Orelabrutinib in Non-Active Secondary Progressive Multiple Sclerosis: Design of the Monarch Phase 3 Randomized Controlled Trial

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Background

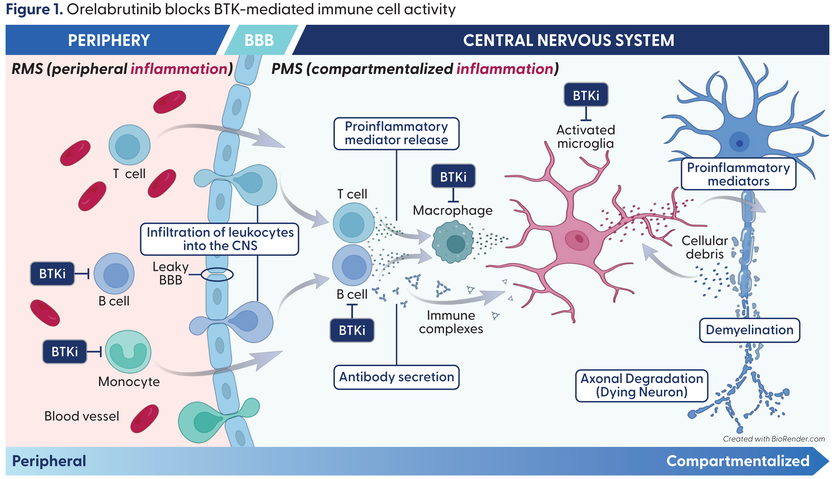
Secondary Progressive Multiple Sclerosis

- Secondary progressive multiple sclerosis (SPMS) follows an initial relapsing-remitting course and is defined by disability progression
  - » In non-active SPMS (naSPMS), progression continues in the absence of both relapses and new focal inflammatory activity detected by MRI
- None of the current approved therapies specifically targets naSPMS
- Disability progression in naSPMS is driven in part by CNS-compartmentalized inflammation rather than by the peripherally driven focal inflammation that characterizes relapsing disease[1]
- Thus, therapies that modulate both peripheral immune activity and CNS-compartmentalized inflammation may provide benefit in this population

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[2]
- Orelabrutinib is a potent, highly selective, CNS-penetrant BTKi that blocks BTK-mediated signaling in both CNS-resident and peripheral immune cells[3,4] **(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[4]

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, relapsing multiple sclerosis.

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

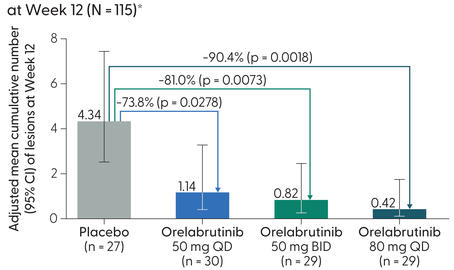
Design
- Randomized, double-blind, placebo-controlled trial in 158 adults with relapsing-remitting MS; 1:1:1:1 to placebo, orelabrutinib 50 mg QD (n = 37), 80 mg QD (n = 40), or 50 mg BID (n = 41)
  - » Placebo participants (n = 40) crossed over to orelabrutinib 50 mg QD at Week 13; all participants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

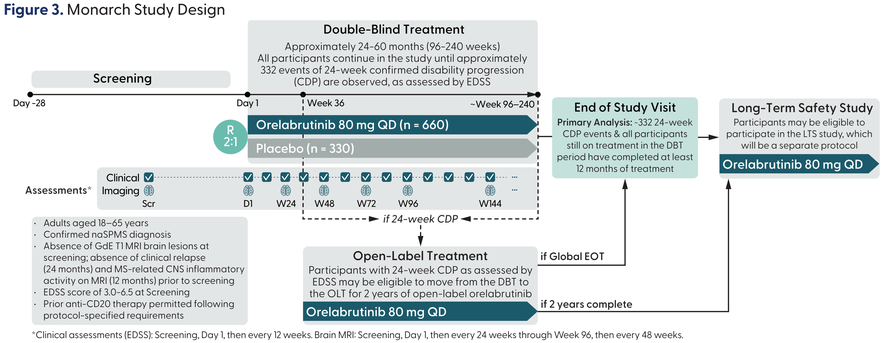
The adjusted mean cumulative number, percent reduction (orelabrutinib vs placebo) associated with the 95% CI and p-values are estimated from a Poisson regression model with a Pearson scale parameter with a log link function and offset by log number of scans as of Week 12. Baseline number of GdE T1 brain 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

- Monarch is a global, randomized, double-blind, placebo-controlled Phase 3 trial (NCT07299019)
  - » An estimated 990 participants will be randomized 2:1 to receive once-daily oral orelabrutinib 80 mg or placebo for approximately 24-60 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. Monarch Study Design



*Clinical assessments (EDSS): 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.

References: 1) Cree et al. *Neurology* 2021; **2)** Krämer et al. *Nat Rev Neurol* 2023; **3)** Zhang et al. AACR 2020; **4)** Xu et al. ACTRIMS 2025; **5)** Montalban et al. *Lancet Neurol* 2025.

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Abbreviations: AE=adverse event; AUC0-t=area under the plasma concentration-time curve from time zero to the last measurable concentration; AUC0-∞=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; CDP=confirmed disability progression; CI=confidence interval; CL/F=apparent clearance; Cmax=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; naSPMS=non-active secondary progressive multiple sclerosis; NCI=National Cancer Institute; OLT=open-label treatment period; PHS=post-hoc set; PK=pharmacokinetic; PKPD=pharmacokinetics/pharmacodynamics; 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; TEAE=treatment-emergent adverse event; Tmax=time to achieve maximum concentration; W=week.

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Eligibility

Key Inclusion Criteria
- Adults ≥ 18 to ≤ 65 years
- Current diagnosis of SPMS in accordance with the clinical course criteria revised in 2013
- Previous diagnosis of RRMS or prior clinical history consistent with RRMS in accordance with 2024 McDonald diagnostic criteria[5]
- Absence of GdE T1 brain lesions as measured by MRI at screening and absence of historical MRI (if available) evidence of MS-related inflammatory activity within 12 months prior to screening based on GdE T1 or new or unequivocally enlarging T2 CNS lesions
- 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 PPMS according to the 2024 revision of the McDonald diagnostic criteria[5]
- 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 confirmed disability progression (CDP) events, confirmed over at least 24 weeks (24-week CDP), 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

Key Secondary Endpoints
- Time to onset of CDP events on EDSS, confirmed over at least 12 weeks (12-week CDP)
- The total number of new or enlarging T2 lesions on MRI scans of the brain
- 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

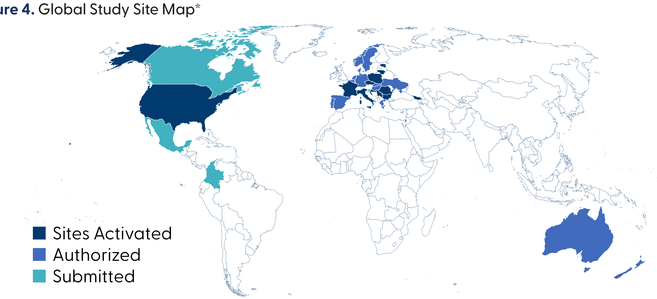
Objective

Monarch is an ongoing study to evaluate the safety and efficacy profile of orelabrutinib in patients with naSPMS

Enrollment

The Monarch trial is enrolling across international sites **(Figure 4)**

Figure 4. Global Study Site Map*



*Last updated Sept 30, 2026

Summary

- There is a high unmet medical need for safe and effective treatment of naSPMS
- 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 naSPMS
- The Phase 3 Monarch Trial (NCT07299019) is designed to evaluate orelabrutinib as a potential treatment for naSPMS
- **Monarch is open and actively enrolling participants globally**
- Results will inform whether orelabrutinib delays disability progression in participants with naSPMS

Monarch Trial (NCT07299019)