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Presentation #777

Efficacy and Safety of Tolebrutinib Versus Placebo in Primary Progressive Multiple Sclerosis: Results From the Phase 3 PERSEUS Trial

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Background

- Treatment options remain limited for people living with primary progressive MS (PPMS) with only one approved therapy[1]
- Tolebrutinib is an oral, brain-penetrant, and bioactive Bruton's tyrosine kinase (BTK) inhibitor that modulates persistent immune activation within the CNS, including disease-associated microglia and B cells[2,3]
  - In phase 3 pivotal trials, tolebrutinib treatment reduced the risk of disability accumulation by 31% relative to placebo in non-relapsing secondary progressive MS[4] and 29% relative to teriflunomide in relapsing MS[5]

Objective: To present results from the phase 3 PERSEUS trial evaluating the efficacy and safety of tolebrutinib vs. placebo in PPMS

Potential Implications of Tolebrutinib in MS Pathophysiology

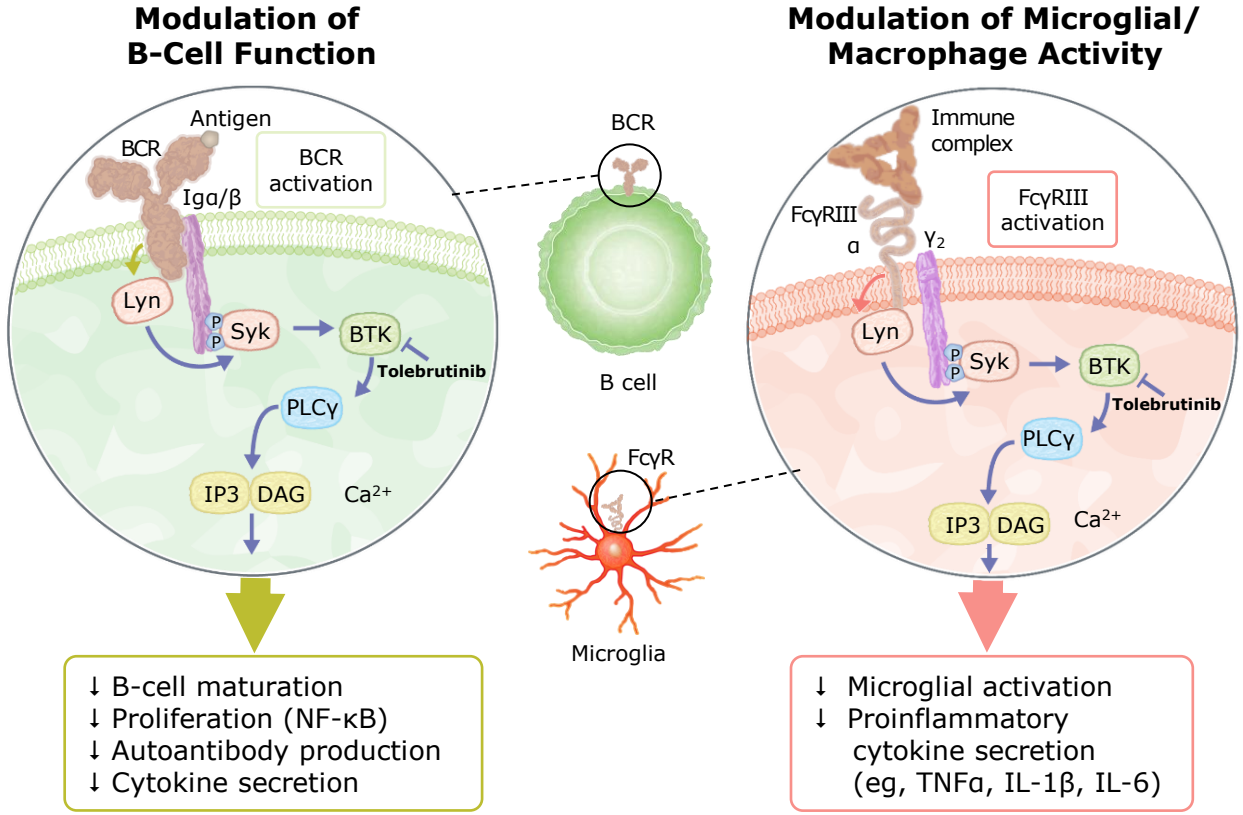
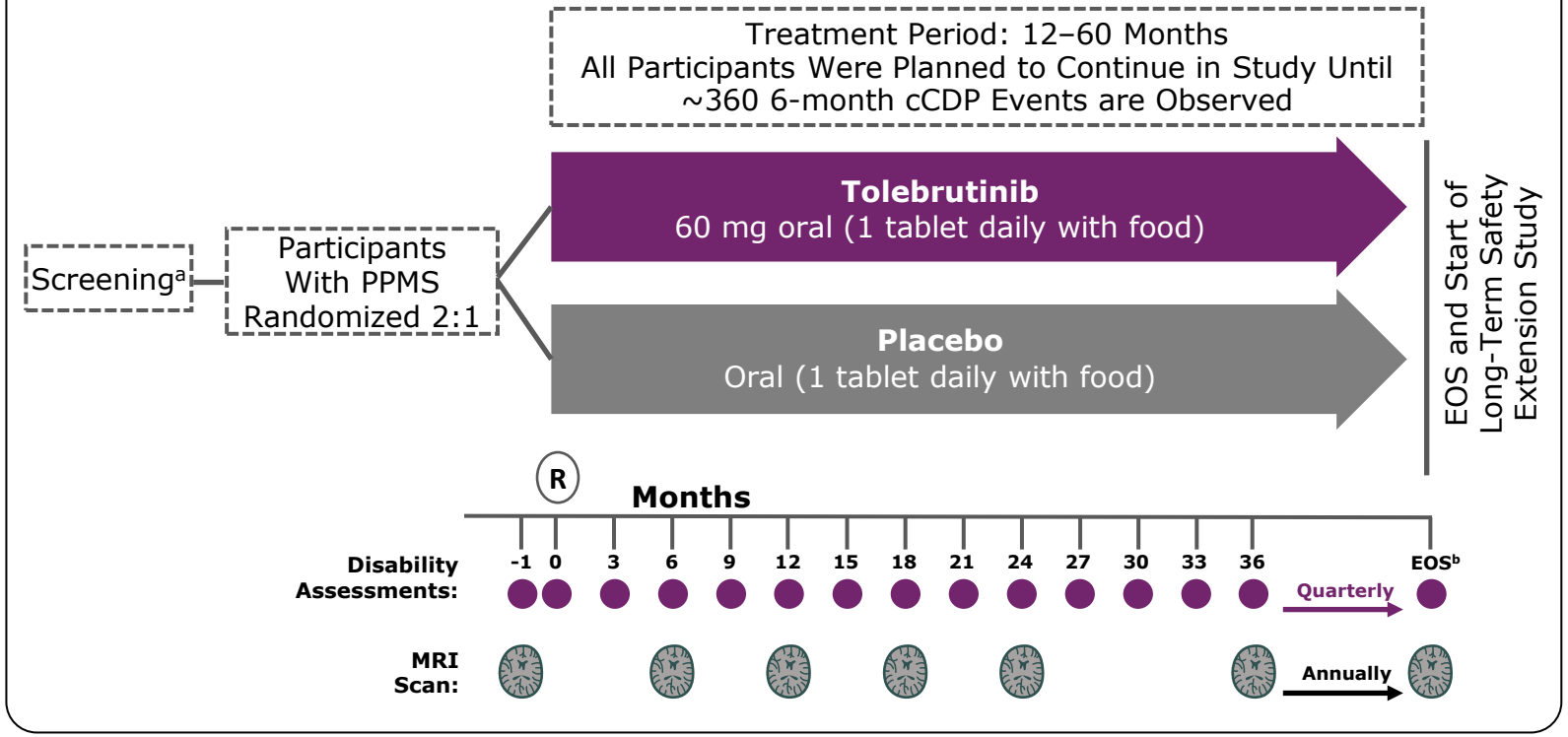


Figure adapted from Hendricks RW, et al. *Nature Chem Biol* 2011;7:4-5. BCR=B cell receptor; CNS=central nervous system; DAG=diacylglycerol; FcγR=Fc gamma receptor; Ig=immunoglobulin; IL=interleukin; IP3=inositol trisphosphate; Lyn=Lyn tyrosine kinase; NF-κB=nuclear factor kappa B; P=phosphorylation; PLC=phospholipase C; Syk=spleen tyrosine kinase; TNF=tumor necrosis factor. 1. Albelo-Martínez M, Rizvi S. *Neurotherapeutics*. 2025;22:e00601. 2. Turner TJ, et al. *Drugs R D* 2024;24:263–74. 3. Gruber RC, et al. *Nat Commun* 2024;15:10116. 4. Fox RJ, et al. *N Engl J Med* 2025;392:1883–92. 5. Oh J, et al. *N Engl J Med* 2025;392:1893–904.

PERSEUS: Trial Design

Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Event-Driven Trial in Participants With PPMS



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, previous intolerance, or perceived lack of efficacy to ocrelizumab[c]

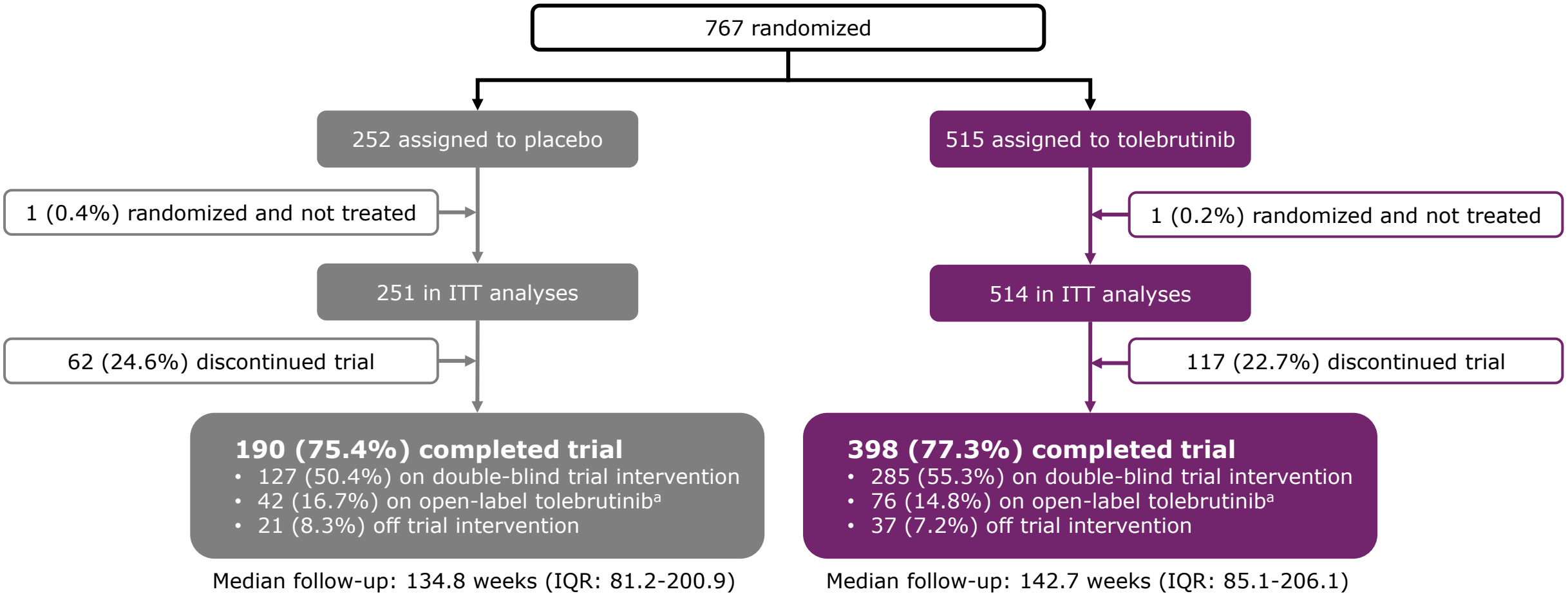
[a]The 28-day screening period was considered Month −1. [b]EOS safety follow-up visit occurred 4 weeks after the last dose of study treatment for participants not entering the long-term safety study. [c]Eligibility criterion applies to some countries early in study enrollment with subsequent global implementation. 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.

Main Endpoints

Trial Endpoints	
Primary endpoint[a]	• Time to onset of 6-month composite CDP (cCDP), defined as a sustained increase from baseline over ≥6 months in any of the following: – EDSS by ≥1.0-points when the baseline score is ≤5.5 or ≥0.5 points when the baseline score is >5.5 – Timed 25-Foot Walk (T25-FW) by 20% – 9-Hole Peg Test (9-HPT) by 20%
Secondary endpoints include:	• Time to onset of 6-month CDP (EDSS only) • Time to onset of 3-month cCDP • Total number of new or enlarging T2 lesions • Time to onset of 6-month CDI • % change in brain volume
Safety and tolerability	• Adverse events

[a]The trial was originally designed with 6-month CDP as the primary endpoint but later amended to 6-month cCDP to enable completion of the trial within a feasible time and with maintained trial integrity.
CDI=confirmed disability improvement; CDP=confirmed disability progression; EDSS=Expanded Disability Status Scale; PPMS=primary progressive MS.

Participant Disposition



[a]Participants who experienced 6-month CDP were offered rescue treatment with open-label tolebrutinib or a DMT approved for PPMS in their country.
CDP=confirmed disability progression; DMT=disease-modifying therapy; IQR=interquartile range; ITT=intent to treat; PPMS=primary progressive MS.

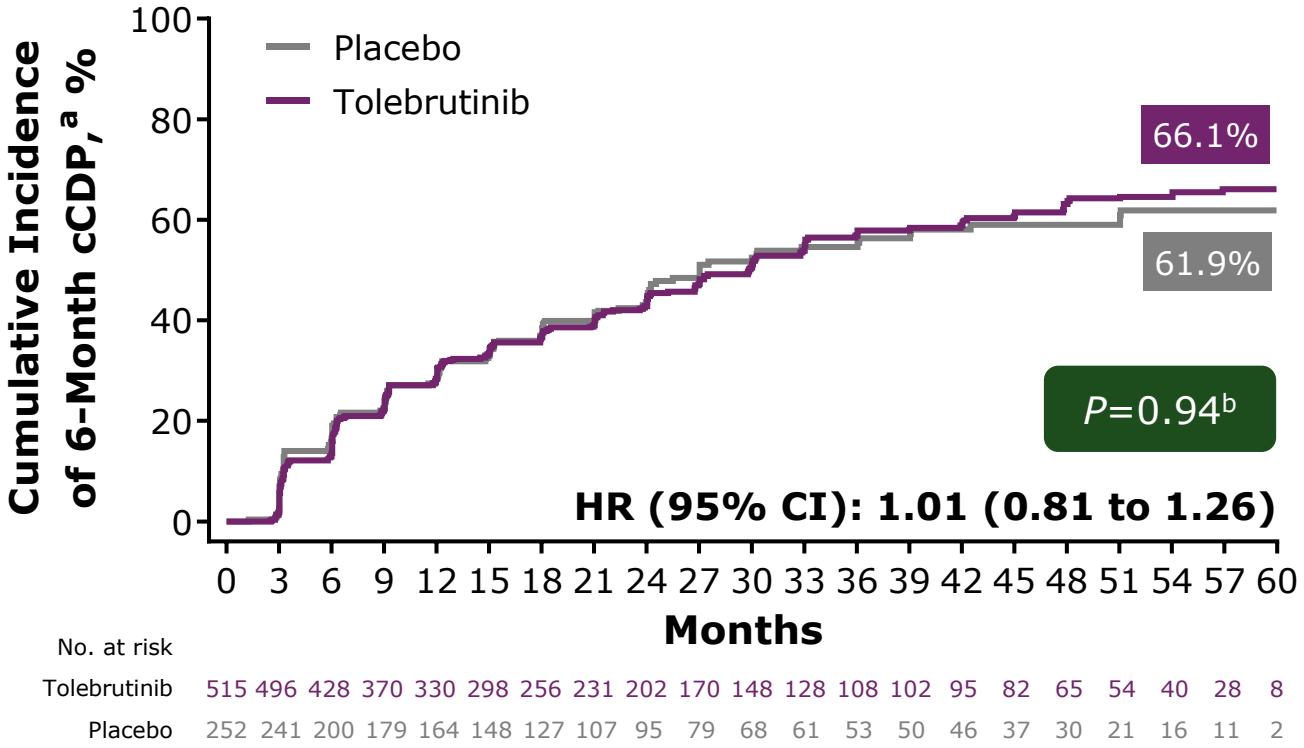
Baseline Characteristics

	Characteristic	Placebo (N=252)	Tolebrutinib (N=515)
	Age, years	45.0 (7.7)	45.4 (7.3)
	Male, n (%)	134 (53.2)	282 (54.8)
	Time since symptom onset, years	7.0 (4.4)	8.1 (5.3)
	Time since PPMS diagnosis, years	3.7 (4.0)	4.5 (4.5)
	Participants with ≥1 Gd+ T1 lesions, n (%)	35 (14.1)	51 (10.0)
	T2 lesion volume, cm^3, median (IQR)	12.1 (5.2–22.2)	10.2 (4.6–22.4)
	Participants with ≥1 prior DMTs, n (%)	99 (39.3)	219 (42.5)
Components of cCDP	**EDSS score[a]** Mean (SD) Median (IQR)	 4.9 (1.3) 5.0 (3.8–6.0)	 4.9 (1.4) 5.0 (3.8–6.0)
Components of cCDP	**T25-FW, sec, median (IQR)**	9.1 (6.2–16.0)	8.7 (6.1–15.2)
Components of cCDP	**9-HPT, sec, median (IQR)**	30.2 (24.8–38.1)	29.1 (24.2–37.9)

- Baseline characteristics were generally well-balanced across treatment arms
- Compared to the ORATORIO PPMS trial[1], fewer participants in PERSEUS had Gd+ T1 lesions at baseline and a higher proportion were previously treated

Values are mean (SD) unless otherwise indicated.
[a]Average of screening and Day 1 EDSS scores.
9-HPT=9-Hole Peg Test; cCDP=composite confirmed disability progression; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; IQR=interquartile range; PPMS=primary progressive MS; SD=standard deviation; T25-FW=Timed 25-Foot Walk. 1. Montalban X, et al. *N Engl J Med* 2017;376:209-20.

Primary Endpoint: Time to 6-Month cCDP

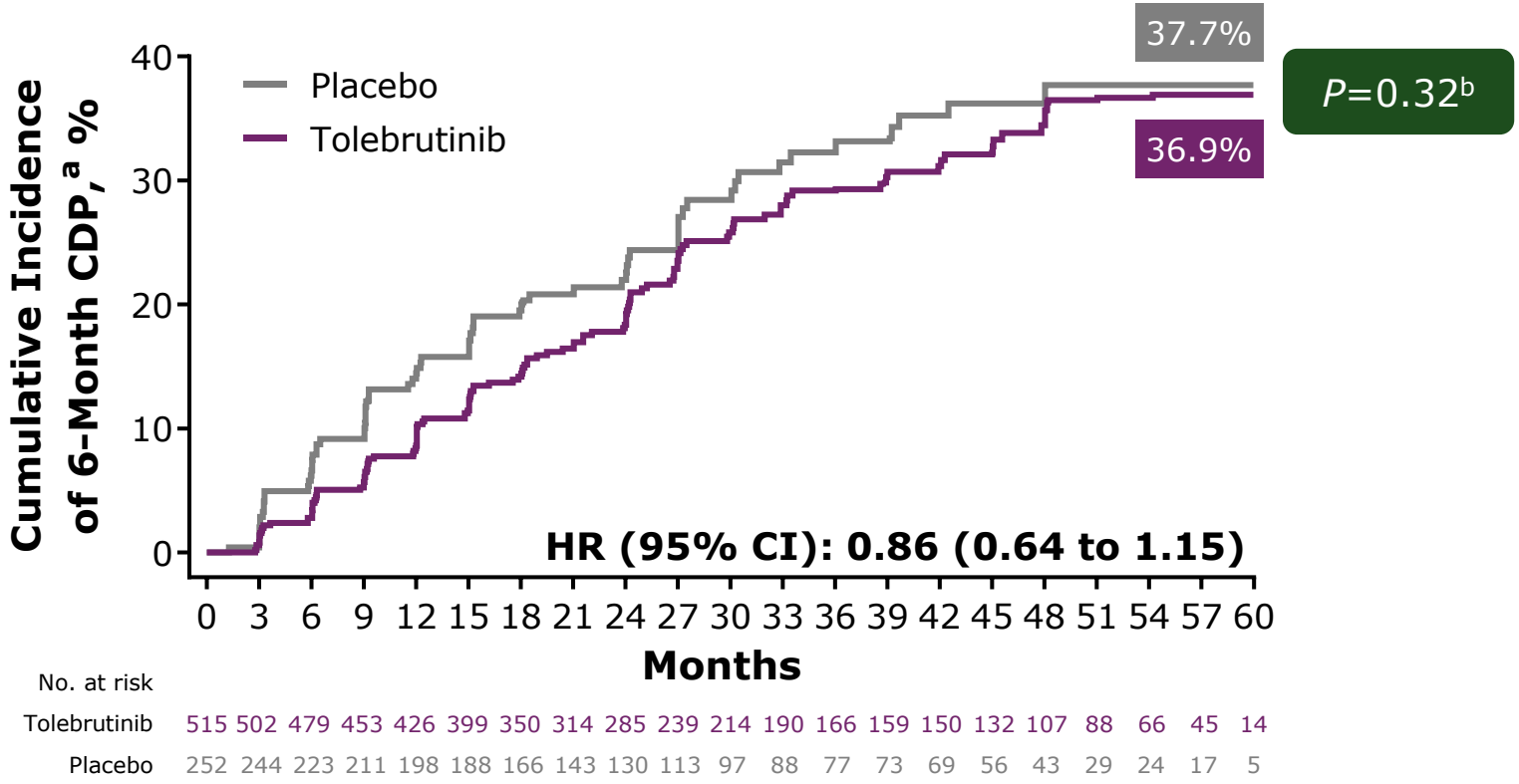


Decomposition of 6-month cCDP	Placebo (N=252)	Tolebrutinib (N=515)
Observed 6-month cCDP events[c]	119	254
Increase in EDSS (% of 6-month cCDP events)	43 (36%)	69 (27%)
≥20% increase in T25-FW (% of 6-month cCDP events)	65 (55%)	149 (59%)
≥20% increase in 9-HPT (% of 6-month cCDP events)	11 (9%)	36 (14%)

- Tolebrutinib did not reduce the risk of 6-month cCDP versus placebo in PPMS

[a]6-month cCDP was defined as an increase over ≥6 months of EDSS by ≥1.0-point when the baseline score is ≤5.5 or ≥0.5 points when the baseline score is >5.5, T25-FW by 20%, or 9-HPT by 20%.
[b]P-value is from Cox proportional hazards model. [c]cCDP event status was imputed for participants who completed the trial, met the criteria for cCDP sustained for at least 3 months, and continued to meet the cCDP criteria through the final trial assessment but did not reach the 6-month confirmation visit (placebo: n=3; tolebrutinib: n=6).
9-HPT=9-Hole Peg Test; cCDP=composite confirmed disability progression; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio; PPMS=primary progressive MS; T25-FW=Timed 25-Foot Walk.

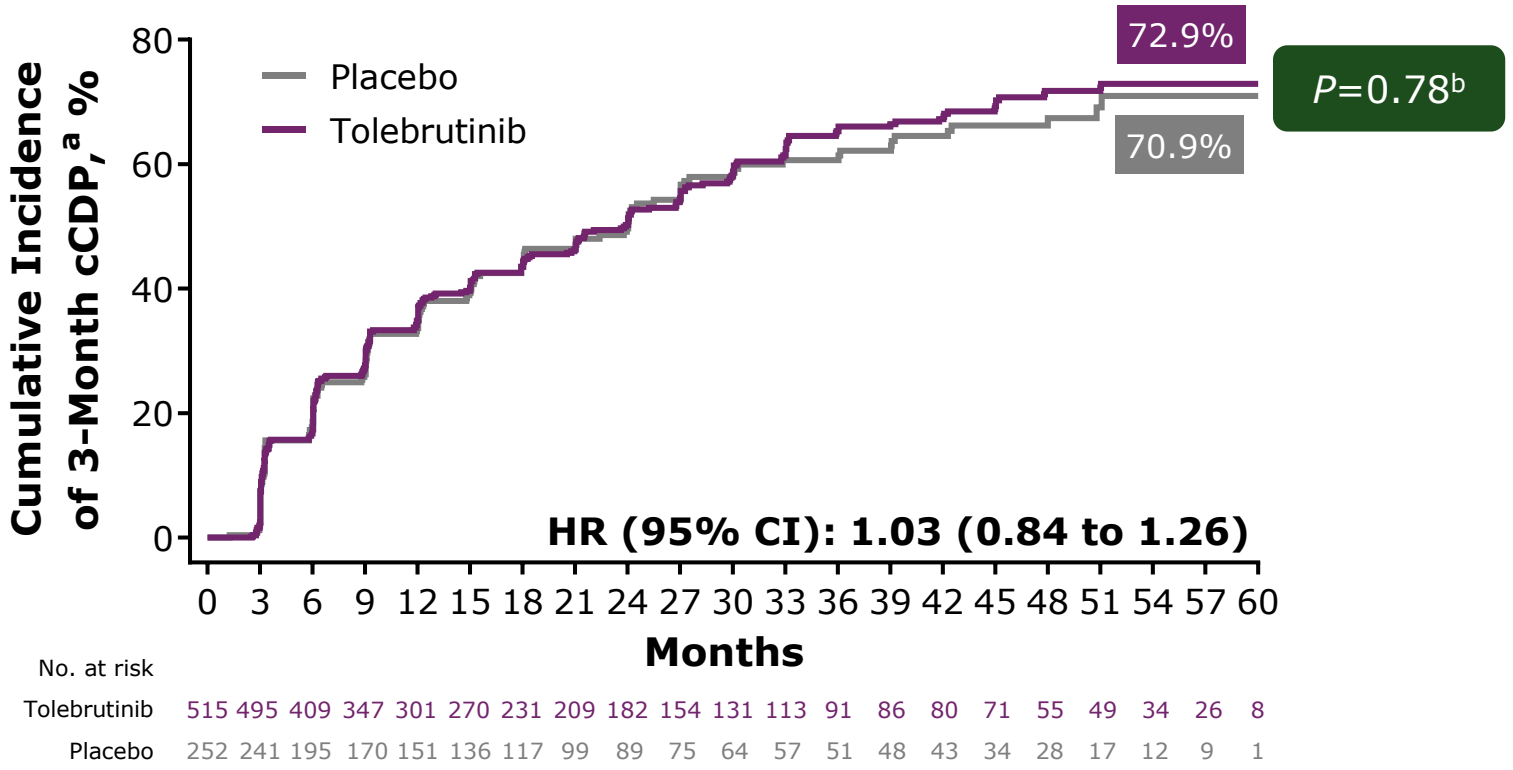
Secondary Endpoint: Time to 6-Month CDP



- KM curves of time to 6-month CDP (using EDSS progression events) indicated a trend favoring tolebrutinib versus placebo in PPMS but was not statistically significant

[a]6-month CDP was defined as an increase of ≥1.0 point from baseline EDSS score when baseline score is ≤5.5 or an increase of ≥0.5 points when baseline score is >5.5, confirmed over ≥6 months. [b]Nominal p-value from Cox proportional hazards model.
CDP=confirmed disability progression; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio; KM=Kaplan-Meier; PPMS=primary progressive MS.

Secondary Endpoint: Time to 3-Month cCDP

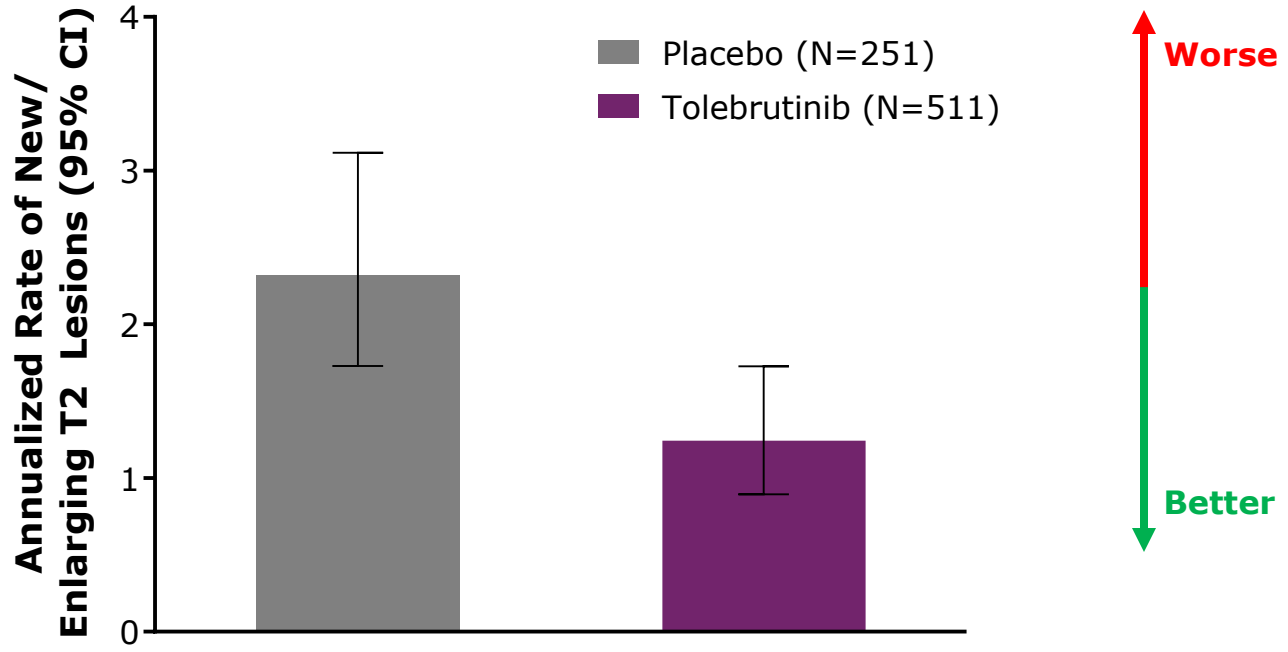


- There was no between-group difference in the risk of 3-month cCDP in PPMS

[a]3-month cCDP was defined as an increase over ≥3 months of EDSS by ≥1.0-point when the baseline score is ≤5.5 or ≥0.5 points when the baseline score is >5.5, T25-FW by 20%, or 9-HPT by 20%. [b]Nominal p-value is from Cox proportional hazards model.
9-HPT=9-Hole Peg Test; cCDP=composite confirmed disability progression; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio; PPMS=primary progressive MS; T25-FW=Timed 25-Foot Walk.

Secondary Endpoint: New/Enlarging T2 Lesions

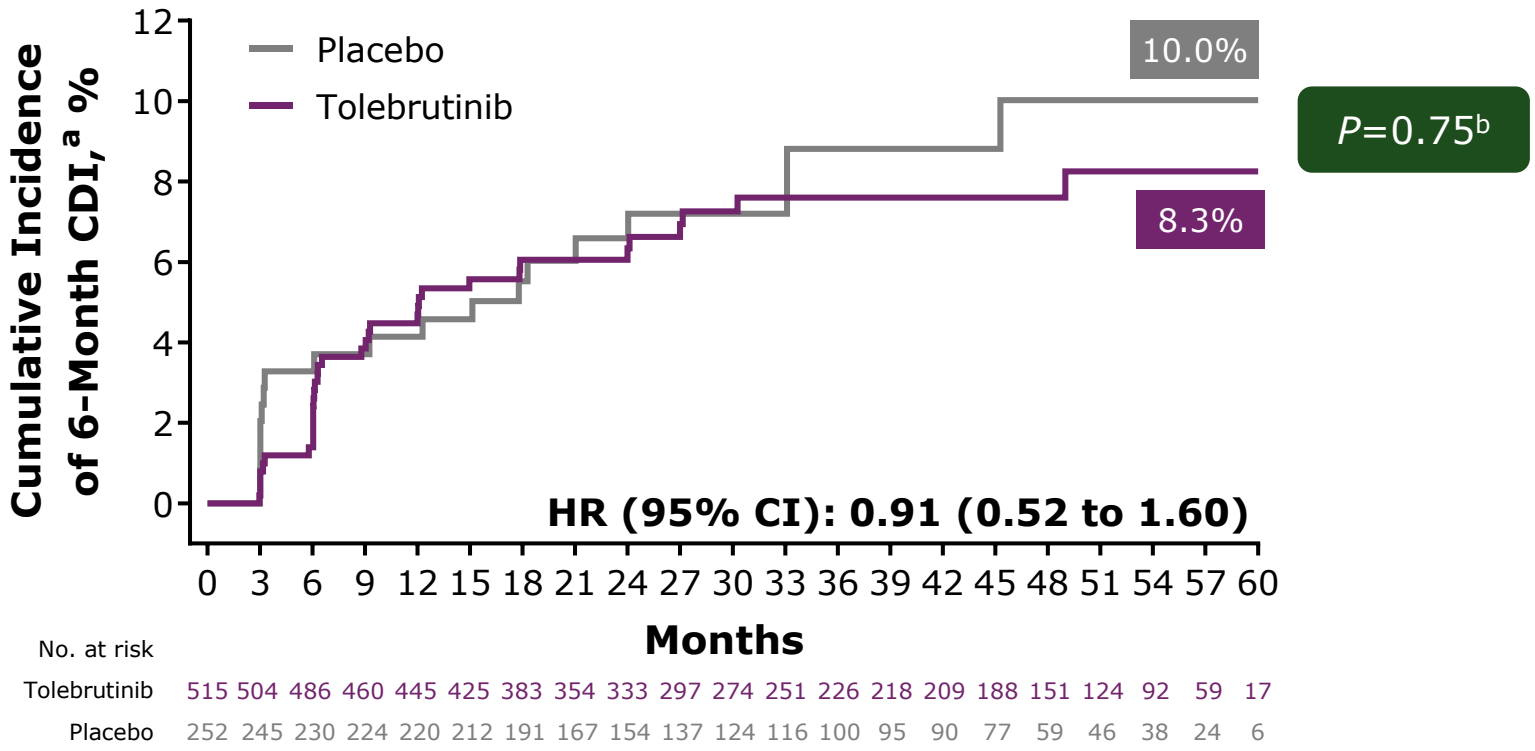
Adjusted rate ratio (95% CI): 0.54 (0.35 to 0.83), *P*=0.005[a]



- Tolebrutinib was associated with fewer new/enlarging T2 lesions versus placebo in PPMS

[a]Nominal p-value.
CI=confidence interval; PPMS=primary progressive MS.

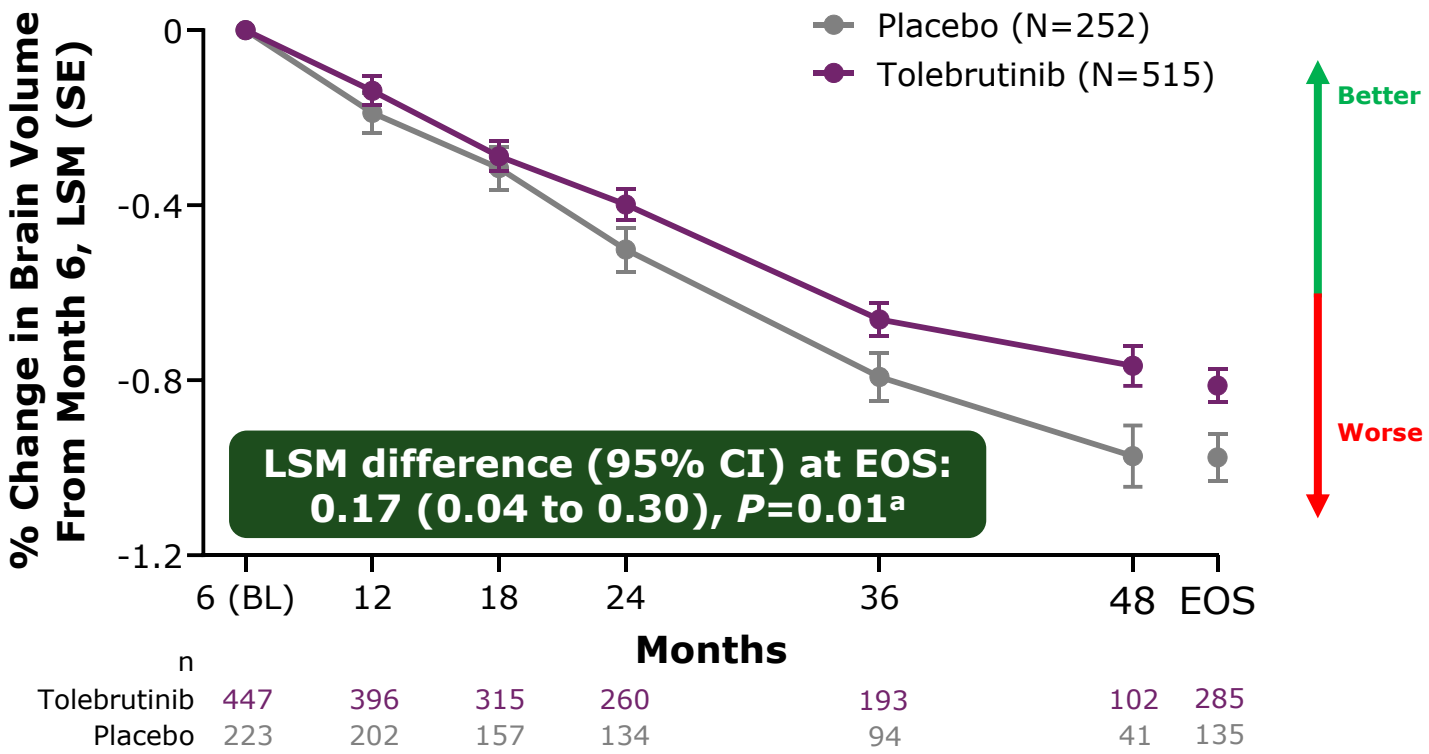
Secondary Endpoint: Time to 6-Month CDI



- There was no between-group difference in the rate of 6-month CDI in PPMS

[a]6-month CDI was defined as a decrease of ≥1.0 point from baseline EDSS score confirmed over ≥6 months. [b]Nominal p-value is from Cox proportional hazards model.
CDI=confirmed disability improvement; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio; PPMS=primary progressive MS.

Secondary Endpoint: Brain Volume Loss



- Tolebrutinib was associated with less brain volume loss at EOS versus placebo in PPMS

[a]Nominal p-value.
BL=baseline; CI=confidence interval; EOS=end of study; LSM=least squares mean; PPMS=primary progressive MS; SE=standard error.

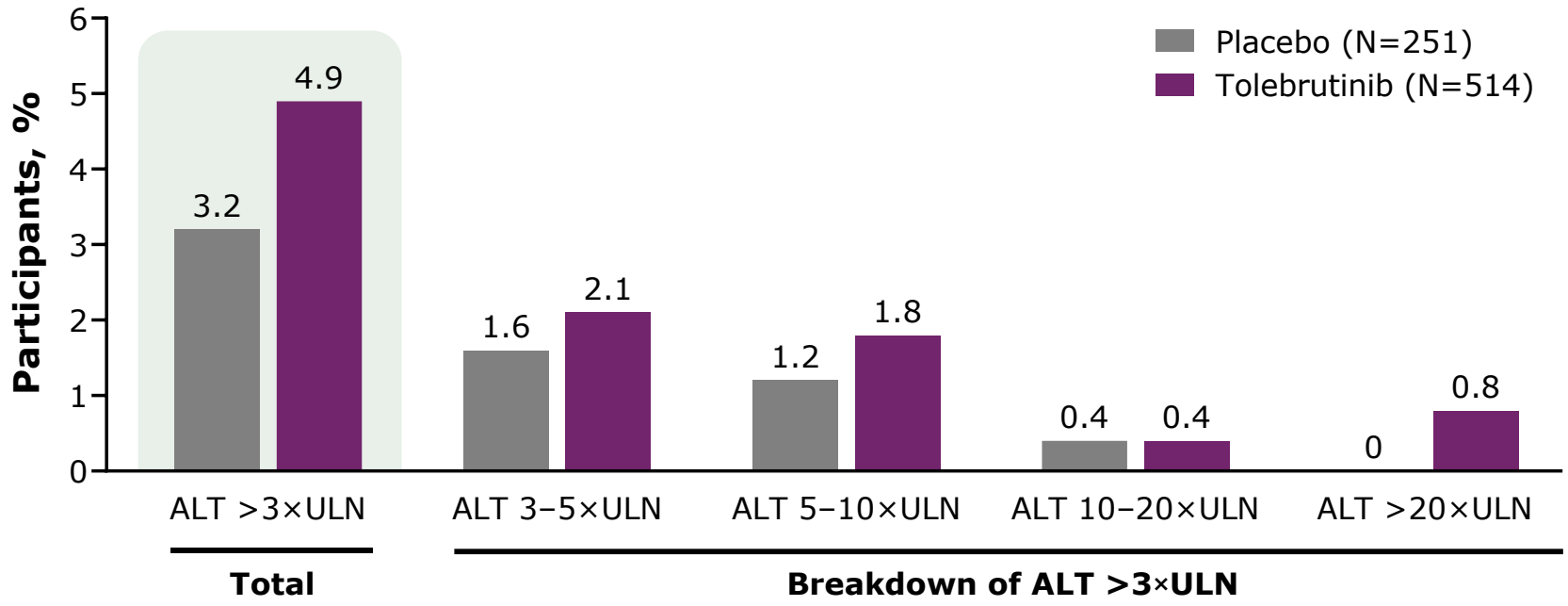
Adverse Events

Event, n (%)	Placebo (N=251)	Tolebrutinib (N=514)
Any TEAE	204 (81.3%)	433 (84.3%)
Any serious TEAE	22 (8.8%)	73 (14.2%)
Any TEAE leading to treatment discontinuation	8 (3.2%)	27 (5.3%)
Deaths[a]	2 (0.8%)	4 (0.8%)
Most common TEAEs (≥5% in the tolebrutinib arm)		
COVID-19	40 (15.9%)	117 (22.8%)
Urinary tract infection	36 (14.3%)	66 (12.8%)
Fall	16 (6.4%)	59 (11.5%)
Nasopharyngitis	31 (12.4%)	57 (11.1%)
Headache	25 (10%)	53 (10.3%)
Influenza	19 (7.6%)	47 (9.1%)
Back pain	28 (11.2%)	43 (8.4%)
Upper respiratory tract infection	14 (5.6%)	30 (5.8%)
Accidental overdose	8 (3.2%)	30 (5.8%)
Arthralgia	14 (5.6%)	29 (5.6%)

- Based on preliminary analysis, the general adverse event profile was consistent with previous tolebrutinib studies. Adverse events of COVID-19 and falls were observed at a higher rate in the tolebrutinib arm

[a]Two participants on placebo (cardiomyopathy and suicide). Four participants on tolebrutinib (aspiration pneumonia, unknown cause, cerebral edema, cardiac arrest).
PPMS=primary progressive MS; TEAE=treatment-emergent adverse event.

Liver Safety



- A small (0.8%) proportion of participants in the tolebrutinib group experienced peak ALT increases of >20×ULN, all occurring with an onset within the first 90 days of treatment and all resolving without sequelae
- One participant on tolebrutinib with a history of drug-induced liver injury secondary to PPI/NSAID use met criteria for Hy's law and fully recovered. This case occurred prior to the implementation of a revised protocol with more stringent monitoring

ALT=alanine aminotransferase; BILI=bilirubin; NSAID=non-steroidal anti-inflammatory drug; PPI=proton-pump inhibitor; PPMS=primary progressive MS; ULN=upper limit of normal.

Disability Effects of Tolebrutinib in Phase 3 Trials

			Time to onset of 6-month CDP/CDW		
Trial	**Population**	**Comparator**	**Risk Reduction**	**HR (95% CI)**	**P-value**
HERCULES[1]	nrSPMS	Placebo	31%	0.69 (0.55, 0.88)	0.003
GEMINI 1 & 2[2]	RMS	Teriflunomide	29%	0.71 (0.53, 0.95)	0.023[a]
PERSEUS	PPMS	Placebo	14%	0.86 (0.64, 1.15)	n.s.

- Disability effects of tolebrutinib appear directionally consistent across the spectrum of MS with more robust effects in nrSPMS

[a]Nominal p-value.
CI=confidence interval; CDP=confirmed disability progression; CDW=confirmed disability worsening; HR=hazard ratio; nrSPMS=non-relapsing secondary progressive MS; n.s.=not significant; PPMS=primary progressive MS; RMS=relapsing MS.
1. Fox RJ, et al. *N Engl J Med* 2025;392:1883–92. 2. Oh J, et al. *N Engl J Med* 2025;392:1893–904.

Conclusions

- The PERSEUS trial did not meet the primary endpoint of time to onset of 6-month cCDP
- There were no significant between-group differences for any of the secondary disability endpoints
- On MRI, tolebrutinib showed nominally significant reductions in new/enlarging T2 lesions and brain volume loss versus placebo
- Safety findings, including the risk of drug-induced liver injury, were consistent with previous phase 3 trials in non-relapsing secondary progressive MS and relapsing MS[1,2]

Disability accumulation observed in the PERSEUS PPMS population appears to be less impacted by the BTK inhibitor tolebrutinib than seen in other tolebrutinib MS trials

1. Fox RJ, et al. *N Engl J Med* 2025;392:1883–92. 2. Oh J, et al. *N Engl J Med* 2025;392:1893–904.
BTK= Bruton's tyrosine kinase; cCDP=composite confirmed disability progression; EDSS=Expanded Disability Status Scale; MRI=magnetic resonance imaging; PPMS=primary progressive MS.

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