Efficacy and Safety of Orelabrutinib in Relapsing-Remitting Multiple Sclerosis: 24-Week Results of the 80 mg Dose from a Phase 2 Randomized, Double-Blind, Placebo-Controlled Study

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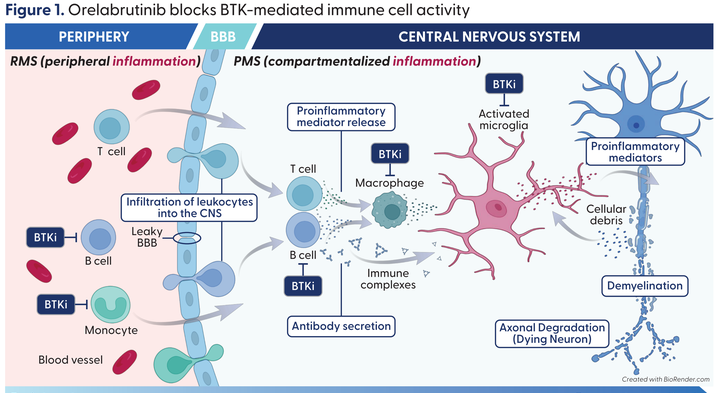
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Background

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[1]
- Orelabrutinib is a potent, highly selective, CNS-penetrant BTKi that blocks BTK-mediated signaling in both CNS-resident and peripheral immune cells[2,3] **(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[3]

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.

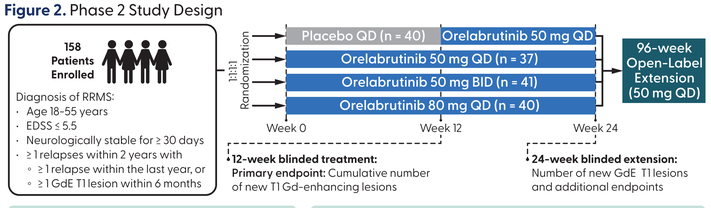
Objective

To present the 24-week efficacy and safety profile of orelabrutinib in participants with RRMS

Methods

- A Phase 2, randomized, double-blind, placebo-controlled trial (NCT04711148) evaluated 158 adults with RRMS **(Figure 2)**
- This poster focuses on the 80 mg QD dose, which has been selected for further clinical development, and the total orelabrutinib populations; additional dose-level data are available via QR code

Figure 2. Phase 2 Study Design



Key Endpoints:
- **Primary:** Cumulative number of new gadolinium-enhancing (GdE) T1 brain lesions at Week 12
- **Secondary:** MRI efficacy, Annualized Relapse Rate (ARR), Expanded Disability Status Scale (EDSS), and 24-week safety
- **Exploratory:** Additional MRI outcomes, PK/PD

Analysis Populations:
- **Intent-to-treat (ITT) (N=158):** All randomized subjects. Primary set for all disposition and clinical efficacy analyses
- **Post-hoc Set (PHS) (n=115):** MRI endpoints; Excludes participants who missed MRI data points in the first 12 weeks due to force majeure events*
- **Safety (N=158):** All randomized subjects who received at least one dose of study drug. (Note: For 24-week orelabrutinib safety analyses, n=151, as 7 placebo subjects did not transition to active treatment at Week 13)

*COVID-19, Ukraine war, US FDA partial clinical hold

References: 1) Krämer et al. *Nat Rev Neurol* 2023; 2) Zhang et al. AACR 2020; 3) Xu et al. ACTRIMS 2025.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARR = annualized relapse rate; AST = aspartate aminotransferase; BBB = blood-brain barrier; BID = twice daily; BTK = Bruton's tyrosine kinase; BTKi = Bruton's tyrosine kinase inhibitor; CI = confidence interval; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; EDSS = Expanded Disability Status Scale; FDA = Food and Drug Administration; GdE = gadolinium-enhancing; ITT = intent-to-treat; LFT = liver function test; MRI = magnetic resonance imaging; MS = multiple sclerosis; N/n = number of participants; OR = odds ratio; PD = pharmacodynamics; PHS = post-hoc set; PK = pharmacokinetics; PMS = progressive multiple sclerosis; QD = once daily; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; T1 = T1-weighted; T2 = T2-weighted; TBL = total bilirubin; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Results

Baseline Characteristics

- Baseline characteristics were generally comparable across the two treatment arms **(Table 1)**

Table 1. Baseline Demographic and Clinical Characteristics

Baseline Characteristics (ITT) Mean (SD)	Placebo/Orelabrutinib 50 mg QD (N = 40)[a]	Orelabrutinib 80 mg QD (N = 40)
Age, years	35.6 (10.4)	34.8 (9.6)
Female, n (%)	24 (60.0)	29 (72.5)
Time since MS diagnosis, years	4.4 (5.3)	4.8 (5.8)
Number of relapses in the last 2 years	1.7 (0.8)	1.6 (0.8)
EDSS Score	2.58 (1.6)	2.80 (1.3)
Patients with GdE T1 lesions at baseline, n (%)	12 (30.0)	18 (45.0)
Number of GdE T1 lesions	1.2 (3.1)	3.6 (9.3)
Volume of T2 lesions, cm^3	17.48 (13.9)	17.60 (13.7)
Participants who were treatment-naïve, n (%)	25 (62.5)	21 (52.5)

[a]The "Placebo/Orelabrutinib 50 mg QD" group received placebo during Weeks 1-12 and orelabrutinib 50 mg QD during Weeks 13-24.

Efficacy: Primary Endpoint Was Met at Week 12 and Maintained Through Week 24

- Orelabrutinib 80 mg QD significantly reduced cumulative new GdE T1 lesions at Week 12 vs placebo in the PHS population: 90.4% (80 mg QD, p = 0.0018)[3] **(Figure 3a)**
  - » Results sustained through Week 24: 92.3% (80 mg QD, p = 0.0037)
- Results were consistent in the ITT population where orelabrutinib significantly reduced the adjusted mean cumulative number of new GdE T1 lesions at Week 12 vs placebo: 80.5% (80 mg QD, p = 0.0013)
  - » Results sustained through Week 24: 81.6% (80 mg QD, p = 0.0022)
- Suppression of acute inflammatory activity was observed as early as Week 4 and sustained through the 24-week double-blind period with 80 mg QD orelabrutinib **(Figure 3b)**

Figure 3a. Primary Endpoint: Cumulative number of new GdE T1 brain lesions at Week 12 (PHS population)[3]*

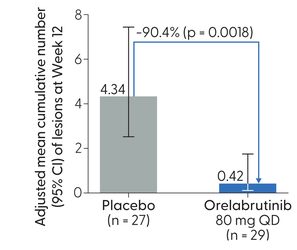
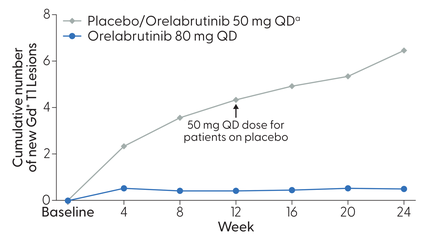


Figure 3b. Secondary Endpoint: Cumulative number of new GdE T1 brain lesions at Weeks 16, 20, and 24 (PHS population)[3]*



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.
[a]The "Placebo/Orelabrutinib 50 mg QD" group received placebo during Weeks 1-12 and orelabrutinib 50 mg QD during Weeks 13-24.
*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. Additional dose-level data are available via QR code.

Efficacy: Orelabrutinib 80 mg QD Improved Relapse-Free Rates While Maintaining Stable Disability Through Week 24

- Relapse-free rates were 90% with orelabrutinib 80 mg QD vs 70% in the placebo/orelabrutinib 50 mg QD group[a] (OR: 4.05; 95% CI 1.14–14.41; p < 0.05) **(Figure 4)**
  - » The adjusted Annualized Relapse Rate (ARR) remained consistently low across all groups (0.04 to 0.14)
- Mean EDSS scores remained stable from baseline through Week 24, with no significant differences vs placebo; mean change -0.22 to 0.05 **(Figure 5)**

Figure 4. Relapse-Free Rates at Week 24*

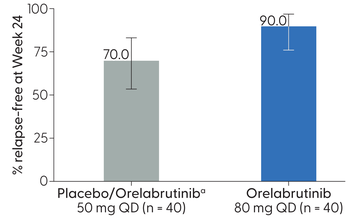
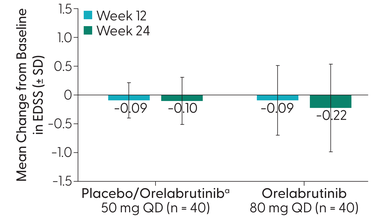


Figure 5. EDSS scores from Baseline through Week 24*



[a]The "Placebo/Orelabrutinib 50 mg QD" group received placebo during Weeks 1-12 and orelabrutinib 50 mg QD during Weeks 13-24. These results are from the ITT population.
*Additional dose-level data are available via QR code.

Safety: Predictable and Manageable Safety Profile With No Deaths Over the 24-week Double-Blind Period

- **Overall Safety:** Orelabrutinib safety was predictable and manageable over the 24-week double-blind period, with the majority of TEAEs being mild to moderate (CTCAE Grade 1 or 2) **(Table 2)**
- **No deaths were reported** throughout the Phase 2 RRMS study, including the double-blind, open-label extension, and safety follow-up periods through Week 124

Table 2. Overall Summary of Treatment-Emergent Adverse Events*

Safety Adverse Events (24 Weeks), n (%)	Placebo/Orelabrutinib 50 mg QD (N = 40)[a]	Orelabrutinib 80 mg QD (N = 40)	Total Orelabrutinib (N = 151)[b]
All TEAEs	18 (45.0)	23 (57.5)	91 (60.3)
TEAEs with CTCAE Grade ≥ 3	1 (2.5)	2 (5.0)	10 (6.6)
Serious TEAEs	1 (2.5)	0	3 (2.0)
TEAEs leading to drug interruption	2 (5.0)	2 (5.0)	13 (8.6)
TEAEs leading to drug withdrawn	0	0	4 (2.6)
TEAEs leading to death	0	0	0
Liver-related TEAEs	4 (10.0)	2 (5.0)	18 (11.9)

[a]The "Placebo/Orelabrutinib 50 mg QD" group received placebo during Weeks 1-12 and orelabrutinib 50 mg QD during Weeks 13-24. These results are from the Safety population.
[b]Total Orelabrutinib includes events from Weeks 1-24 in the orelabrutinib dose groups, and events occurring in Weeks 13-24 for subjects in Placebo/Orelabrutinib group who switched to Orelabrutinib.
*Additional dose-level data are available via QR code.

- Most frequently reported TEAEs (≥ 5% in orelabrutinib-treated participants): ALT increased, headache, COVID-19, rash, neutrophil count decreased, and hemorrhage **(Table 3)**

Table 3. Most Common Treatment-Emergent Adverse Events*

Most Common TEAEs (≥ 5%), n (%)	Placebo/Orelabrutinib 50 mg QD (N = 40)[a]	Orelabrutinib 80 mg QD (N = 40)	Total Orelabrutinib (N = 151)[b]
Alanine aminotransferase increased	3 (7.5)	1 (2.5)	14 (9.3)
Headache	4 (10.0)	3 (7.5)	11 (7.3)
COVID-19	1 (2.5)	4 (10.0)	10 (6.6)
Rash	0	3 (7.5)	9 (6.0)
Neutrophil count decreased	1 (2.5)	2 (5.0)	8 (5.3)
Hemorrhage subcutaneous	1 (2.5)	3 (7.5)	8 (5.3)

[a]The "Placebo/Orelabrutinib 50 mg QD" group received placebo during Weeks 1-12 and orelabrutinib 50 mg QD during Weeks 13-24. These results are from the Safety population.
[b]Total Orelabrutinib includes events from Weeks 1-24 in the Orelabrutinib dose groups, and events occurring in Weeks 13-24 for subjects in Placebo/Orelabrutinib group who switched to Orelabrutinib.
*Additional dose-level data are available via QR code.

Hepatic Safety: Early, Transient LFT Elevations with One Reversible Hy's Law Case

- Most liver-related TEAEs (such as ALT/AST elevations) occurred in the first 12 weeks of treatment and were transient and resolved upon dose interruption or treatment discontinuation* **(Table 4)**
- One orelabrutinib-treated participant met Hy's law laboratory criteria (in the 50 mg BID dose group); the event resolved completely after treatment discontinuation, and was the only such case reported in the study*

Table 4. Hepatic Safety**

Safety Adverse Events (24 Weeks), n/N*** (%)	Placebo/Orelabrutinib 50 mg QD (N = 40)[a]	Orelabrutinib 80 mg QD (N = 40)	Total Orelabrutinib (N = 151)[b]
ALT > 3x ULN	2/40 (5.0)	1/40 (2.5)	9/147 (6.1)
AST > 3x ULN	0/40	1/40 (2.5)	4/146 (2.7)
ALP > 1x ULN	1/40 (2.5)	3/40 (7.5)	5/147 (3.4)
Total Bilirubin (TBL) > 1 × ULN	2/40 (5.0)	2/40 (5.0)	12/147 (8.2)
Concurrent ALT or AST > 3× ULN and TBL > 2× ULN	0/40	0/40	1/147 (0.7)
Concurrent ALT or AST > 3× ULN and ALP < 2× ULN and TBL > 2× ULN	0/40	0/40	1/147 (0.7)

[a]The "Placebo/Orelabrutinib 50 mg QD" group received placebo during Weeks 1-12 and orelabrutinib 50 mg QD during Weeks 13-24. These results are from the Safety population.
[b]Total Orelabrutinib includes events from Weeks 1-24 in the Orelabrutinib dose groups, and events occurring in Weeks 13-24 for subjects in Placebo/Orelabrutinib group who switched to Orelabrutinib.
*Post-onset evaluation for alternative causes, including viral serology and hepatic imaging, could not be performed due to regional conflict (Ukraine war); a causal relationship to study treatment could not be excluded.
**Additional dose-level data are available via QR code.
***N = Total samples collected across treatment groups.

Conclusions

- Orelabrutinib, a potent, highly selective, CNS-penetrant BTK inhibitor, demonstrated a favorable 24-week benefit-risk profile, characterized by rapid and sustained suppression of disease activity as measured by MRI
- The 24-week safety profile was predictable and manageable with most TEAEs being Grade 1-2, with no reported deaths through the treatment period
- Collectively, these findings provide a foundational benefit-risk justification for ongoing global Phase 3 studies of orelabrutinib 80 mg in progressive MS

Monarch (NCT07299019, MSToronto Poster EP2594) and PriMroSe (NCT07067463, MSToronto Poster EP2602) are currently actively enrolling patients with progressive MS

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

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Additional dose-level data