Obexelimab Demonstrated Reduction in Disease Activity in Relapsing Multiple Sclerosis: 24-Week Results from the MoonStone Phase 2 Trial

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Background

- Obexelimab is a humanized, bifunctional monoclonal antibody designed to inhibit B-cell activity through co-engagement of CD19 and the inhibitory receptor FcγRIIb. This approach is intended to mimic natural inhibitory signaling pathways that regulate B-cell activation[1-3] **(Figure 1)**
- Obexelimab does not induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) and does not result in cytolytic B-cell depletion[4]
- Obexelimab demonstrated potent inhibition of B-cell antibody production, proliferation, cytokine secretion, and antigen presentation to T cells[2,5,6] **(Figure 2)**
- Given B-cell-targeting has known clinical benefit in MS[6] and obexelimab's unique inhibitory mechanism, obexelimab was evaluated in relapsing MS (RMS) patients
- MoonStone (NCT06564311) is the first randomized, double-blind, placebo-controlled Phase 2 trial evaluating the efficacy and safety of obexelimab in patients with RMS
- Obexelimab met the primary endpoint, demonstrating a 95% relative reduction in the cumulative number of new GdE T1 lesions at Week 8 and 12 (p = 0.0009)[7]

Figure 1. Obexelimab binding to CD19 and FcγRIIb

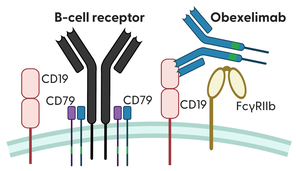
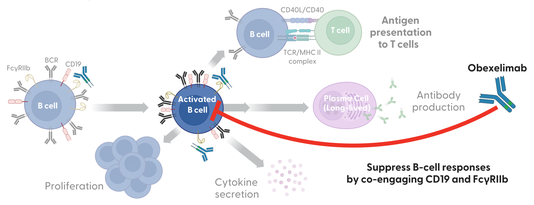


Figure 2. Obexelimab binding to activated B cells inhibits downstream immune cell activity



Objectives

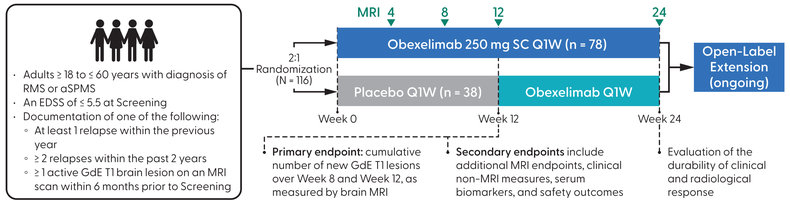
To evaluate the durability of efficacy and safety of obexelimab through 24 weeks, including the open-label period following placebo crossover

Methods

MoonStone Trial (NCT06564311): Double-blind, randomized, placebo-controlled Phase 2 study **(Figure 3)**

- At Week 12, eligible participants entered the open-label period (OLP), receiving obexelimab 250 mg SC weekly through Week 24, followed by an open-label extension for an additional 52 weeks
- Efficacy (MRI measures: Total GdE T1 lesions and T2 lesion volume, relapse rate, and Expanded Disability Status Scale [EDSS]) and safety (adverse events [AEs] through Week 24) were assessed

Figure 3. MoonStone study design schematic



Obexelimab is an investigational drug and has not been approved by the US Food and Drug Administration or any regulatory body worldwide.

Abbreviations: ADCC = antibody-dependent cellular cytotoxicity; AE = adverse event; AESI = adverse event of special interest; aSPMS = active secondary progressive multiple sclerosis; BCR = B-cell receptor; CD19 = cluster of differentiation 19; CD40 = cluster of differentiation 40; CD40L = CD40 ligand; CD79 = cluster of differentiation 79; CDC = complement-dependent cytotoxicity; CI = confidence interval; EDSS = Expanded Disability Status Scale; FcγRIIb = Fcγ receptor IIb; GdE = gadolinium-enhancing; MHC II = major histocompatibility complex class II; MRI = magnetic resonance imaging; MS = multiple sclerosis; N/n = number of participants; NCT = ClinicalTrials.gov identifier; OLP = open-label period; Q1W = once weekly; RCP = randomized controlled period; RMS = relapsing multiple sclerosis; SC = subcutaneous; SD = standard deviation; T1 = T1-weighted; T2 = T2-weighted; TCR = T-cell receptor; TEAE = treatment-emergent adverse event; UTI = urinary tract infection.

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Results

Baseline Characteristics

Baseline characteristics of participants in the randomized controlled period (RCP) were generally balanced between obexelimab (n = 78) and placebo (n = 38) arms **(Table 1)**

Analysis population

- **Safety Population (RCP) (N = 116):** All randomized participants who received at least one dose of obexelimab or the matching placebo dose in the RCP. 116 participants were randomized 2:1 obexelimab vs placebo across 32 sites. Of these, 109 entered the OLP with 105/109 (96.3%) completing the regimen through Week 24

Table 1. Baseline characteristics of the RCP population

Baseline Characteristics	Obexelimab (n = 78)	Placebo (n = 38)
Age, mean (SD), years	42.2 (9.3)	41.7 (9.9)
Female, n (%)	52 (66.7)	29 (76.3)
Time since diagnosis at Screening, mean (SD), years	7.4 (8.4)	7.8 (9.0)
EDSS score, median (range)	2.5 (0.0 - 5.5)	3.0 (0.0 - 5.5)
Participants with GdE T1 hyperintense lesions at Screening, n (%)	17 (21.8)	8 (21.1)

MRI Efficacy

- In the OLP, GdE T1 lesion-free rates were 95.5% (continuous obexelimab) vs 91.4% (crossover from placebo) at Week 24 **(Figure 4A)**
- The average total number of GdE T1 lesions remained low in participants always on treatment (0.04 lesions) and continued to decline in those who switched from placebo at Week 12 (0.14 lesions) **(Figure 4B)**
  - The mean T2 lesion volume trended downward through Week 24, with a -0.23 cc change from baseline, and new/enlarging T2 lesion counts were lower among continuously treated participants

Relapse Rate

- The annualized relapse rates through Week 24 observed for both the obexelimab and placebo to obexelimab arms were low at 0.179 and 0.059, respectively, with > 90% of participants in both arms relapse free at Week 24 **(Table 2)**
  - The number of relapses during Week 12 to Week 24 decreased in comparison with those during baseline to Week 12 in the obexelimab arm

Table 2. Annualized relapse rates through Week 24

Relapse Rates RCP group	Through Week 24	
	Obexelimab to Obexelimab (n = 78)	Placebo to Obexelimab (n = 38)
Patients with relapses, n (%)	6 (7.7)	1 (2.6)
Number of Relapses Baseline – Week 12, n (%)	5 (6.4)	1 (2.6)
Number of Relapses Week 12 – Week 24, n (%)	1 (1.3)	0
Days to First Relapse, Mean (SD)	46.5 (34.8)	9 (Not Calculable)
Crude Rate of Relapses/Year	0.179	0.059
Relapse-Free at Week 24* n (%) (95% CI)	65 (91.5) (82.5, 96.8)	34 (97.1) (85.1, 99.9)

*Excludes patients without available EDSS results

Expanded Disability Status Scale

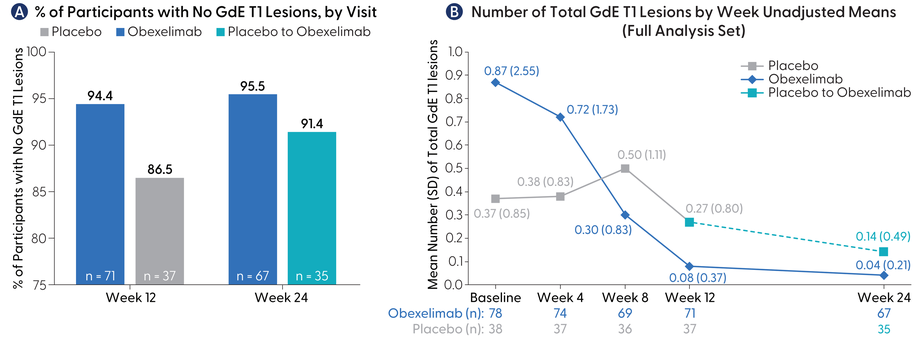
- EDSS remained stable through Week 24 in both arms; mean change from baseline was -0.01 with continuous obexelimab and 0.00 with crossover **(Table 3)**

Table 3. EDSS through Week 24

EDSS RCP group	Unadjusted Mean Change from Baseline		Unadjusted Mean	
	Obexelimab to Obexelimab	Placebo to Obexelimab	Obexelimab to Obexelimab	Placebo to Obexelimab
Baseline*			2.96	2.97
Week 12	0.03	-0.05**	3.03	2.95**
Week 24	-0.01	0.00#	2.96	2.93

*Baseline represents EDSS measurements at RCP baseline, prior to study drug administration. **Prior to obexelimab administration. #Change from Obexelimab Day 1 (-Week 12 dose).

Figure 4. MRI efficacy using obexelimab in the MoonStone Trial through Week 24



- **> 90% of participants recorded no GdE T1 lesions at Week 24**, demonstrating a reduction and prevention of acute focal inflammation

Means are unadjusted and not based on the outcome of a statistical model. The assessment window for the MRI endpoints increased from 4 weeks in RCP to 12 weeks in OLP (Week 12 to Week 24). Given the typical 2–6 week lifecycle of GdE T1 lesions, this 12-week interval captures cumulative activity over a longer observation period.

Safety

- Overall safety profile was stable and predictable through 24 weeks, with no new safety signals
- Grade ≥ 3 events, AEs leading to discontinuation, and adverse events of special interest (AESIs) were confined to the first 12 weeks and incidences were similar in both arms **(Table 4)**
- Common AEs (composite of all trial groups through Week 24) included UTI (11.3%), injection site erythema (8.7%), headache (6.1%), and nasopharyngitis (6.1%)
  - Three serious TEAEs (bacterial infection, infection, hypersensitivity) were reported, all resolved
- AESI incidence was 7.8% overall (Grade ≥ 2 hypersensitivity 7.0%, Grade 3 infections 1.7%, Grade 2 injection site reactions 3.5%)

Table 4. Summary of treatment-emergent adverse events throughout the study

Treatment-emergent adverse events (TEAEs)	RCP		OLP			RCP + OLP
	Obexelimab (n = 78)	Placebo (n = 38)	Obexelimab to Obexelimab (n = 72)	Placebo to Obexelimab (n = 37)	Total (n = 109)	Obexelimab (n = 115)
All TEAEs, n (%)	48 (61.5)	14 (36.8)	32 (44.4)	17 (45.9)	49 (45.0)	73 (63.5)
TEAEs of Grade ≥ 3, n (%)	4 (5.1)	1 (2.6)	0	2 (5.4)	2 (1.8)	6 (5.2)
Serious TEAEs, n (%)	3 (3.8)	0	0	0	0	3 (2.6)
TEAEs leading to treatment discontinuation, n (%)	4 (5.1)	1 (2.6)	0	2 (5.4)	2 (1.8)	6 (5.2)
TEAEs leading to death, n	0	0	0	0	0	0
Most Common TEAEs (≥ 5%), n (%)						
Urinary tract infection	6 (7.7)	0	5 (6.9)	4 (10.8)	9 (8.3)	13 (11.3)
Injection site erythema	9 (11.5)	0	1 (1.4)	1 (2.7)	2 (1.8)	10 (8.7)
Nasopharyngitis	2 (2.6)	1 (2.6)	4 (5.6)	2 (5.4)	6 (5.5)	7 (6.1)
Headache	6 (7.7)	3 (7.9)	2 (2.8)	1 (2.7)	3 (2.8)	7 (6.1)
Injection site pruritus	2 (2.6)	2 (5.3)	0	0	0	2 (1.7)
All AESIs	6 (7.7)	0	0	3 (8.1)	3 (2.8)	9 (7.8)
Hypersensitivity	5 (6.4)	0	0	3 (8.1)	3 (2.8)	8 (7.0)
Injection site reaction	3 (3.8)	0	0	1 (2.7)	1 (0.9)	4 (3.5)
Infection	2 (2.6)	0	0	0	0	2 (1.7)

Conclusions

- Obexelimab demonstrated robust and continued suppression of inflammatory MRI disease activity through Week 24, with > 90% of participants free of GdE T1 lesions, low lesion counts, and declining T2 lesion volume
- The safety profile remained predictable and consistent through 24 weeks, with no new safety signals observed during the open-label period
- These findings support B-cell inhibition through CD19/FcγRIIb co-engagement as a differentiated therapeutic approach in RMS

References: 1) Chu et al. *Mol Immunol* 2008; Zenas data on file; **2)** Abeles et al. *Annu Rev Immunol* 2024; **3)** Verbeek et al. *Front Immunol* 2019; **4)** Chu et al. *J Transl Autoimmun* 2021; **5)** Chu et al. *Arthritis Rheumatol* 2014; **6)** Greenfield & Hauser. *Ann Neurol* 2018; **7)** Okuda et al. ACTRIMS 2026.

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