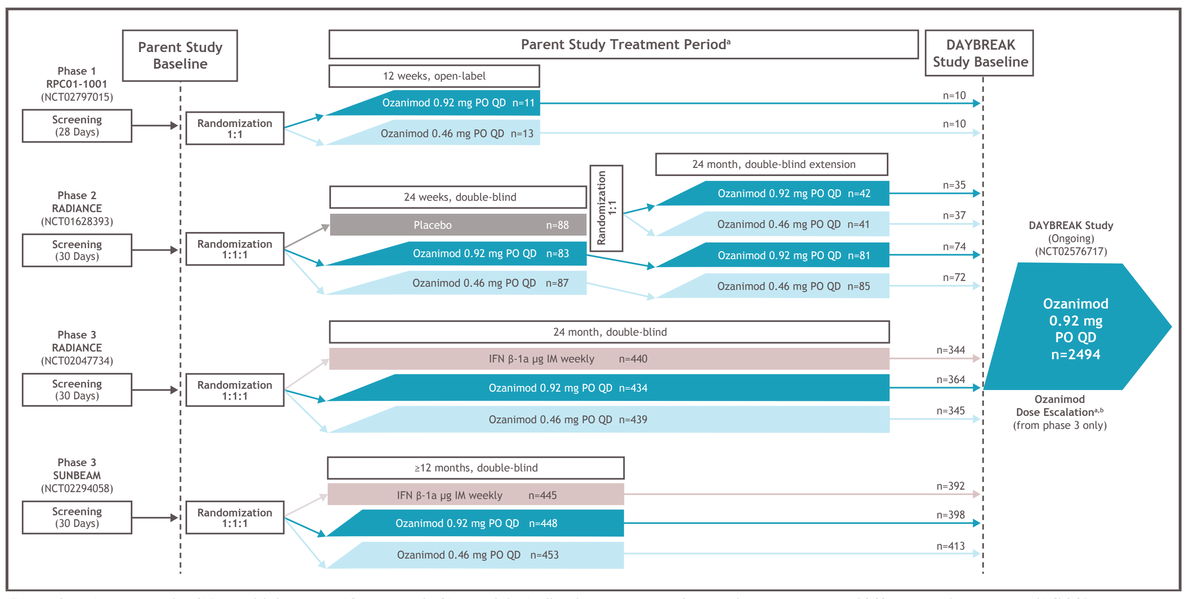
Background

- Ozanimod, a sphingosine 1-phosphate receptor 1 and 5 modulator, is approved in the United States for the treatment of adults with relapsing forms of MS (RMS) and in the European Union for the treatment of adults with relapsing-remitting multiple sclerosis (MS)[1,2]
- Ozanimod has been evaluated for treatment of RMS in phase 1 clinical pharmacology and in phase 2 and 3 efficacy and safety studies[3-6]
  - In phase 3 trials, oral ozanimod 0.46 or 0.92 mg daily for up to 24 months was superior to intramuscular interferon (IFN) β-1a 30 µg weekly with regard to annualized relapse rate (ARR), number of gadolinium-enhancing (GdE) lesions, and new/enlarging T2 lesions on magnetic resonance imaging (MRI), and was generally well tolerated[5,6]
- Participants with RMS who completed earlier ozanimod clinical trials were eligible to enroll in an ongoing, multicenter, open-label extension study (DAYBREAK; ClinicalTrials.gov ID: NCT02576717; EudraCT: 2015-002500-91) aimed at characterizing the long-term safety and efficacy of ozanimod 0.92 mg in RMS
- **Objectives:** to characterize the long-term safety and efficacy of ozanimod in participants with RMS in DAYBREAK
  - **Primary objective:** safety in the overall population
  - **Secondary objectives:**
    - ARR, time to first confirmed relapse, and 3-month and 6-month confirmed disability progression (CDP-3 and CDP-6) in the overall population
    - New/enlarging T2 and GdE MRI brain lesions in a subset of participants who entered DAYBREAK from an active-controlled phase 3 trial

Methods

- Upon completion of a phase 1, 2, or 3 trial, participants were eligible to receive ozanimod 0.92 mg/d in the single-arm, open-label, phase 3 DAYBREAK extension trial (**Figure 1**)
  - Began 16 October 2015, at 227 sites in 27 countries; estimated completion October 2022
  - Data cutoff: 20 December 2019
- Statistical analyses
  - 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/enlarging T2 lesions per scan and number of GdE lesions by visit on MRI were analyzed using descriptive statistics in the subgroup who entered DAYBREAK from a phase 3 parent trial
  - Kaplan-Meier analysis was used to evaluate time to first confirmed relapse and time to onset of CDP-3 and CDP-6
  - Except where noted, baseline = day 1 of DAYBREAK
  - Efficacy data were summarized for the overall population and by pooled parent trial treatment group (intent-to-treat population): placebo followed by ozanimod 0.46 mg/d (n=37) or 0.92 mg/d (n=35), intramuscular IFN β-1a 30 µg/wk (n=740), or ozanimod 0.46 mg/d (n=838) or 0.92 mg/d (n=844)

Figure 1. Parent Studies and DAYBREAK OLE Study Design



IFN, interferon; IM, intramuscular; OLE, open-label extension; PO, per os (oral); QD, once daily. [a]In all trials, upon initiation of ozanimod, participants received 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on days 1–4, 0.46 mg (equivalent to ozanimod HCl 0.5 mg) on days 5–7, and then their assigned dose of 0.46 mg or 0.92 mg (equivalent to ozanimod HCl 1 mg) on day 8 and thereafter. All participants entering the phase 2 dose-blinded extension period 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 active-controlled phase 3 trials, irrespective of prior treatment assignment (to maintain the blinding in the parent trials); 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.

Results

Study Population

- This interim analysis (data cutoff 20 December 2019) included 2494 participants with a mean (standard deviation [SD]) duration of exposure to either dose of ozanimod of 49.5 (13.6) months during the parent trials and DAYBREAK
  - Mean (SD) duration of exposure to ozanimod 0.92 mg in DAYBREAK was 35.4 (8.0) months, amounting to 7355.4 person-years (PY)
- At DAYBREAK entry, mean (SD) age was 37.7 (9.2) years; 66.9% were female; 99.2% were white; and 90.1% were from Eastern Europe
  - Mean (SD) age at symptom onset was 29.5 (8.9) years and mean (SD) Expanded Disability Status Scale score was 2.6 (1.3)
  - Baseline demographics and disease characteristics were generally consistent across parent trial treatment groups

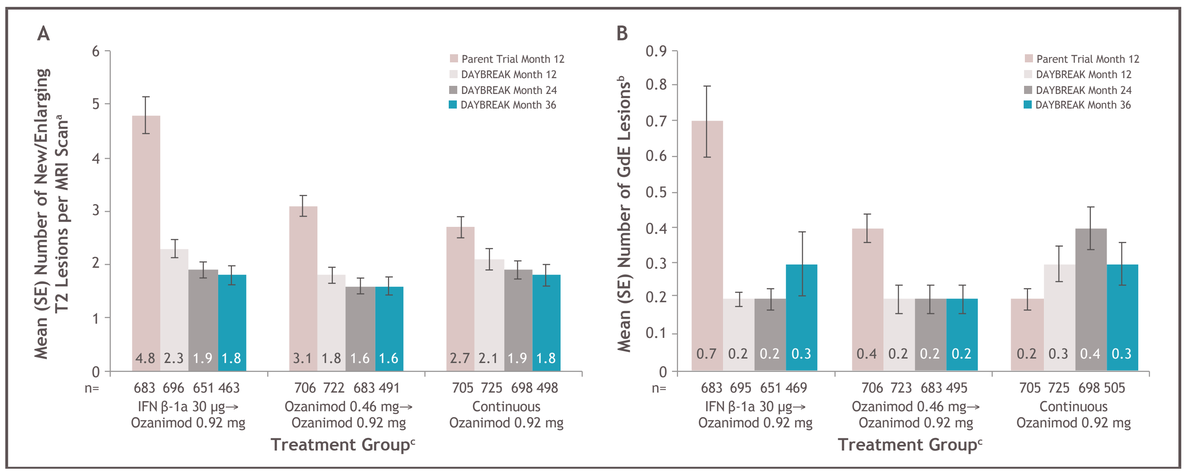
Efficacy

- Ozanimod was associated with a low ARR in DAYBREAK, which was similar across parent trial treatment groups (**Figure 2A**)
- During the first 36 months of DAYBREAK, 75% of participants remained relapse free (**Figure 2B**)
- At DAYBREAK month 36, mean number of new/enlarging T2 lesions per scan ranged from 1.6–1.8 (**Figure 3A**) and mean number of GdE lesions ranged from 0.2–0.3 (**Figure 3B**) across phase 3 parent trial treatment groups
- Most participants in phase 3 or DAYBREAK did not experience disability progression (**Figure 4**)
- During DAYBREAK, 270/2494 (10.8%) participants had 3-month CDP and 214/2494 (8.6%) had 6-month CDP by the data cutoff

Figure 2. (A) ARR[a] and (B) Time to First Confirmed Relapse During DAYBREAK (ITT Population)[b]

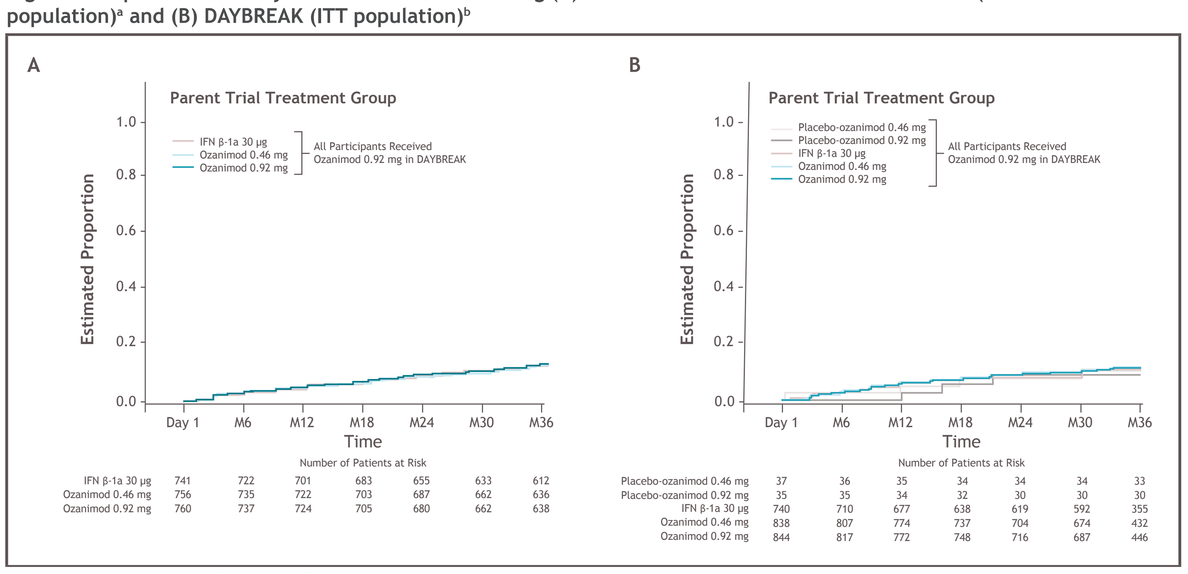
ARR, annualized relapse rate; CI, confidence interval; GdE, gadolinium-enhancing; IFN, interferon; ITT, intent-to-treat.
[a]Based on the negative binomial regression model, adjusted for region (Eastern Europe vs rest of world), age at parent trial baseline, and the parent trial baseline number of GdE lesions. The natural log transformation of time on treatment is used as an offset term to adjust for subjects having different exposure times.
[b]The study period includes DAYBREAK day 1 through last treatment date or the data-cutoff date.

Figure 3. Number of (A) New/Enlarging T2 Lesions Per Scan and (B) GdE Lesions Per Visit (Phase 3 ITT Population)



GdE, gadolinium-enhancing; IFN, interferon; ITT, intent-to-treat; MRI, magnetic resonance imaging; SE, standard error.
[a]The cumulative number of new/enlarging T2 lesions relative to baseline (parent trial baseline for the parent trials, DAYBREAK baseline for DAYBREAK) was determined at the participant level, and the mean value was calculated as the cumulative number of lesions divided by the cumulative number of scans relative to that baseline.
[b]Mean number of GdE lesions is calculated per visit.
[c]T2 and GdE lesions were analyzed only in the subset of participants who entered DAYBREAK from an active-controlled phase 3 trial.

Figure 4. Kaplan-Meier Analysis of Time to CDP-3 During (A) the Phase 3 Parent Trials and DAYBREAK (Phase 3 ITT population)[a] and (B) DAYBREAK (ITT population)[b]



CDP, confirmed disability progression; IFN, interferon; ITT, intent-to-treat.
[a]The study period includes parent trial day 1 through the data-cutoff date. Participants randomized to ozanimod 0.46 mg or IFN β-1a in the parent trials switched to ozanimod 0.92 mg 12 to 24 months after parent trial baseline.
[b]The study period includes DAYBREAK day 1 through the data-cutoff date.

Safety

- Treatment-emergent adverse events (TEAEs) were generally similar to parent trial observations
  - The most common TEAEs were nasopharyngitis, headache, and upper respiratory tract infection (**Table 1**)
- Rates of serious adverse events (SAEs) were similar when assessed by parent trial treatment group (**Table 1**)
- There were no serious opportunistic infections
- Exposure-adjusted incidence rates (IRs) of TEAEs and SAEs have decreased over time (data not shown)
- During the parent trials and DAYBREAK combined, 1.2% of the participants exposed to either dose of ozanimod developed malignancies (IR 320.8/100,000 PY); this IR is consistent with malignancy rates among MS patients treated with other DMTs[7]
- A reduction in absolute lymphocyte count (ALC) is an expected pharmacodynamic effect of ozanimod. Lymphopenia was reported as an AE according to investigator determination (**Table 1**)
  - 8.4% of participants developed grade 4 lymphopenia during DAYBREAK
  - If grade 4 lymphopenia was confirmed upon repeat testing, participants suspended treatment until ALC was >0.5 x 10^9 cells/L; 25 (1.0%) participants had a confirmed grade 4 lymphopenia
  - Two participants (<0.1%) discontinued for lymphopenia

Table 1. Overall Safety of Ozanimod During DAYBREAK

	Placebo→Ozanimod 0.46 mg→Ozanimod 0.92 mg (N=37) n (%)	Placebo→Ozanimod 0.92 mg→Ozanimod 0.92 mg (N=35) n (%)	IFN β-1a 30 µg→ Ozanimod 0.92 mg (N=736) n (%)	Ozanimod 0.46 mg→ Ozanimod 0.92 mg (N=840) n (%)	Continuous Ozanimod 0.92 mg (N=846) n (%)	Total DAYBREAK (N=2494) n (%)
Any TEAE	30 (81.1)	25 (71.4)	618 (84.0)	684 (81.4)	682 (80.6)	2039 (81.8)
Severe TEAEs	2 (5.4)	3 (8.6)	54 (7.3)	55 (6.5)	39 (4.6)	153 (6.1)
Serious TEAEs	4 (10.8)	2 (5.7)	67 (9.1)	83 (9.9)	80 (9.5)	236 (9.5)
TEAEs leading to permanent treatment discontinuation	1 (2.7)	1 (2.9)	21 (2.9)	19 (2.3)	14 (1.7)	56 (2.2)
TEAEs in ≥5% of total DAYBREAK population						
Nasopharyngitis	4 (10.8)	7 (20.0)	140 (19.0)	151 (18.0)	145 (17.1)	447 (17.9)
Headache	2 (5.4)	6 (17.1)	102 (13.9)	119 (14.2)	119 (14.1)	348 (14.0)
URTI	5 (13.5)	7 (20.0)	76 (10.3)	79 (9.4)	80 (9.5)	247 (9.9)
Lymphopenia[a]	3 (8.1)	6 (17.1)	79 (10.7)	83 (9.9)	69 (8.2)	240 (9.6)
ALC decreased	7 (18.9)	2 (5.7)	60 (8.2)	61 (7.3)	69 (8.2)	199 (8.0)
Back pain	5 (13.5)	5 (14.3)	50 (6.8)	58 (6.9)	56 (6.6)	174 (7.0)
GGT increased	1 (2.7)	3 (8.6)	59 (8.0)	50 (6.0)	40 (4.7)	153 (6.1)
Hypertension	4 (10.8)	2 (5.7)	53 (7.2)	51 (6.1)	36 (4.3)	146 (5.9)
UTI	6 (16.2)	3 (8.6)	32 (4.3)	42 (5.0)	42 (5.0)	125 (5.0)

AE, adverse event; ALC, absolute lymphocyte count; GGT, gamma-glutamyl transferase; IFN, interferon; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.
[a]A reduction in ALC is an expected pharmacodynamic effect of ozanimod. Lymphopenia was reported as an AE according to investigator determination.

Conclusions

- In DAYBREAK, ozanimod was associated with low ARR and low new/enlarging T2 and GdE lesion counts over time
- Most participants were relapse free and did not experience disability progression
- Ozanimod was generally well tolerated and no new safety concerns emerged with long-term use

References

1. Zeposia [US package insert]. Summit, NJ: Celgene Corporation; 2020. **2.** Zeposia [EU summary of product characteristics]. Utrecht, Netherlands: Celgene Distribution B.V.; 2020. **3.** Cohen JA, et al. *Lancet Neurol*. 2016;15(4):373-381. **4.** Cohen JA, et al. *Mult Scler*. 2019;25(9):1255-1262. **5.** Comi G, et al. *Lancet Neurol*. 2019;18(11):1009-1020. **6.** Cohen JA, et al. *Lancet Neurol*. 2019;18(11):1021-1033. **7.** Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157-167.

Disclosures

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