Orelabrutinib in Primary Progressive Multiple Sclerosis: Design of the PriMroSe Phase 3 Randomized Controlled Trial

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EP2602

Background

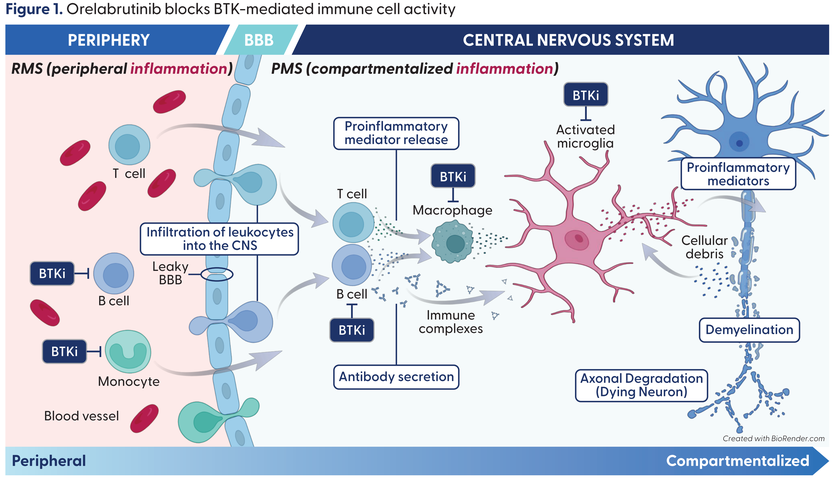
Primary Progressive Multiple Sclerosis

- Primary progressive multiple sclerosis (PPMS) is characterized by gradual accumulation of neurologic disability from disease onset, without discrete relapses, and accounts for approximately 10–15% of all MS cases[1,2]
- There is only one approved disease-modifying therapy available for PPMS, and slowing disability progression remains an urgent unmet need[3-5]
- Progression in PPMS is driven in part by inflammation compartmentalized within the CNS behind a largely intact blood-brain barrier[3]
- Thus, targeting peripheral inflammation alone is not sufficient to slow progression; therapies that also modulate CNS-compartmentalized inflammation may provide benefit in progressive disease

Orelabrutinib Mechanism of Action

- Bruton's Tyrosine Kinase inhibitors (BTKi) act on both B and myeloid cells implicated in multiple sclerosis (MS)
- BTKis with CNS penetration may address CNS-compartmentalized neuroinflammation, a less accessible driver of MS disease progression[6]
- Orelabrutinib is a potent, highly selective, CNS-penetrant BTKi that blocks BTK-mediated signaling in both CNS-resident and peripheral immune cells[7,8] **(Figure 1)**
- Twelve-week efficacy and short-term safety of orelabrutinib in a Phase 2 study in relapsing-remitting MS (RRMS) have been reported previously[8]

Figure 1. Orelabrutinib blocks BTK-mediated immune cell activity



BBB, blood-brain barrier; BTKi, Bruton's Tyrosine Kinase inhibitors; CNS, central nervous system; PMS, progressive multiple sclerosis; RMS, remitting multiple sclerosis.

Clinical Experience in MS: Phase 2 RRMS Trial Summary (NCT04711148)

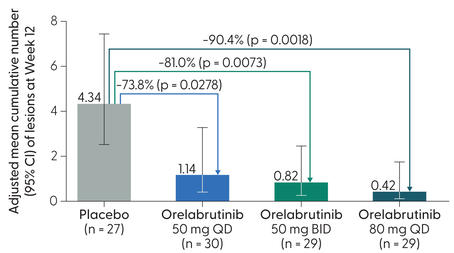
Design Randomized, double-blind, placebo-controlled trial in 158 adults with relapsing-remitting MS; 1:1:1:1 to placebo, orelabrutinib 50 mg QD (n = 37), 80 mg QD (n = 40), or 50 mg BID (n = 41)
- » Placebo participants (n = 40) crossed over to orelabrutinib 50 mg QD at Week 13; all participants were eligible for a 96-week open-label extension (50 mg QD)

Primary Endpoint
- MRI endpoint assessing new GdE T1 lesions at Week 12

Secondary Endpoints
- GdE T1 lesions and new or enlarging T2 lesions at Weeks 12, 16, 20, and 24 and safety

Results
- **The primary endpoint was met:** Orelabrutinib achieved statistically significant reductions in cumulative new GdE T1 lesions at Week 12 (73.8% to 90.4% reduction vs placebo) **(Figure 2)**
- **24-week profile:**
  - » Orelabrutinib demonstrated a favorable 24-week benefit-risk profile, characterized by rapid and sustained suppression of disease activity as measured by MRI, alongside a predictable and manageable safety profile
  - » Most treatment-emergent adverse events (TEAEs) were Grade 1-2; liver-related TEAEs occurred predominantly in the first 12 weeks and were transient, resolving on dose interruption or discontinuation
  - » No deaths were reported

Figure 2. Cumulative number of new GdE T1 brain lesions at Week 12 (N = 115)*



*The primary endpoint and the secondary endpoints of MRI imaging were analyzed based on the PHS population (n = 115) in which subjects did not miss any one of the three MRI assessments within the first 12 weeks of treatment.

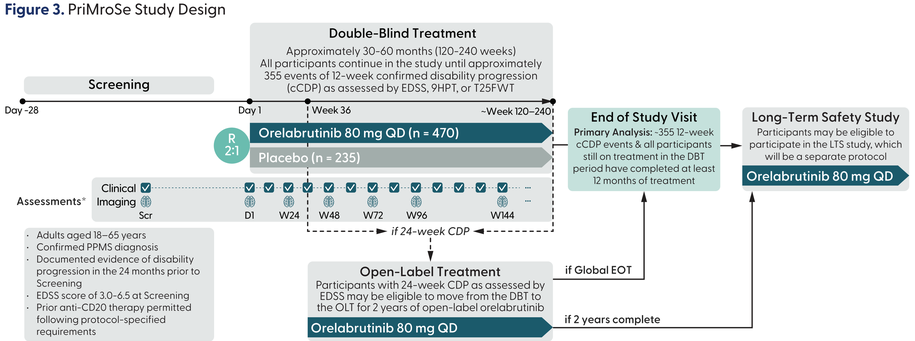
The adjusted mean cumulative number, percent reduction (orelabrutinib vs placebo) associated with the 95% CI and p-values are estimated from a Poisson regression model with a Pearson scale parameter with a log link function and offset by log number of scans as of Week 12. Baseline number of GdE T1 brain lesions is included in the model as a continuous covariate. 12-week data reported at ACTRIMS 2025 (Poster P094); 24-week data (Poster P1446) and PKPD (Poster EP2593) reported at MSToronto 2026.

Methods

Study Design

- PriMroSe is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 trial (NCT07067463)
  - » An estimated 705 participants will be randomized 2:1 to receive once-daily oral orelabrutinib 80 mg or placebo for approximately 30–60 months (range due to the event-driven primary endpoint) **(Figure 3)**
  - » Minimum treatment duration of 12 months
    - Liver function tests (LFTs) are performed during the first 12 weeks of treatment
  - » Participants ending treatment enter a 4-week Safety Follow-up

Figure 3. PriMroSe Study Design



*Clinical assessments (EDSS, T25FWT, 9HPT): Screening, Day 1, then every 12 weeks. Brain MRI: Screening, Day 1, then every 24 weeks through Week 96, then every 48 weeks.

Orelabrutinib is an investigational drug and not approved for treatment of multiple sclerosis by the US Food and Drug Administration or any health authority.

Acknowledgments: The authors thank the investigators, study staff, and patients who participated in this study. Medical writing and poster production support were provided by Acumen Medical Communications, funded by Zenas BioPharma.

Disclosures: This study was funded by Zenas BioPharma. F.D. and S.C. are Zenas BioPharma employees and hold stock/stock options; D.Z. was a Zenas BioPharma employee at the time of this abstract's development. R.J.F. has received consulting fees from Astoria Biologica, Biogen, Bristol Myers Squibb, Galvani, Immunic, InnoCare Pharma, Kiniksa, Novartis, Sanofi, SetPoint Medical, Siemens, Sudo Biosciences, and TG Therapeutics; has served on advisory committees for AB Science, Biogen, Immunic, Novartis, and Sanofi; and has received clinical trial contract and research grant funding from Sanofi and Synaptogenix. F.D.L. has research support from NMSS, NIH, Novartis, and BMS; consulting/advisory board/DSMB relationships with EMD Serono, Novartis, Sanofi/Genzyme, Roche/Genentech, Amgen, BMS, Viatris, Immunic, Avotres, Neuralight, SetPoint Medical, Sudo Biosciences, Cognito Therapeutics, ImmPACT Bio, InnoCare Pharma, Kite Pharma, Zenas BioPharma, Ardanza Biopharma, AbbVie, and Autolus; stock options in Avotres, Neuralight, and Lapix Therapeutics; and speaker fees from Sanofi.

Abbreviations: 9HPT = 9-Hole Peg Test; AE = adverse event; AUC0–t = area under the plasma concentration-time curve from time zero to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; BBB = blood-brain barrier; BID = twice daily; BTK = Bruton's Tyrosine Kinase; BTKi = Bruton's Tyrosine Kinase inhibitor; cCDP = composite confirmed disability progression; CDP = confirmed disability progression; CI = confidence interval; CL/F = apparent clearance; C_{max} = maximum plasma concentration; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; D = day; DBT = double-blind treatment period; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EOT = end of treatment; GdE = gadolinium-enhancing; IV = intravenous; LFT = liver function test; LTS = long-term safety; MRI = magnetic resonance imaging; MS = multiple sclerosis; N/n = number of participants; NCI = National Cancer Institute; OLT = open-label treatment period; PD = pharmacodynamics; PK = pharmacokinetics; PMS = progressive multiple sclerosis; PO = oral; PPMS = primary progressive multiple sclerosis; QD = once daily; R = randomization; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; Scr = screening; SPMS = secondary progressive multiple sclerosis; $t_{1/2}$ = half-life; T1 = T1-weighted; T2 = T2-weighted; T25FWT = Timed 25-Foot Walk Test; TEAE = treatment-emergent adverse event; T_{max} = time to achieve maximum concentration; W = week.

Eligibility

Key Inclusion Criteria
- Adults ≥ 18 to ≤ 65 years
- Current diagnosis of PPMS according to the 2024 revision of the McDonald diagnostic criteria[9]
- Documented evidence of disability progression independent of clinical relapse observed during the 24 months before screening
- Expanded Disability Status Scale (EDSS) score between 3.0 and 6.5, inclusive, at screening

Key Exclusion Criteria
- Diagnosis of RRMS or SPMS according to the 2024 revision of the McDonald diagnostic criteria[9]
- Other neurological disorders that may mimic MS
- Chronic, systemic immunologic disorder (other than MS, well-controlled Type 2 diabetes mellitus, or well-controlled thyroid disease); any conditions requiring PO, IV, intramuscular, or intraarticular corticosteroid therapy
- Moderate/severe liver impairment or unstable chronic liver disease
- Significant active infections within 4 weeks of screening or history of recurrent infections
- Prior use of B-cell-depleting agents unless last dose ≥ 6 months prior to screening, B-cell count ≥ 7 cells/μL, and no related infection during screening

Endpoints

Primary Endpoint
- Time to onset of composite confirmed disability progression (cCDP) events, confirmed over at least 12 weeks (12-week cCDP), defined as follows:
  - » EDSS score increase ≥ 1.0 point from baseline when the baseline score is ≤ 5.0, or ≥ 0.5 points from baseline when the baseline score is > 5.0, *OR*
  - » ≥ 20% increase in the Timed 25-Foot Walk Test (T25FWT), *OR*
  - » ≥ 20% increase in the 9-Hole Peg Test (9HPT)

Key Secondary Endpoints
- Time to onset of cCDP events, confirmed over at least 24 weeks (24-week cCDP)
- Time to onset of CDP, defined as EDSS score increase ≥ 1.0 point from baseline when the baseline score is ≤ 5.0, or ≥ 0.5 points from baseline when the baseline score is > 5.0, confirmed over at least 24 weeks (24-week CDP)
- Safety as assessed by the nature, severity, and incidence of adverse events (AEs) (graded according to National Cancer Institute Common Terminology Criteria for AEs [NCI CTCAE] version 5.0), vital signs, ECGs, and clinical laboratory safety parameters
- PK parameters: C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, CL/F, and steady state parameters

References: 1) National MS Society 2025; Wallin et al. *Neurology* 2019; Campbell et al. *Mult Scler Relat Disord* 2014; Zenas BioPharma analysis; **2)** Andersson et al. *Arch Neurol* 1999; **3)** Cree et al. *Neurology* 2021; **4)** Montalban et al. *N Engl J Med* 2017; **5)** Filippi et al. *J Neurol* 2025; **6)** Krämer et al. *Nat Rev Neurol* 2023; **7)** Zhang et al. AACR 2020; **8)** Xu et al. ACTRIMS 2025; **9)** Montalban et al. *Lancet Neurol* 2025.

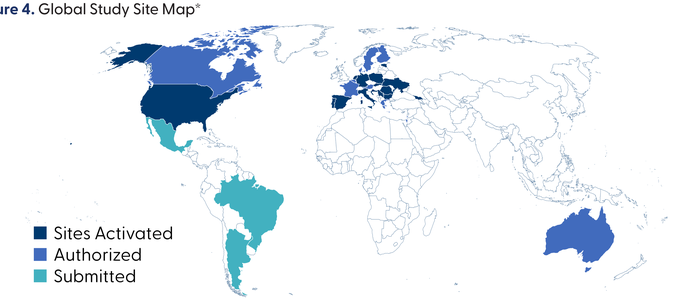
Objective

PriMroSe is an ongoing study to evaluate the safety and efficacy profile of orelabrutinib in participants with PPMS

Enrollment

The PriMroSe Trial is enrolling across international sites **(Figure 4)**

Figure 4. Global Study Site Map*



*Last updated Sept 30, 2026

Summary

- With only one currently approved therapy, there is a high unmet medical need in treating patients with PPMS who are at high risk of irreversible functional loss
- Orelabrutinib is a potent, highly selective, CNS-penetrant BTK inhibitor that blocks BTK-mediated signaling in peripheral immune cells and CNS-resident microglia, providing a rationale for targeting both peripheral and CNS-compartmentalized inflammation in PPMS
- The Phase 3 PriMroSe Trial (NCT07067463) is designed to evaluate the efficacy and safety of orelabrutinib in PPMS
- **PriMroSe is open and actively enrolling participants globally**
- Results will inform whether orelabrutinib delays disability progression in patients with PPMS

PriMroSe Trial (NCT07067463)