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Presentation #O135

Efficacy and Safety of Tolebrutinib Versus Teriflunomide in Relapsing Multiple Sclerosis: Results From the Phase 3 GEMINI 1 and 2 Trials

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Background and Objective

- Current MS therapies reduce acute focal inflammation, but are less effective at slowing disability accumulation
- Tolebrutinib is a brain-penetrant and bioactive Bruton's tyrosine kinase (BTK) inhibitor that modulates persistent immune activation within the central nervous system, including disease-associated microglia and B cells[1-3]

Objective: To evaluate the efficacy and safety of tolebrutinib compared with teriflunomide in participants with relapsing MS

Tolebrutinib Modulates B-Cell and Disease-Associated Microglia Activity

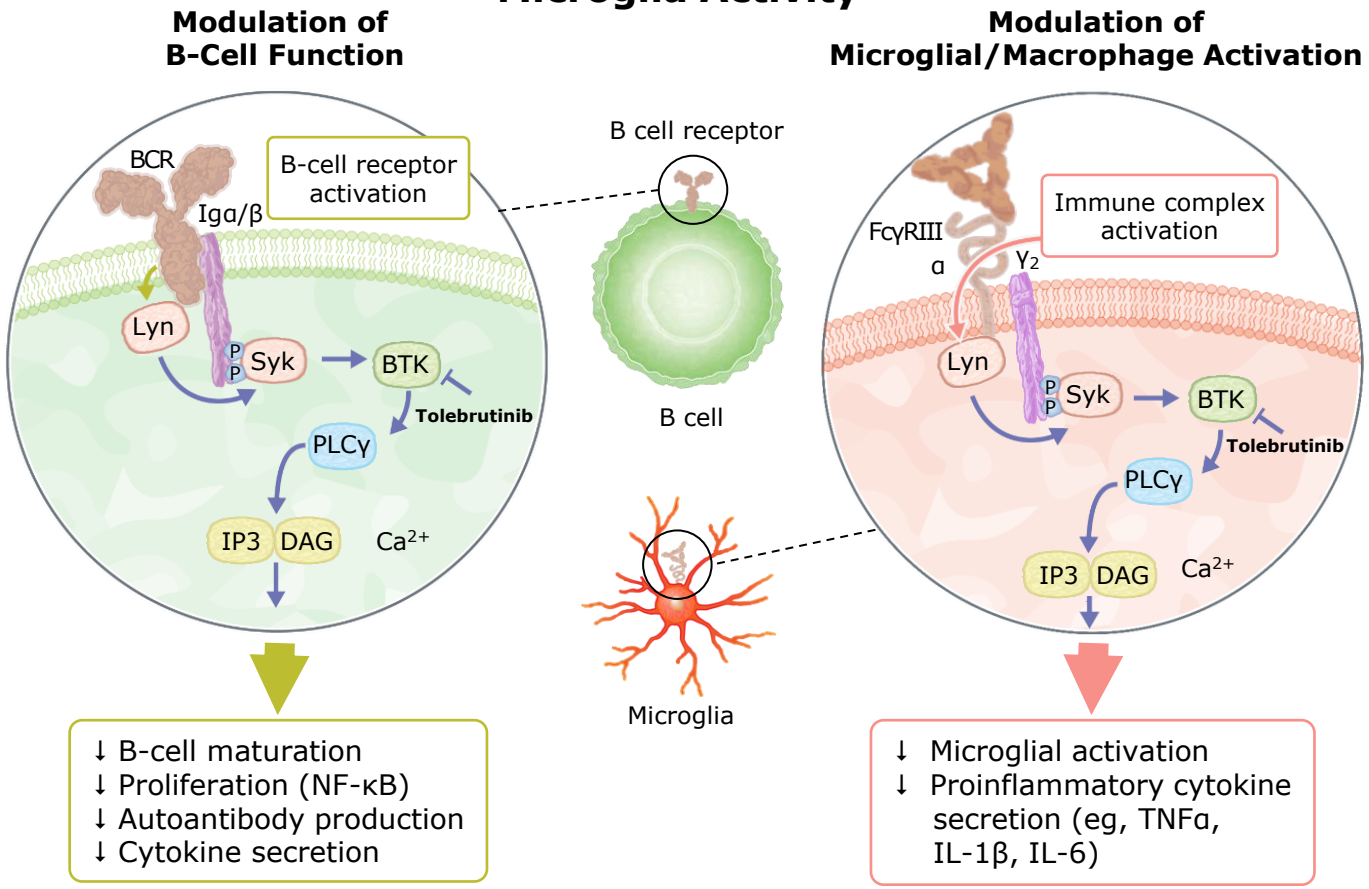
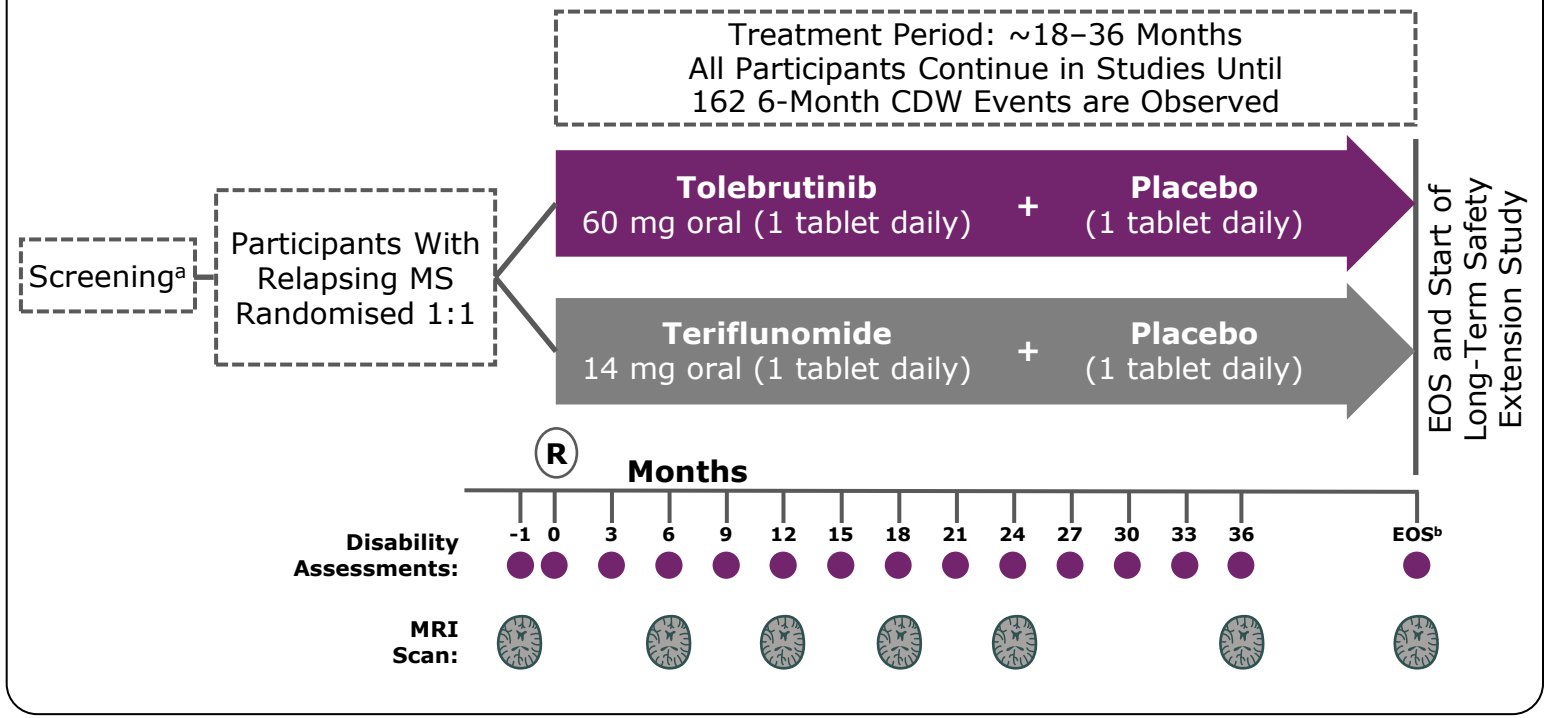


Figure adapted from Hendricks RW, et al. *Nature Chem Biol.* 2011;7:4-5. Tolebrutinib is investigational and has not been approved by the US Food and Drug Administration or any other regulatory agency worldwide. BCR=B cell receptor; DAG=diacylglycerol; FcγR=Fc gamma receptor; Ig=immunoglobulin; IL=interleukin; IP3=inositol triphosphate; NF=nuclear factor; PLC=phospholipase C; TNF=tumor necrosis factor.

1. Cabanis MJ, et al. *Clin Transl Sci.* 2024;17:e13693. 2. Turner TJ, et al. *Drugs R D.* 2024;24:263-274. 3. Krämer J, et al. *Nat Rev Neurol*. 2023;19:289-304.

GEMINI 1 and 2: Study Design

Phase 3, Multicentre, Randomised, Double-Blind, Double-Dummy, Active-Controlled, Parallel-Group, Event-Driven Trials



Key Inclusion Criteria

- Age 18–55 years
- Diagnosis of relapsing MS
- EDSS score ≤5.5
- At least 1 of the following:
  - ≥1 relapse within previous year
  - ≥2 relapses within previous 2 years
  - ≥1 gadolinium (Gd)-enhancing T1 brain lesion on MRI within previous year

Key Exclusion Criteria

- Prior diagnosis of primary progressive MS or non-relapsing secondary progressive MS

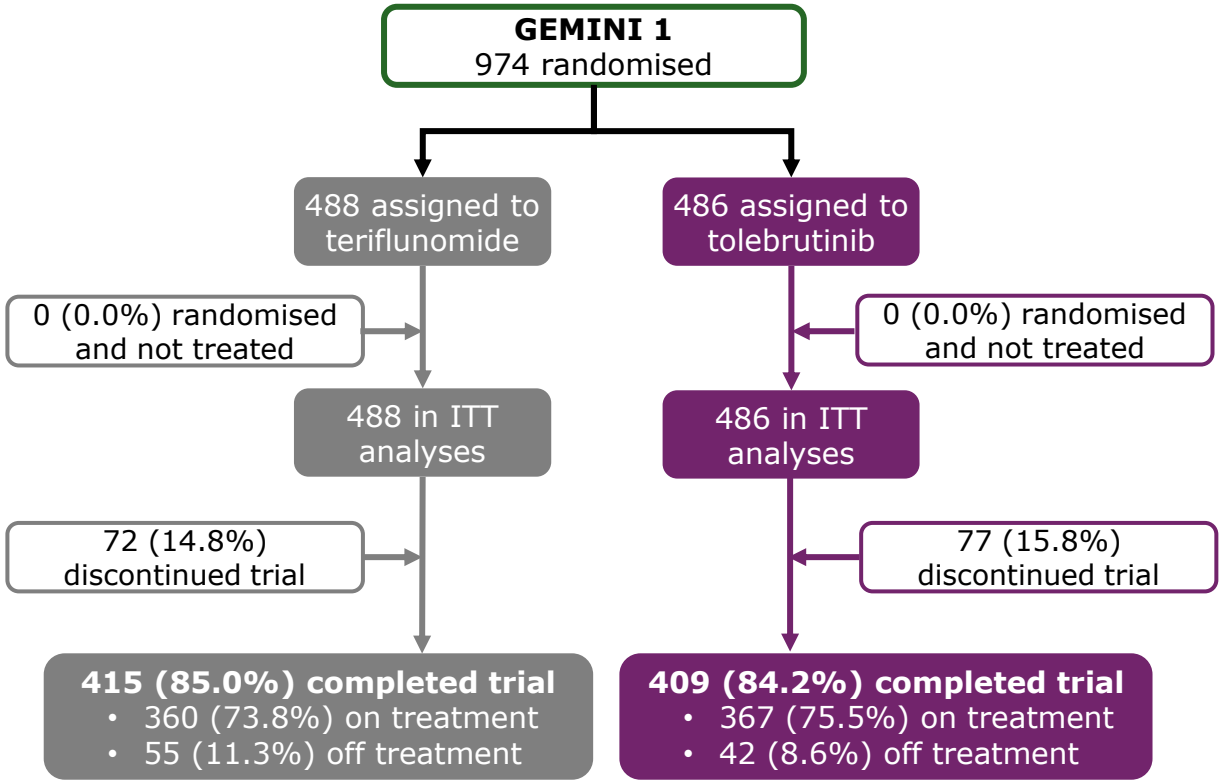
[a]The 28-day screening period was considered Month –1. [b]EOS safety follow-up visit occurred 4 weeks after the last dose of study treatment for participants not entering the long-term safety study.
CDW=confirmed disability worsening; EDSS=Expanded Disability Status Scale; EOS=end of study; MRI=magnetic resonance imaging; R=randomisation.

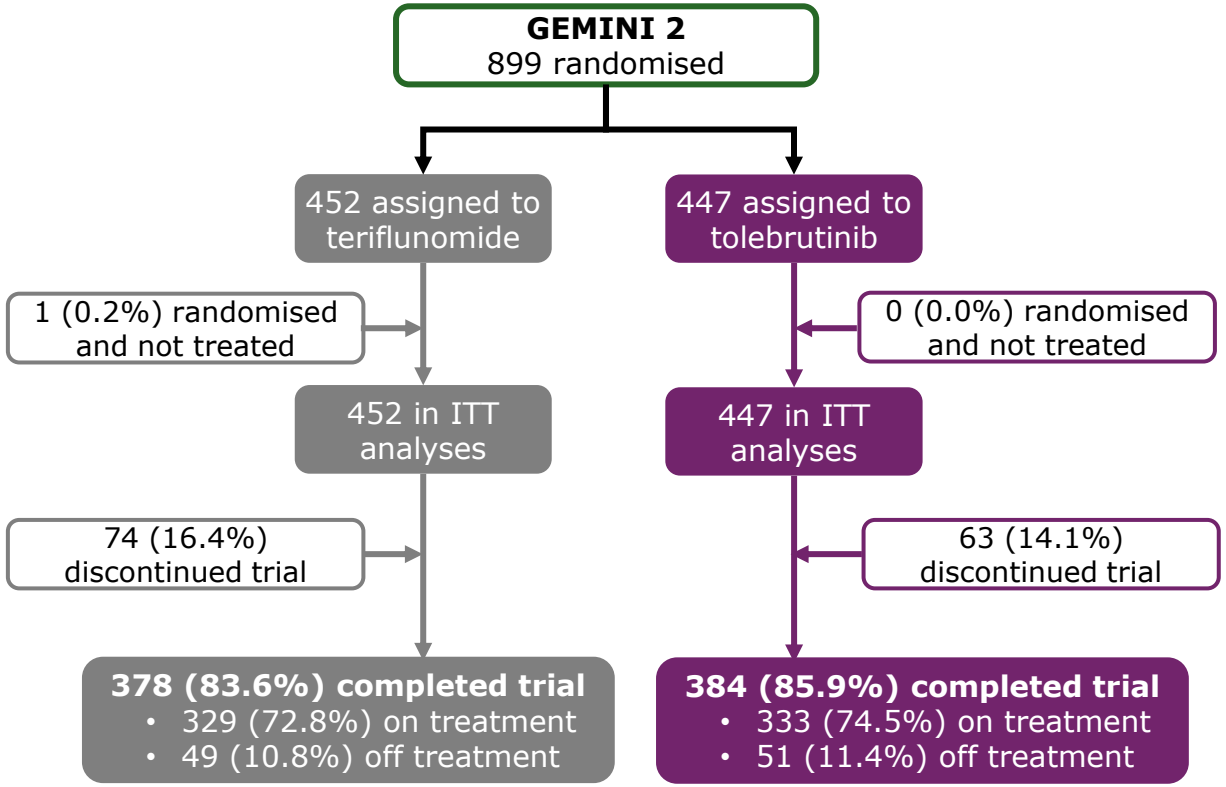
Main Endpoints

Trial Endpoints		
Primary endpoint *(within each trial)*	• Annualised relapse rate *(number of adjudicated MS relapses in a year)*	
Secondary endpoints include:[a]	**Pre-specified pooled analysis** • Time to onset of 6-month CDW • Time to onset of 3-month CDW • Time to onset of 6-month CDI	**By individual trial** • Total number of new Gd-enhancing T1 brain lesions • Total number of new/enlarging T2 brain lesions • % change in brain volume
Safety and tolerability	• Adverse events	

[a]Secondary endpoints also include change in Symbol Digit Modalities Test score and change in California Verbal Learning Test – Second Edition score, which are currently being analysed.
CDI=confirmed disability improvement; CDW=confirmed disability worsening; Gd=gadolinium.

Participant Disposition





ITT=intent to treat.

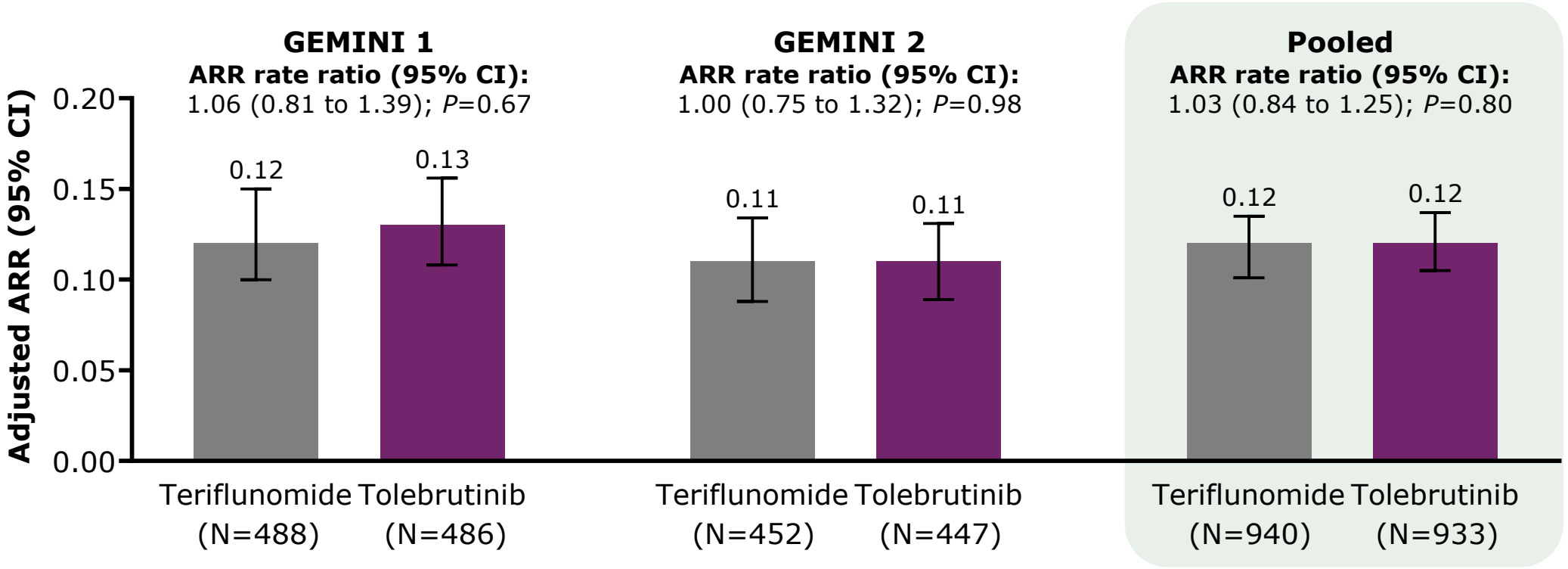
Baseline Characteristics

Characteristic	GEMINI 1		GEMINI 2	
	Teriflunomide (N=488)	Tolebrutinib (N=486)	Teriflunomide (N=452)	Tolebrutinib (N=447)
Age, years	36.6 (9.4)	36.8 (9.0)	36.1 (9.3)	36.6 (9.3)
Female, n (%)	325 (66.6)	334 (68.7)	293 (64.8)	300 (67.1)
MS subtype, n (%)				
Relapsing remitting	483 (99.0)	480 (98.8)	450 (99.6)	444 (99.3)
Secondary progressive	5 (1.0)	6 (1.2)	2 (0.4)	3 (0.7)
EDSS score[a]				
Mean (SD)	2.37 (1.20)	2.42 (1.19)	2.32 (1.19)	2.42 (1.17)
Median (IQR)	2.0 (1.5–3.0)	2.0 (1.5–3.0)	2.0 (1.5–3.0)	2.3 (1.5–3.3)
Time since relapsing MS symptom onset, years	7.1 (7.2)	7.3 (7.3)	5.9 (6.9)	6.2 (6.9)
Number of relapses within previous 1 year	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	1.1 (0.5)
Participants with ≥1 Gd-enhancing T1 lesion, n (%)	186 (38.4)	168 (34.7)	146 (32.6)	145 (32.4)
Number of Gd-enhancing T1 lesions	1.5 (4.2)	1.3 (3.7)	1.0 (3.2)	1.0 (2.4)
T2 lesion volume, cm^3, median (IQR)	10.7 (4.9–19.4)	11.6 (4.8–19.5)	7.7 (3.5–15.4)	8.3 (3.8–15.5)
Participants who were treatment-naïve, n (%)	291 (59.6)	315 (64.8)	300 (66.4)	301 (67.3)

- Baseline characteristics were well-balanced across both treatment arms and between trials

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

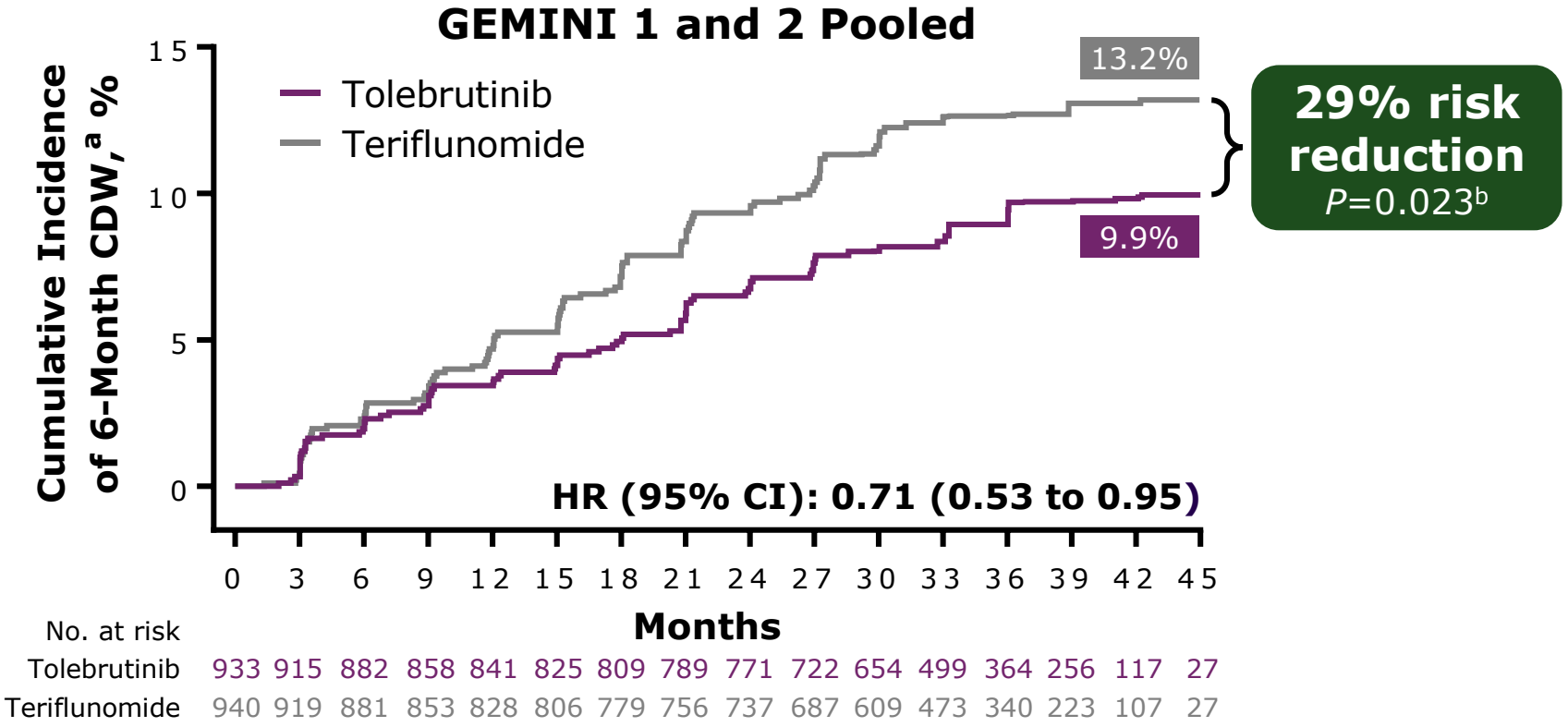
Primary Endpoint: Annualised Relapse Rate



- ARR was low in the teriflunomide arm in both GEMINI 1 and 2 and no difference was observed between tolebrutinib and teriflunomide

ARR=annualised relapse rate; CI=confidence interval.

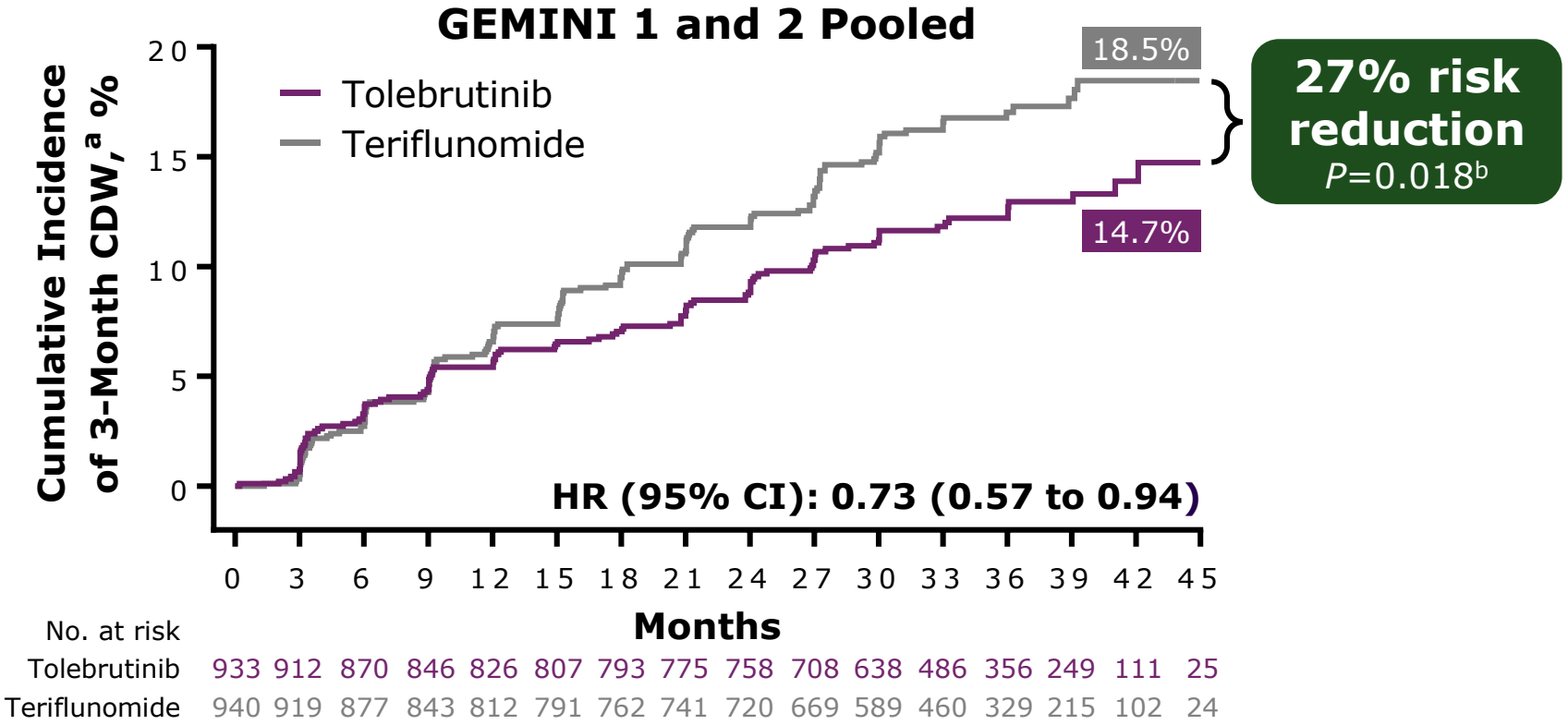
Key Secondary Endpoint: Time to 6-Month CDW



- For 6-month CDW, tolebrutinib demonstrated clear separation from teriflunomide (29% relative risk reduction) in a population with very low relapse activity

[a]6-month CDW is defined as a sustained increase from baseline in EDSS score of ≥1.5 points when baseline score is 0, ≥1.0 points when baseline score is 0.5 to ≤5.5 or ≥0.5 points when baseline score is >5.5, confirmed over ≥6 months. [b]Nominal p-value (stratified log-rank test).
CDW=confirmed disability worsening; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

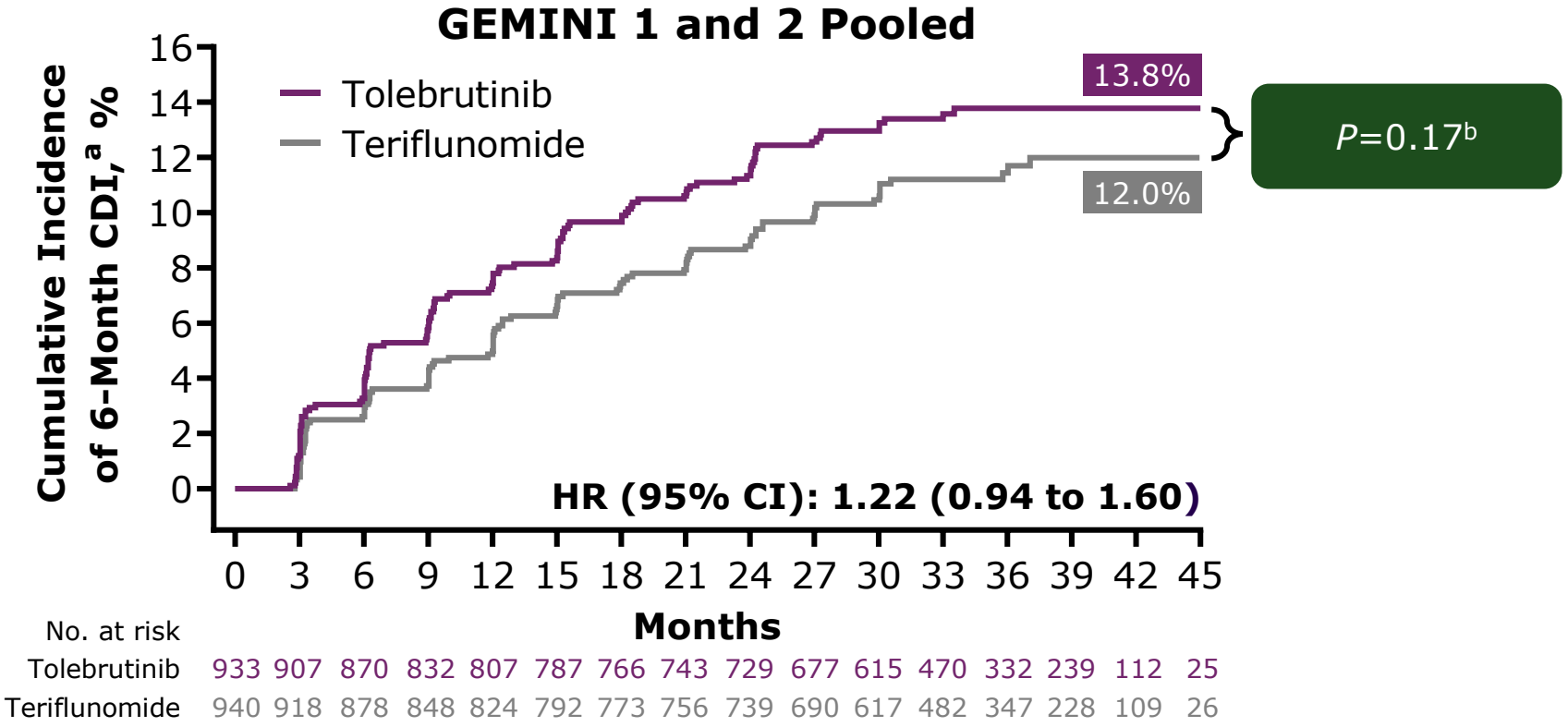
Secondary Endpoint: Time to 3-Month CDW



- Tolebrutinib demonstrated similar effects on time to 3-month CDW

[a]3-month CDW is defined as a sustained increase from baseline in EDSS score of ≥1.5 points when baseline score is 0, ≥1.0 points when baseline score is 0.5 to ≤5.5 or ≥0.5 points when baseline score is >5.5, confirmed over ≥3 months. [b]Nominal p-value (stratified log-rank test).
CDW=confirmed disability worsening; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

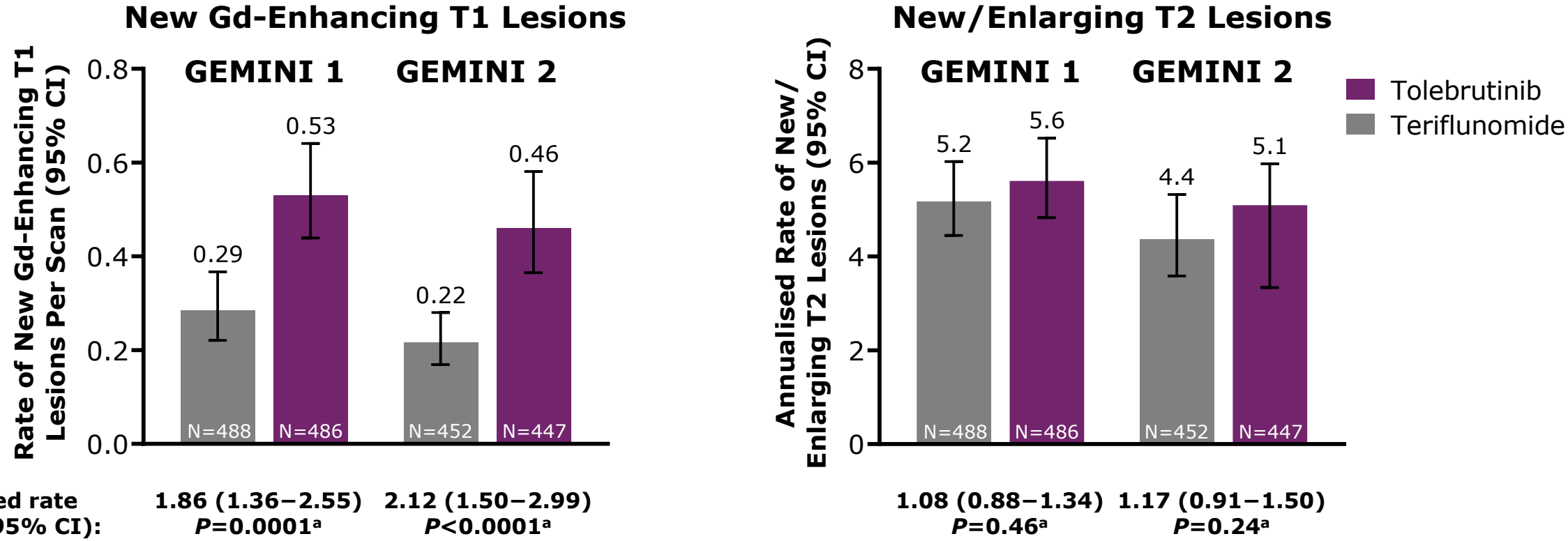
Secondary Endpoint: Time to 6-Month CDI



- There was a numerically higher rate of 6-month CDI in the tolebrutinib arm compared to teriflunomide

[a]6-month CDI is defined as a decrease of ≥1.0 point from baseline EDSS score confirmed over ≥6 months. [b]Nominal p-value (stratified log-rank test).
CDI=confirmed disability improvement; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

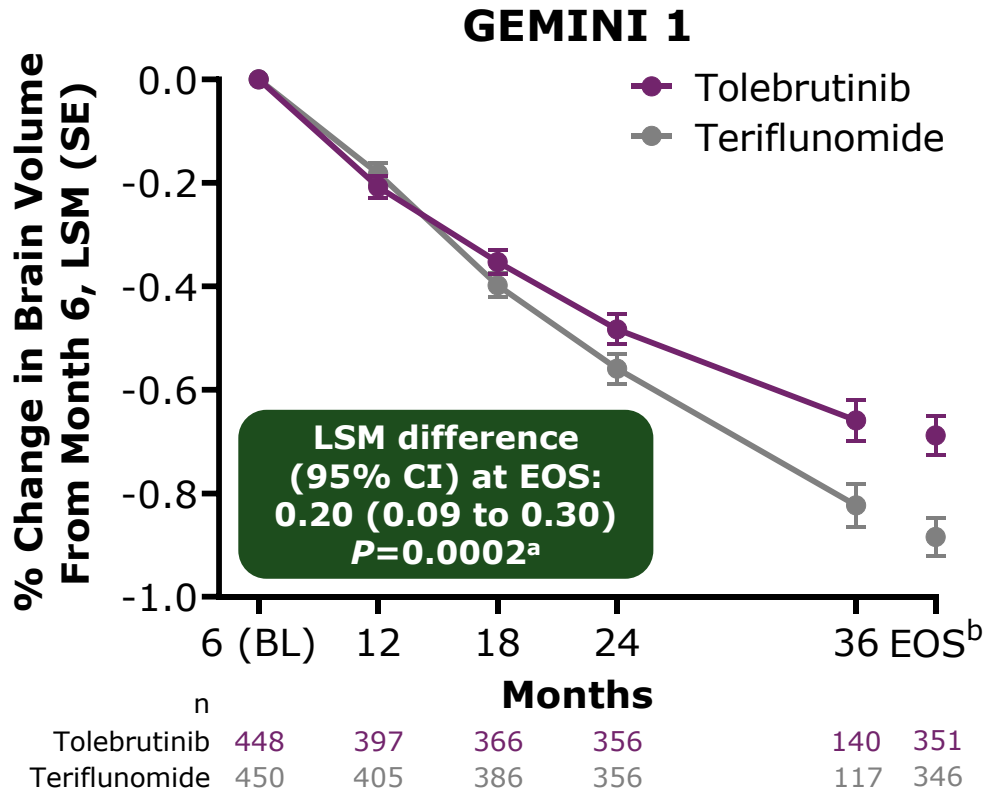
Secondary Endpoint: Brain Lesions on MRI

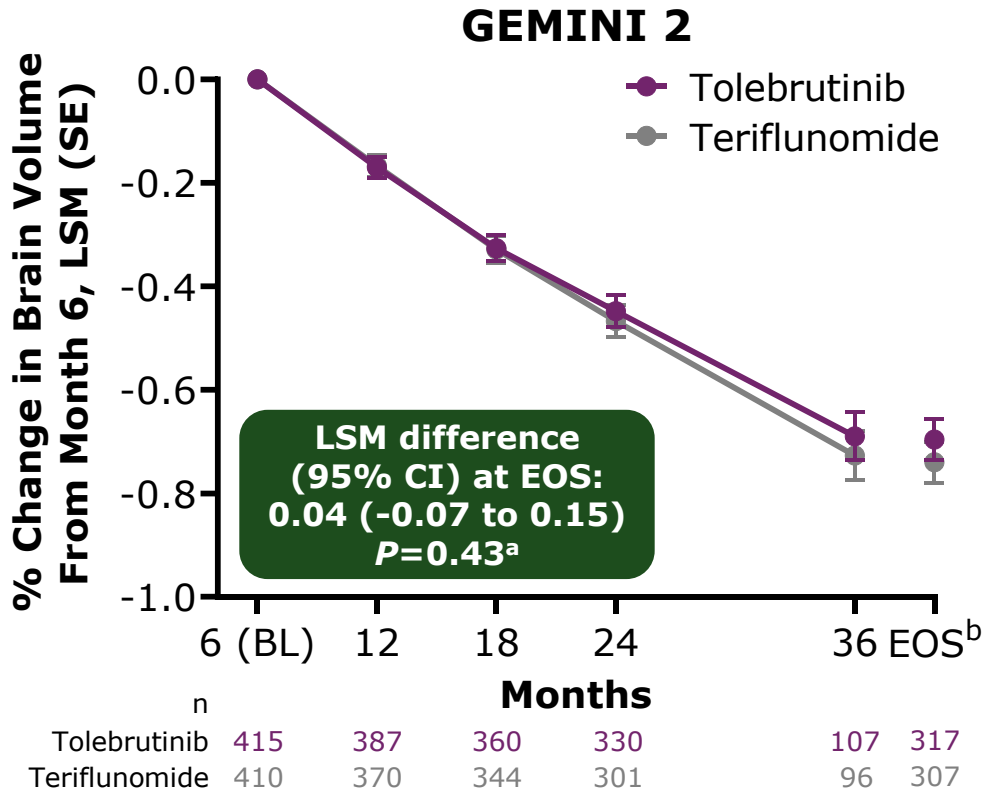


- The number of new Gd-enhancing T1 lesions was higher in the tolebrutinib arm; the number of new/enlarging T2 lesions was similar between both treatment arms

Data are mean (95% CI).
[a]Nominal p-value.
CI=confidence interval; Gd=gadolinium; MRI=magnetic resonance imaging.

Secondary Endpoint: Brain Volume Loss (BVL)





- Changes in BVL with tolebrutinib were approaching what is observed in the natural progression of healthy adults

Note: BVL is measured as percentage change in brain volume from Month 6 to exclude the potential confounding effect of pseudoatrophy.
[a]Nominal p-value. [b]The mean trial duration was 30 months for GEMINI 1 and 29 months for GEMINI 2.
BL=baseline; EOS=end of study; LSM=least squares mean; SE=standard error.

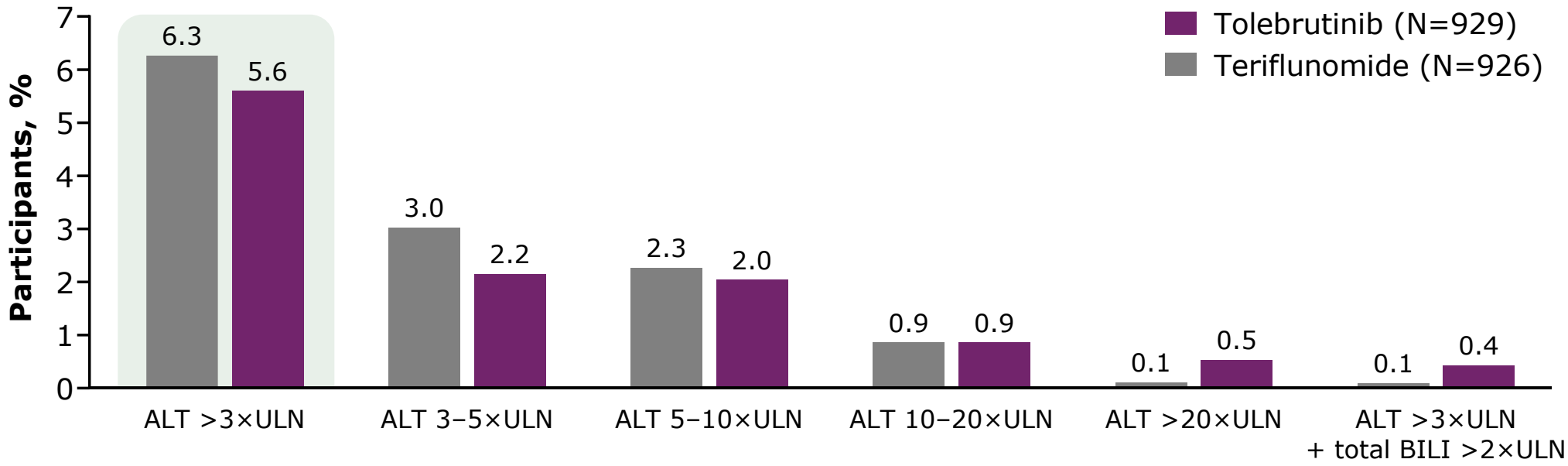
Adverse Events

Event, n (%)	GEMINI 1 and 2	
	Teriflunomide (N=939)	Tolebrutinib (N=933)
Any TEAE	810 (86.3%)	792 (84.9%)
Any serious TEAE	77 (8.2%)	91 (9.8%)
Any TEAE leading to treatment discontinuation	41 (4.4%)	42 (4.5%)
Deaths[a]	2 (0.2%)	1 (0.1%)
Most common TEAEs (≥5% in the tolebrutinib arm)		
COVID-19 infection	252 (26.8%)	225 (24.1%)
Nasopharyngitis	105 (11.2%)	119 (12.8%)
Headache	98 (10.4%)	117 (12.5%)
Upper respiratory tract infection	82 (8.7%)	77 (8.3%)
Alopecia	146 (15.5%)	73 (7.8%)
Urinary tract infection	57 (6.1%)	59 (6.3%)
Back pain	55 (5.9%)	58 (6.2%)
Viral upper respiratory tract infection	59 (6.3%)	50 (5.4%)

- Based on preliminary analysis, adverse events were generally balanced

[a]In the teriflunomide arm, 1 participant completed suicide by firearm and 1 participant died by fatal brain oedema and subarachnoid haemorrhage (both were assessed as unrelated to teriflunomide by the investigator). In the tolebrutinib arm, 1 participant died from homicidal gunshot wound that was assessed as unrelated to tolebrutinib by the investigator.
TEAE=treatment-emergent adverse event.

Liver Safety



- All cases of ALT >3×ULN resolved without sequelae
- A small (0.5%) proportion of participants in the tolebrutinib group experienced peak ALT increases of >20×ULN, all occurring within the first 90 days of treatment

ALT=alanine aminotransferase; BILI=bilirubin; ULN=upper limit of normal.

Conclusions

- There was no significant difference in ARR between tolebrutinib and teriflunomide
- Tolebrutinib demonstrated a 29% risk reduction in 6-month CDW vs. teriflunomide
- The number of new Gd-enhancing T1 lesions was higher in the tolebrutinib vs. teriflunomide arm
- Liver enzyme elevations (>3× ULN) were observed in 5.6% of tolebrutinib participants, a signal reported with other BTK inhibitors in MS
  - All cases resolved without sequelae
  - Frequent liver monitoring in the first 90 days has been implemented

Tolebrutinib showed a clear reduction in disability accumulation despite no differences in relapses vs. teriflunomide

These results are consistent with the hypothesis that acute focal inflammation and smoldering neuroinflammation are two distinct biological processes

ARR=annualised relapse rate; BTK=Bruton's tyrosine kinase; CDW=confirmed disability worsening; Gd=gadolinium; ULN=upper limit of normal.