Effect of Obexelimab on Serum Biomarkers and MS Disease Activity Score: Results from the Phase 2 MoonStone Trial in Relapsing Multiple Sclerosis

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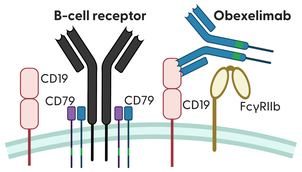
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Background

- 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]
- 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



Objectives

To evaluate the effects of obexelimab on serum biomarkers associated with disease activity and B-cell-targeting therapies in MoonStone participants

Methods

- MoonStone Trial (NCT06564311): Double-blind, randomized, placebo-controlled Phase 2 study in RMS
  - » Patients randomized 2:1 received weekly SC 250 mg obexelimab or placebo for 12 weeks in the RCP
  - » At Week 24, the study continued as an OLE for an additional 52 weeks
- Serum samples were collected pre-dose at Day 1 and at Weeks 12, 16, 20 and 24 for NfL measurement by Quanterix; for the MSDA test, pre-dose Day 1 and Week 12 samples were analyzed by Octave Biosciences
- The MSDA test, a clinically validated 18-protein serum biomarker assay, assesses disease activity
  - » The 18 proteins contributing to the MSDA score reflect immunomodulation, neuroinflammation, myelin biology, and neuroaxonal integrity
  - » MSDA scores ranging from 1.0 – 10.0 are associated with likelihood of MS disease activity **(see Figure 3)**
  - » MSDA scores and 17 individual proteins (excluding NfL) were assessed at pre-dose Day 1 and Week 12
  - » All MSDA outcomes were statistically analyzed using ANCOVA with treatment group as the main predictor, and age, sex, baseline GdE T1 lesion status (0 vs ≥ 1), and corresponding pre-dose Day 1 values as covariates

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; ANCOVA = analysis of covariance; BAFF = B-cell Activating Factor; CD19 = cluster of differentiation 19; CD79 = cluster of differentiation 79; CDC = complement-dependent cytotoxicity; CI = confidence interval; CNS = central nervous system; CXCL13 = C-X-C motif chemokine ligand 13; DA = disease activity; EDSS = Expanded Disability Status Scale; FcγRIIb = Fcγ receptor IIb; GdE = gadolinium-enhancing; IQR = interquartile range; MS = multiple sclerosis; MSDA = Multiple Sclerosis Disease Activity; n = number of participants; NCT = ClinicalTrials.gov identifier; NfL = neurofilament light chain; OLE = open-label extension; RCP = randomized controlled period; RMS = relapsing multiple sclerosis; SC = subcutaneous; SD = standard deviation; SERPINA9 = serpin family A member 9; T1= T1-weighted; T2 = T2-weighted; TNFSF13B = tumor necrosis factor superfamily member 13B.

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; **8)** Chitnis et al. *Clin Immunol* 2023; **9)** Khademi et al. *Mult Scler* 2011; **10)** Zhu et al. *Brain Commun* 2024; **11)** Cambridge et al. *Arthritis Res* 2006; **12)** Lavie et al. *Ann Rheum Dis* 2007; **13)** Ho et al. *Neuroimmunol Neuroinflamm* 2023; **14)** Högelin et al. *Clin Immunol* 2024; **15)** Kreuzaler et al. *J Immunol* 2012.

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Results

Baseline Characteristics

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

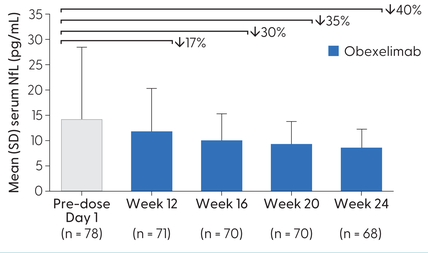
Table 1. Demographics and baseline characteristics for RCP population

Baseline Characteristics	Obexelimab (n = 78)	Placebo (n = 38)	Total (n = 116)
Active Secondary Progressive, n (%)	3 (3.8)	3 (7.9)	6 (5.2)
Age, mean (SD), years	42.2 (9.3)	41.7 (9.9)	42.0 (9.5)
Female, n (%)	52 (66.7)	29 (76.3)	81 (69.8)
Disease duration, mean (SD), years	7.4 (8.4)	7.8 (9.0)	7.5 (8.6)
EDSS score, median (range)	2.5 (0.0–5.5)	3.0 (0.0–5.5)	3.0 (0.0–5.5)
No. of T2 lesions, mean (SD)	45.3 (29.6)	51.8 (37.7)	47.4 (32.5)
No. of GdE T1 lesions, mean (SD), range (Min-Max)	0.9 (2.5) (0.0–15.0)	0.4 (0.9) (0.0–4.0)	0.7 (2.2) (0.0–15.0)
Participants with GdE T1 lesions, n (%)	17 (21.8)	8 (21.1)	25 (21.6)
1 lesion	3 (3.8)	4 (10.5)	7 (6.0)
2 lesions	8 (10.3)	3 (7.9)	11 (9.5)
3 lesions	0 (0.0)	0 (0.0)	0 (0.0)
≥ 4 lesions	6 (7.7)	1 (2.6)	7 (6.0)
No. of relapses within the previous year, n (%)			
0 relapses	5 (6.4)	1 (2.6)	6 (5.2)
1 relapse	65 (83.3)	36 (94.7)	101 (87.1)
2 relapses	8 (10.3)	1 (2.6)	9 (7.8)

Serum Neurofilament Light Chain Levels

- Serum NfL decreased from pre-dose Day 1 at Weeks 12, 16, 20, and 24 following obexelimab treatment with mean reductions of 17%, 30%, 35%, and 40%, respectively **(Figure 2)**
- No decrease in NfL was observed in the placebo arm at Week 12, as the mean (SD) NfL values were 12.8 (7.7) pg/mL pre-dose Day 1 and 11.8 (6.0) at Week 12

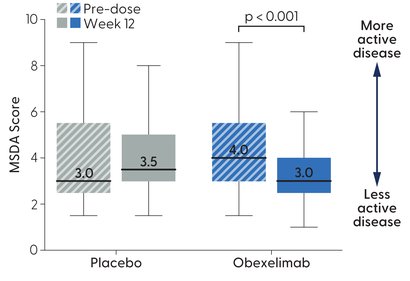
Figure 2. Percent change in mean serum NfL concentration from pre-dose Day 1 by visit with obexelimab treatment



MS Disease Activity Scores

- At Week 12, compared to placebo, MSDA scores were significantly reduced from pre-dose Day 1 in the obexelimab group (p < 0.001), indicating modulation of disease-related biological activity **(Figure 3)**

Figure 3. DA score at pre-dose Day 1 and Week 12, by treatment group*



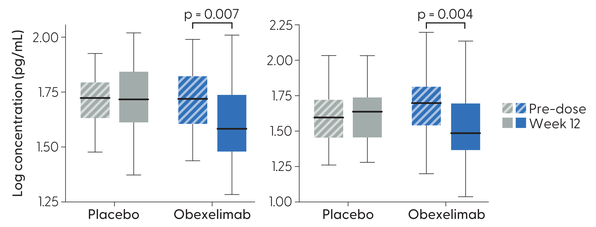
*The center line of the box indicates the median value, while the box itself encompasses the IQR. The whiskers extend to the data points within ±1.5 times the IQR from the lower and upper quartiles.

Serum CXCL13 and SERPINA9 Levels

- Obexelimab treatment significantly reduced serum CXCL13 and SERPINA9 levels from pre-dose Day 1 to Week 12 vs placebo **(Figure 4)**
  - » CXCL13: B-cell chemoattractant involved in immune cell cluster formation in the CNS[8,9]
  - » SERPINA9: associated with neuroaxonal integrity and increased in neuroinflammation[8,10]

*The center line of the box indicates the median value, while the box itself encompasses the IQR. The whiskers extend to the data points within ±1.5 times the IQR from the lower and upper quartiles.

Figure 4. Serum CXCL13 (left) and SERPINA9 (right) at pre-dose Day 1 and Week 12*



Serum BAFF Levels

- B-cell Activating Factor (BAFF) levels increased significantly with obexelimab treatment at Week 12 vs placebo, consistent with indirect pharmacodynamic effects observed with B-cell-targeted therapies **(Figure 5)**[11-13]
  - » BAFF: an activating and survival cytokine for B cells
  - » Circulating BAFF levels are hypothesized to increase with B-cell-targeted therapies due to the loss or reduction of BAFF receptor-expressing B cells that normally consume the cytokine, resulting in free BAFF accumulation[14,15]

*The center line of the box indicates the median value, while the box itself encompasses the interquartile range (IQR). The whiskers extend to the data points within ±1.5 times the IQR from the lower and upper quartiles.

Figure 5. BAFF levels at pre-dose Day 1 and Week 12*

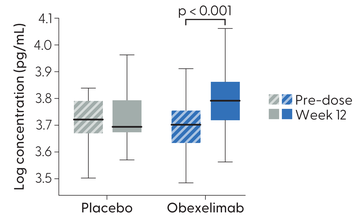


Table 2. Treatment effect of obexelimab vs placebo on MSDA score and serum biomarkers

Biomarker	Treatment Effect (95% CI)*	P-value	Direction
Disease Activity (DA) Score	-0.98 (-1.45, -0.50)	< 0.001	Favors Treatment (↓ disease activity)
Individual analyte CXCL13	-0.12 (-0.19, -0.06)	0.007**	Favors Treatment (↓ CXCL13)
Individual analyte SERPINA9	-0.14 (-0.21, -0.07)	0.004**	Favors Treatment (↓ SERPINA9)
Individual analyte BAFF (TNFSF13B)	0.09 (0.05, 0.13)	< 0.001**	Consistent with mechanism (↑ BAFF, expected with B-cell-targeting)

ANCOVA analysis was adjusted for sex, age, the corresponding baseline value, and baseline GdE T1 lesion status (≥ 1 vs 0)
*Reported as the treatment difference for change from pre-dose Day 1
**Bonferroni adjusted p-value for 17 analytes

Summary

- Serum samples collected during the RCP of the MoonStone Trial in RMS patients were evaluated for the effects of obexelimab on serum biomarkers associated with disease activity and B-cell-targeting therapies
- Baseline characteristics of the participants in the RCP were generally balanced
- Following obexelimab treatment, serum NfL decreased from pre-dose Day 1 starting at Week 12, with mean reductions of 17% (Week 12), 30% (Week 16), 35% (Week 20), and 40% (Week 24)
- At Week 12, MSDA scores were significantly reduced from pre-dose Day 1 in the obexelimab group
- Obexelimab treatment significantly reduced serum CXCL13 and SERPINA9 levels at Week 12, while levels of BAFF were significantly increased

Conclusions

- Obexelimab treatment was associated with favorable changes across key serum biomarkers of RMS pathophysiology, consistent with its proposed mechanism of action
- Reduction in NfL suggests attenuated neuroaxonal injury, while decreases in MSDA score, CXCL13, and SERPINA9 point to broad suppression of disease-related biological activity, providing biological context for the MoonStone clinical efficacy findings and supporting a mechanism of non-cytolytic B-cell inhibition
- Increases in BAFF are consistent with the expected pharmacodynamic response to B-cell-targeted therapy[12-15]
- Together, these biomarker findings reinforce obexelimab's mechanism of action and support its continued evaluation across autoimmune diseases mediated by B-cell activity