Pharmacokinetics of Orelabrutinib in a Phase 2 Study in Relapsing Remitting Multiple Sclerosis

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Background

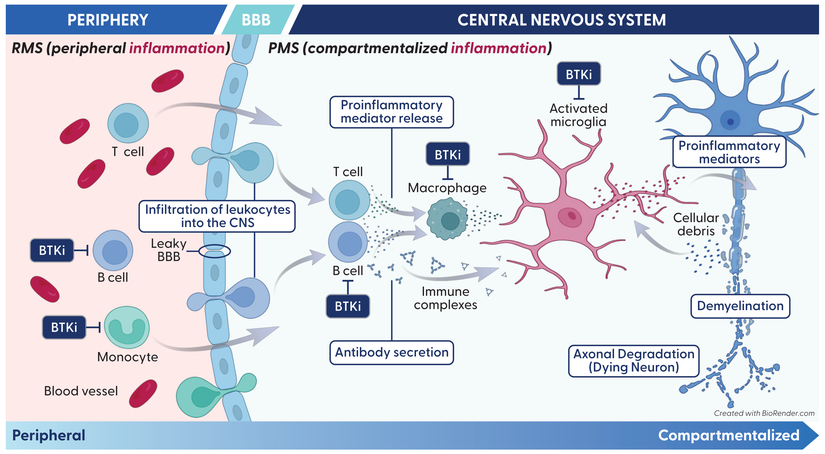
Orelabrutinib Mechanism of Action

- Multiple sclerosis (MS) involves both peripheral immune cell activation and compartmentalized inflammation within the central nervous system (CNS)
- Current disease-modifying therapies primarily target peripheral mechanisms, with less characterized effects in the CNS; thus, CNS penetration is an important pharmacologic consideration for MS therapies
- Bruton's Tyrosine Kinase inhibitors (BTKi) act on both B and myeloid cells implicated in MS. BTKis with CNS penetration therefore have the potential to address CNS-compartmentalized neuroinflammation, a less accessible driver of MS disease progression[1]
- Consistent BTK target engagement is needed to fully suppress peripheral and CNS-compartmentalized inflammation in MS; achieving this requires a therapy with predictable pharmacokinetics (PK) that supports durable target engagement across the dosing interval
- 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)**

Objectives

To characterize orelabrutinib PK parameters and inter-subject variability in a Phase 2 Relapsing-remitting MS (RRMS) trial (NCT04711148) and predict target engagement and CNS penetration at the 80 mg once-daily (QD) dose

Figure 1. Orelabrutinib blocks BTK-mediated immune cell activity

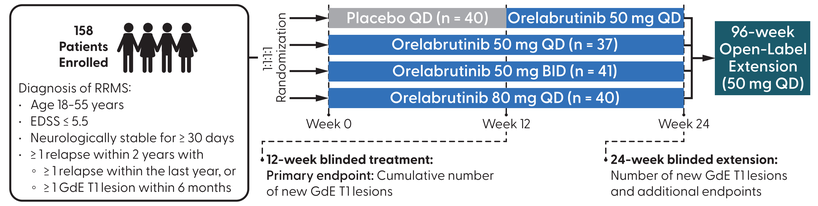


BBB, blood-brain barrier; BTKi, Bruton's Tyrosine Kinase inhibitors; CNS, central nervous system; PMS, progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

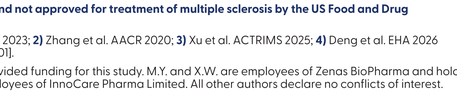
Methods

- A Phase 2, randomized, double-blind, placebo-controlled trial (NCT04711148) evaluated 158 adults with RRMS **(Figure 2)**
- IC_{50} and IC_{90} were derived from in vitro BTK enzyme inhibition assays
- BTK occupancy was assessed in PBMCs at pre-dose, 4 h, and 24 h post-dose in all SAD cohorts; the C_{max}–BTK occupancy (24 h) exposure-response relationship was analyzed by logistic regression
- BTK occupancy (EC_{90} and EC_{99}) was established from a Phase 1 study in healthy subjects,[2] and CSF concentrations were previously established in prior Phase 2 studies of orelabrutinib in lymphoma[4]

Figure 2. Phase 2 study design



Analysis Population and Collection:
- **Intensive PK Population:** 50 mg QD, n = 6; 80 mg QD, n = 8; 50 mg BID, n = 4
- **Intensive sampling collection time:** within 30 mins pre-dose and 30 mins, 1 h , 2 h , 4 h, 8 h, and 24 h post-dose on Day 1 and Day 8



Results

Plasma Pharmacokinetic Profile

- Orelabrutinib demonstrated predictable, dose-proportional PK with low inter-subject variability in patients with RRMS **(Figure 3, Table 1)**
  - » Mean terminal half-life ($t_{1/2}$) was approximately 3 hours across all three dose groups with no plasma accumulation observed upon repeated dosing
  - » Steady-state mean C_{max} ($C_{max,ss}$) values were 729 ng/mL (80 mg QD), 472 ng/mL (50 mg QD), and 489 ng/mL (50 mg BID)
  - » Orelabrutinib exposure (C_{max}, AUC) increased dose-proportionally from 50 mg QD to 80 mg QD, with low inter-subject variability **(Table 1)**
  - » The $C_{max,ss}$ of 729 ng/mL with 80 mg QD dose exceeded the EC_{99} for BTK occupancy (310 ng/mL) by > 2.3-fold[5]

Table 1. Summary of PK parameters (Day 1 and Day 8)

Day 1 (Single Dose)

Parameter	80 mg QD (N = 8)	50 mg QD (N = 6)	50 mg BID (N = 4)
C_{max} (ng/mL)	727 (41.22)	400 (21.06)	343 (23.30)
T_{max} (h), median (range)	1.51 (0.95–24.0)	1.03 (1.00–2.00)	1.50 (0.98–2.03)
$t_{1/2}$ (h)	3.48 (21.49)	3.14 (15.26)	2.62 (32.18)
$AUC_{0-\infty}$ (h*ng/mL)	3718 (18.10)	1901 (20.72)	1832 (7.95)

Day 8 (Steady State)

Parameter	80 mg QD (N = 7)	50 mg QD (N = 6)	50 mg BID (N = 4)
$C_{max,ss}$ (ng/mL)	729 (24.32)	472 (33.93)	489 (30.02)
T_{max} (h), median (range)	1.17 (0.97–2.08)	1.00 (0.97–1.03)	0.99 (0.97–2.05)
$t_{1/2}$ (h)	3.44 (11.39)	3.24 (18.68)	2.47 (16.35)
AUC_{tau} (h*ng/mL)	5009 (50.26)	2171 (17.00)	2064 (25.77)

PK parameters are represented as mean (CV%), except for T_{max}, which is represented as median (min, max). T_{last} for QD and BID cohorts are 24 h and 8 h, tau for QD and BID cohort are 24 h and 12 h.

Inhibition of BTK

- Orelabrutinib inhibits BTK enzymatic activity with an IC_{50} of 1.6 nM (0.7 ng/mL) and an IC_{90} of 8.2 nM (3.5 ng/mL) **(Figure 4)**
- IC_{90} is used as the reference threshold for CNS inhibition in this analysis given its direct derivation from BTK catalytic inhibition

Figure 3. Mean (±SE) plasma orelabrutinib concentration on Day 1 (single dose) and Day 8 (steady state) of 80 mg QD dose

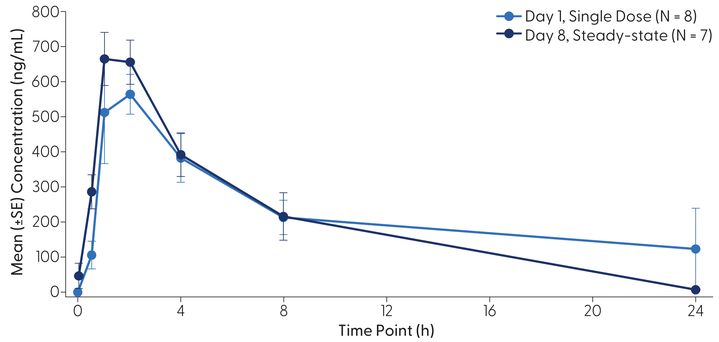
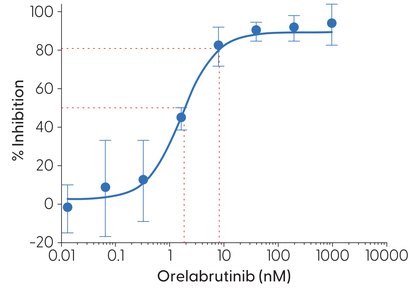


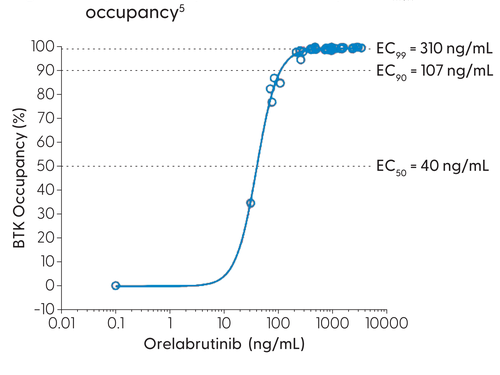
Figure 4. Inhibition of BTK enzyme activity by orelabrutinib



	IC_{50} (nM, n = 3)	IC_{90} (nM, n = 3)
Enzymatic activity	1.6	8.2

*Determined from in vitro enzymatic inhibition assay (n = 3 replicates; analyzed with IDBS XLfit5 software)

Figure 5. Exposure-response relationship for C_{max} vs BTK occupancy[5]



BTK Occupancy Thresholds

- Plasma orelabrutinib concentrations required to achieve EC_{90} and EC_{99} for BTK occupancy in PBMCs were 107 ng/mL and 310 ng/mL, respectively[5] **(Figure 5)**

CNS Exposure Relative to BTK Potency

- **Orelabrutinib achieves CSF concentrations substantially exceeding enzymatic IC_{90}**
  - » The mean orelabrutinib CSF concentration (31.3 ng/mL at steady state) substantially exceeded the enzymatic IC_{90}, supporting sufficient CNS exposure to achieve BTK inhibition[4]
  - » Estimated CSF concentration at the RRMS 80 mg QD dose is 16.7 ng/mL, by dose-proportional extrapolation
  - » Estimated CSF-to-IC_{90} ratio at 80 mg QD is approximately 5-fold, supporting the potential for BTK engagement in the CNS

CSF and IC_{90} at 80 mg QD are estimates, not directly measured. CSF was measured in patients with CNS lymphoma at 150 mg QD, not RRMS; blood-brain barrier integrity may differ between these populations[4]

Conclusions

- Predictable, high-level target engagement within the CNS is critical for progressive MS, where compartmentalized inflammation drives disease activity independent of peripheral immune suppression
- Orelabrutinib's covalent BTK binding[2] and low-variability PK profile support consistent target engagement with QD dosing
- The 80 mg QD regimen achieves plasma exposure exceeding the threshold for sustained ≥ 99% BTK occupancy (EC_{99}) and estimated CNS exposure exceeding the enzymatic IC_{90} by ~5-fold
- Together, the predictable, low-variability PK achieving > 99% target engagement positions orelabrutinib to potentially address the compartmentalized CNS inflammation implicated in progressive MS

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; AUCtau = AUC over the dosing interval; BBB = blood-brain barrier; BID = twice daily; BTK = Bruton's Tyrosine Kinase; BTKi = Bruton's Tyrosine Kinase inhibitor; Cmax = maximum plasma concentration; $C_{max,ss}$ = maximum plasma concentration at steady state; CNS = central nervous system; CSF = cerebrospinal fluid; CV = coefficient of variation; EC50/EC90/EC99 = concentration producing 50%/90%/99% of maximal BTK occupancy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IC50/IC90 = concentration producing 50%/90% of maximal enzymatic inhibition; MS = multiple sclerosis; N/n = number of participants; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PMS = progressive multiple sclerosis; QD = once daily; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SAD = single ascending dose; SE = standard error; T1 = T1-weighted; $t_{1/2}$ = terminal half-life; tau = dosing interval; Tlast = time of the last measurable concentration; Tmax = time to achieve maximum concentration.

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) Krämer et al. *Nat Rev Neurol* 2023; **2)** Zhang et al. AACR 2020; **3)** Xu et al. ACTRIMS 2025; **4)** Deng et al. EHA 2026 Congress; **5)** Prior Phase 1 Study [ICP-CL-001].

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