Pharmacokinetics and Pharmacodynamics of Obexelimab in Patients with Relapsing Multiple Sclerosis: Results from the Phase 2 MoonStone Trial

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Background

- B-cell-targeted therapies have shown efficacy in relapsing multiple sclerosis (RMS), but anti-CD20 agents work by depleting B cells, raising questions about long-term immunologic consequences[1-3]
- Obexelimab is a humanized, bifunctional monoclonal antibody designed to inhibit B-cell activity through co-engagement of CD19 and FcγRIIb (CD32b), two cell surface receptors expressed across the B-cell lineage, including on pro-B cells, pre-B cells, naïve B cells, memory B cells, plasmablasts, and a subset of plasma cells **(Figure 1)**[4-10]
- FcγRIIb is the only Fcγ receptor expressed on B cells, where it acts as an inhibitory receptor to naturally regulate B-cell responses by antigen-antibody complexes.
- This approach is intended to mimic natural inhibitory signaling pathways that regulate B-cell activation **(Figure 2)**
- The pharmacokinetic (PK)/pharmacodynamic (PD) profile of obexelimab in RMS, including central nervous system (CNS) distribution, has not been previously characterized

Figure 1. Obexelimab binding to CD19 and FcγRIIb

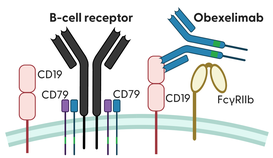
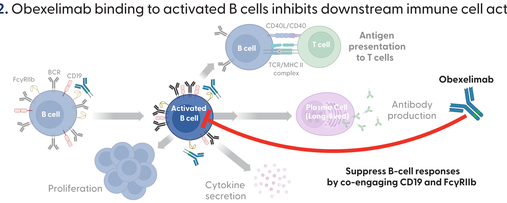


Figure 2. Obexelimab binding to activated B cells inhibits downstream immune cell activity



Objectives

- To characterize the PK and PD profile of obexelimab in RMS patients receiving 250 mg weekly subcutaneous injection over 24 weeks

Methods

- MoonStone Trial (NCT06564311): Double-blind, randomized, placebo-controlled Phase 2 study in RMS
  - » Patients were randomized 2:1 to receive a weekly subcutaneous injection of 250 mg obexelimab or placebo for 12 weeks in the randomized controlled period (RCP)
  - » At Week 12, eligible participants entered the open label period (OLP), receiving obexelimab 250 mg SC weekly through Week 24
  - » At Week 24, the study continued as an open-label extension for an additional 52 weeks
- Serum PK samples were collected pre-dose at Day 1 and at Weeks 4, 8, 12, 16, 20, and 24
- CSF PK samples were collected at baseline, Week 12, and Week 24 in a subset of subjects that underwent lumbar puncture (n = 4)
- Serum and CSF obexelimab concentrations were measured by the Meso Scale Discovery-Electrochemiluminescence assay
- CD20$^+$ B-cell counts and immunoglobulin levels were collected at baseline during screening (Days -28 to -1) and pre-dose at Day 1 and at Weeks 4, 8, 12, 16, 20 and 24
- B-cell counts were measured by standard flow cytometry, and immunoglobulins were quantified by immunoturbidity assay
- CD19 receptor occupancy (RO) samples were collected pre-dose at Day 1 and at Weeks 4, 8, 12, 16, 20, and 24. CD19 RO samples were only collected in North America sites (n = 4 in each treatment group). Flow cytometry detects surface CD19 staining, and staining is lost when obexelimab is bound.

Results

Baseline Characteristics and Disposition

- Baseline characteristics were generally balanced between obexelimab (n = 78) and placebo (n = 38) arms **(Table 1)**
- 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. Demographics and baseline characteristics for RCP population

Baseline Characteristics	Obexelimab (n = 78)	Placebo (n = 38)	Total (n = 116)
Age at Informed Consent, years			
Mean (SD)	42.2 (9.3)	41.7 (9.9)	42.0 (9.5)
Median	42.5	44.0	43.5
Min, Max	22, 59	21, 60	21, 60
Age Group, years, n (%)			
< 40	31 (39.7)	15 (39.5)	46 (39.7)
≥ 40	47 (60.3)	23 (60.5)	70 (60.3)
Sex, n (%)			
Male	26 (33.3)	9 (23.7)	35 (30.2)
Female	52 (66.7)	29 (76.3)	81 (69.8)
Race, n (%)			
White	67 (85.9)	31 (81.6)	98 (84.5)
Asian	5 (6.4)	4 (10.5)	9 (7.8)
Chinese	4 (5.1)	4 (10.5)	8 (6.9)
Other Asian	1 (1.3)	0	1 (0.9)
Other	1 (1.3)	0	1 (0.9)
Not Reported	5 (6.4)	3 (7.9)	8 (6.9)
Ethnicity, n (%)			
Hispanic/Latino	5 (6.4)	2 (5.3)	7 (6.0)
Not Hispanic/Latino	68 (87.2)	33 (86.8)	101 (87.1)
Not Reported	5 (6.4)	3 (7.9)	8 (6.9)
Body Weight, kg			
Mean (SD)	82.1 (22.6)	74.6 (18.3)	79.6 (21.6)
Median	79.1	71.0	76.2

Serum Pharmacokinetics

- Serum obexelimab concentration reached steady state by Week 4 and was sustained through Week 24 **(Table 2)**
- Previous population PK analysis (data on file) identified no demographic covariates that influence obexelimab PK

Table 2. Mean serum obexelimab concentrations by visit and treatment sequence

	Placebo to Obexelimab	Obexelimab to Obexelimab
Mean (SD) Serum Concentration (ng/mL)		
N	36	75
Day 1	-	9.95 (44.00)
Week 4	-	17281.76 (9575.79)
Week 12	162.50 (975.00)	18027.29 (8304.57)
Week 24	22876.54 (8011.01)	20374.41 (9617.66)

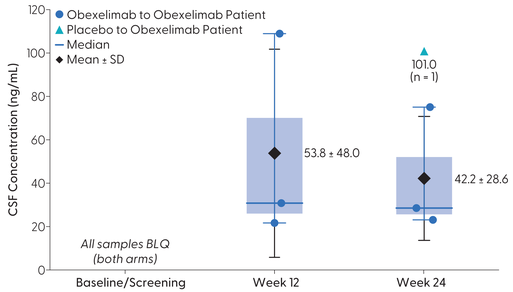
Abbreviations: BCR = B-cell receptor; BLQ = below the limit of quantification; CD19 = cluster of differentiation 19; CD20 = cluster of differentiation 20; CD32b = cluster of differentiation 32b; CD40 = cluster of differentiation 40; CD40L = CD40 ligand; CD79 = cluster of differentiation 79; CNS = central nervous system; CSF = cerebrospinal fluid; FcγRIIb = Fcγ receptor IIb; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LLN = lower limit of normal; MHC II = major histocompatibility complex class II; N/n = number of participants; N/A = not applicable; NCT = ClinicalTrials.gov identifier; OLP = open-label period; PD = pharmacodynamics; PK = pharmacokinetics; RCP = randomized controlled period; RMS = relapsing multiple sclerosis; RO = receptor occupancy; SC = subcutaneous; SD = standard deviation; TCR = T-cell receptor.

Disclosures: This study was funded by Zenas BioPharma. M.C.U. and M.Y. are employees of Zenas BioPharma and hold stock and stock options. M.M. was an employee of Zenas BioPharma at the time of the development of this abstract. J.M.G.D. has received honoraria, travel support, or research grants from Zenas BioPharma, Biogen, Almirall, Novartis, Neuraxpharm, Sanofi, Roche, Juvisé Pharmaceuticals, and BMS. R.B. consulted for Alexion, Amgen, ANI, Biogen, BMS, Genentech, Keenova, Novartis, Sanofi, TG Therapeutics, Vanda and received research grants from Biogen, MSAA, Merck, Novartis, Sanofi, TG Therapeutics, Zenas BioPharma. All other authors declare no conflicts of interest.

Cerebrospinal Fluid Pharmacokinetics

- Obexelimab was detectable in the CSF of all four lumbar puncture patients, representing ~0.22–0.56% of serum concentrations **(Figure 3)**

Figure 3. Mean (±SD) CSF obexelimab concentration at Weeks 12 and 24



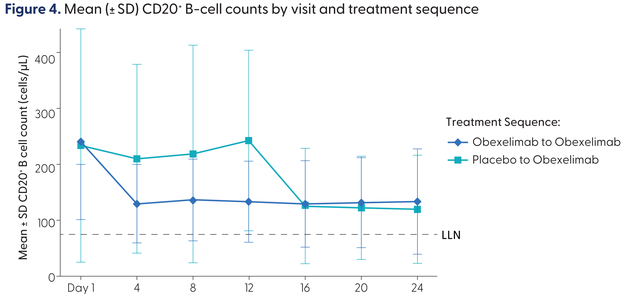
Treatment Sequence	Visit	N*	Mean ± SD CSF Concentration (ng/mL)	Mean ± SD CSF/Serum Ratio (%)	Range of CSF/Serum Ratio (%)
Obexelimab to Obexelimab	Baseline/Screening	3	All BLQ	N/A	N/A
	Week 12	3	53.8 ± 48.0	0.35 ± 0.18	0.22 – 0.56
	Week 24	3	42.2 ± 28.6	0.31 ± 0.13	0.22 – 0.46
Placebo to Obexelimab	Baseline/Screening	2	All BLQ	N/A	N/A
	Week 24	1	101.0	0.32	N/A

*N = number of patients with a CSF sample collected at that visit

B-Cell Counts

- Mean CD20$^+$ B-cell counts decreased from 240.8 to 132.7 cells/µL by Week 4 after which it plateaued and remained within the normal physiological range (74.4–441.1 cells/µL) through the duration of treatment (24 weeks) **(Figure 4)**

Figure 4. Mean (± SD) CD20$^+$ B-cell counts by visit and treatment sequence



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

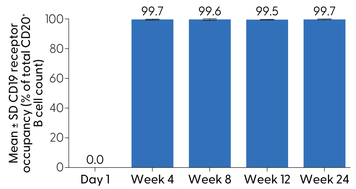
References: 1) Elmoursi et al. *J Allergy Clin Immunol* 2024; **2)** Starvaggi Cucuzza et al. *Neurol Neuroimmunol Neuroinflamm* 2022; **3)** Tallantyre et al. *J Neurol* 2018.; **4)** Abeles et al. *Annu Rev Immunol* 2024; **5)** Barlev et al. *J Clin Invest* 2022; **6)** Beneduce et al. *Cells* 2023; **7)** Duan et al. *Cell Rep* 2023; **8)** Halliley et al. *Immunity* 2015; **9)** Kemkie et al. *Front Immunol* 2020; **10)** Tutt et al. *J Immunol* 2015.

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CD19 Receptor Occupancy

- CD19 RO was 100% at Week 4 of obexelimab treatment and persisted through the duration of treatment (12 or 24 weeks) in the Obexelimab to Obexelimab group **(Figure 5)**

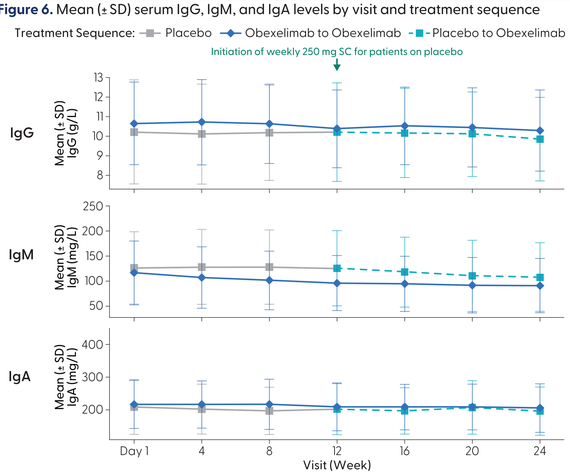
Figure 5. Mean (± SD) CD19 receptor occupancy (% of total CD20$^+$ B cells) by visit



Immunoglobulin Levels

- There were no clinically significant changes in the levels of key immunoglobulins (IgA, IgM, and IgG) in the obexelimab and placebo treated patients through the duration of treatment (12 or 24 weeks) **(Figure 6)**

Figure 6. Mean (± SD) serum IgG, IgM, and IgA levels by visit and treatment sequence



Conclusions

- Obexelimab 250 mg SC weekly achieved sustained steady-state serum concentrations with detectable CNS penetration through Week 24
- Complete CD19 receptor occupancy was achieved by Week 4 and maintained through Week 24
  - » Mean B-cell count was reduced during treatment but remained within the normal range, and immunoglobulin levels (IgG, IgM, and IgA) remained stable through Week 24
- These data support obexelimab's differentiated mechanism of direct B-cell inhibition without causing effector-mediated cytolytic depletion