Baseline Characteristics in the Tolebrutinib Phase 3 Primary Progressive Multiple Sclerosis PERSEUS Clinical Trial

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BACKGROUND

- Treatment options remain limited for people living with primary progressive MS (PPMS) with only one approved therapy, which has modest effects on disability accumulation
- Tolebrutinib is a brain-penetrant and bioactive Bruton's tyrosine kinase (BTK) inhibitor thought to modulate persistent immune activation within the CNS, including disease-associated microglia and B cells[1,2]
  - In phase 3 pivotal trials, tolebrutinib treatment reduced the risk of disability accumulation by 31% relative to placebo in non-relapsing secondary progressive MS[3] and 29% relative to teriflunomide in relapsing MS[4]
- PERSEUS (NCT04458051) is a phase 3 trial evaluating the efficacy, safety, and tolerability of tolebrutinib in participants with PPMS

Potential Implications of Tolebrutinib in MS Pathophysiology

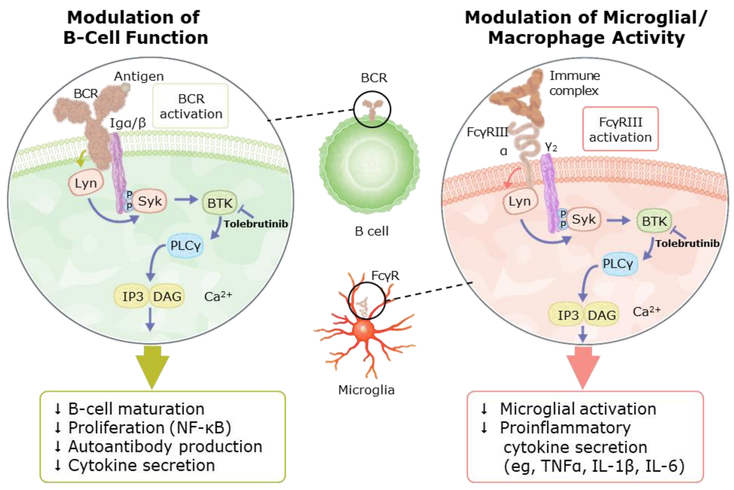
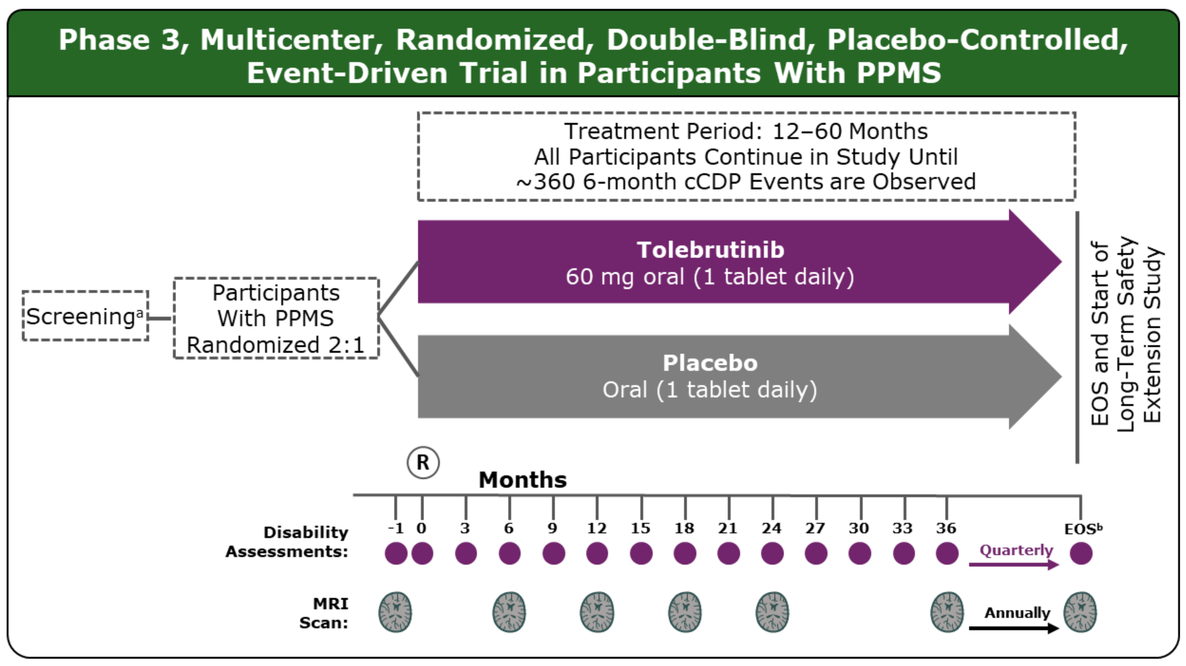


Figure adapted from Hendricks RW, et al. *Nature Chem Biol. 2011*;7:4-5.
BCR=B cell receptor; DAG=diacylglycerol; FcγR=Fc gamma receptor; Ig=immunoglobulin; IL=interleukin; IP3=inositol trisphosphate; NF=nuclear factor; PLC=phospholipase C; PPMS=primary progressive multiple sclerosis; TNF=tumor necrosis factor.
1. Turner TJ, et al. *Drugs R D.* 2024;24:263–274. 2. Gruber RC, et al. *Nat Commun.* 2024;15:10116. 3. Fox RJ, et al. *N Engl J Med*. 2025. Published online April 8, 2025. doi:10.1056/NEJMoa2415988. 4. Oh J, et al. *N Engl J Med*. 2025. Published online April 8, 2025. doi:10.1056/NEJMoa2415985

OBJECTIVE

Define baseline characteristics of participants in the PERSEUS trial

STUDY DESIGN



[a]The 28-day screening period is considered Month -1. [b]EOS safety follow-up visit occurs 4 weeks after the last dose of study treatment for participants not entering the long-term safety study. [c]Eligibility criterion applies to some countries early in study enrollment with subsequent global implementation. Examples of no access to ocrelizumab include being unavailable nationally or not being reimbursed for the approved indication. Individuals previously treated with ocrelizumab or other B-cell depleting therapy were eligible for enrollment following a washout period of 6 months prior to randomization.
cCDP=composite confirmed disability progression; EDSS=Expanded Disability Status Scale; EOS=end of study; MRI=magnetic resonance imaging; R=randomization; PPMS=primary progressive MS.

Key Eligibility Criteria

- Age 18–55 years
- Diagnosis of PPMS
- EDSS score ≥2.0 and ≤6.5 at screening
- Positive cerebrospinal fluid findings (oligoclonal bands and/or elevated immunoglobulin G index)
- Either no access, intolerance, or perceived lack of efficacy to ocrelizumab[c]

Primary Endpoint

- Time to 6-month cCDP defined as a sustained increase from baseline over ≥6 months in ≥1 of the following:
  - EDSS by ≥1.0 points when baseline score is ≤5.5
  - EDSS by ≥0.5 points when score is >5.5
  - Timed 25-foot walk by ≥20%
  - 9-hole peg test by ≥20%

RESULTS

Baseline Demographics

Demographic	All Participants (N=767)
Age, years, mean (SD)	45.3 (7.4)
Male, n (%)	416 (54.2)
Race, n (%)	
White	638 (83.3)
Asian	62 (8.1)
Black or African American	10 (1.3)
Other, unknown, or not reported	56 (7.3)
Ethnicity, n (%)	
Hispanic or Latino	70 (9.1)
Not Hispanic or Latino	673 (87.7)
Unknown	5 (0.7)
Not reported	19 (2.5)

SD= standard deviation

- 75.7% of participants were >40 years old

Baseline Disease Characteristics

Characteristic	All Participants (N=767)
EDSS score[a]	
Mean (SD)	4.9 (1.3)
Median (IQR)	5.0 (3.8–6.0)
Time since symptom onset, years	7.8 (5.0)
Time since PPMS diagnosis, years	4.2 (4.4)
Participants with ≥1 Gd-enhancing T1 lesions, n (%)	86 (11.3)
Number of Gd-enhancing T1 lesions	0.4 (2.4)
Number of T2 lesions, median (IQR)	49 (30–76)
T2 lesion volume, cm³	
Mean (SD)	15.6 (14.7)
Median (IQR)	10.8 (4.7–22.3)
Normalized brain volume, mL	1492.3 (86.4)

Values are mean (SD) unless otherwise indicated. [a]Average of screening and randomization EDSS scores.
EDSS=Expanded Disability Status Scale; Gd=gadolinium; IQR=interquartile range; PPMS=primary progressive multiple sclerosis; SD=standard deviation.

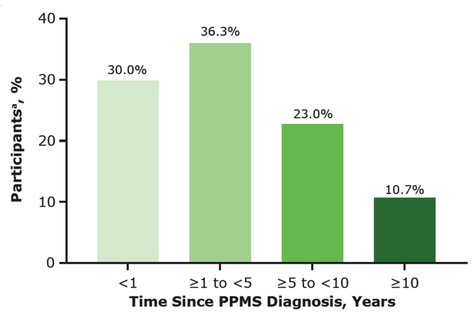
- 88.7% of participants had no Gd-enhancing lesions at baseline

Prior DMT's

DMT history	All Participants (N=767)
Number of prior DMTs, n (%)	
0	449 (58.5)
1	197 (25.7)
2	73 (9.5)
≥3	48 (6.3)
Type of prior DMT with incidence >2%[a], n (%)	
Ocrelizumab	181 (23.6)
Rituximab	77 (10.0)
Interferons	62 (8.1)
Dimethyl fumarate	40 (5.2)
Glatiramer	37 (4.8)
Fingolimod	36 (4.7)
Teriflunomide	28 (3.7)
Natalizumab	18 (2.3)

[a]Prior DMTs with frequency <2% were mitoxantrone (1.3%), siponimod (0.7%), ofatumumab (0.4%), alemtuzumab (0.3%), cladribine (0.3%), siponimod fumarate (0.3%), and diroximel fumarate (0.1%). Participants could have received more than one prior DMT. DMT=disease-modifying therapy.

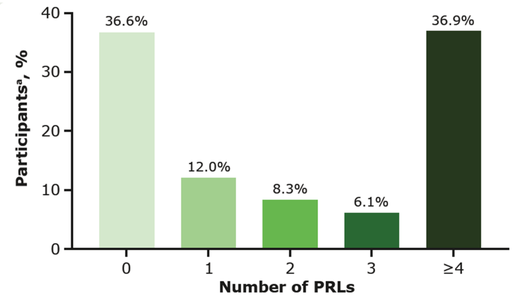
Distribution of Time Since Diagnosis



- Most participants (66.3%) were diagnosed with PPMS within the previous 5 years

an=766. One participant had missing data.
PPMS=primary progressive multiple sclerosis

Distribution of PRLs in the Subset of Participants with PRL Imaging (n=374)



- 63.4% of participants had ≥1 PRLs
- 36.9% of participants had ≥4 PRLs, which was higher than that reported for GEMINI (27.3%) and HERCULES (23.6%)
- The mean (SD) number of PRLs was 4.6 (7.1)

an=374. PRLs were imaged at a subset of sites with imaging capability.
PRL=paramagnetic rim lesion; SD, standard deviation

CONCLUSIONS

- 767 participants with PPMS were enrolled in the tolebrutinib phase 3 PERSEUS trial. At baseline, participants had a mean age of 45.3 years and mean time since PPMS diagnosis of 4.2 years
- Most participants (58.5%) were treatment-naïve. The most common previous treatments were ocrelizumab (23.6%) and rituximab (10.0%)
- The majority of participants (88.7%) had no Gd-enhancing lesions at baseline
- PRLs were present in 63.4% of the participants subset with PRL imaging at baseline

This trial will provide a comprehensive assessment of tolebrutinib efficacy and safety in the PPMS population, for which limited approved treatment options exist.

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