ECTRIMS 2024
Presentation #O136

Efficacy and Safety of Tolebrutinib Versus Placebo in Non-Relapsing Secondary Progressive Multiple Sclerosis: Results From the Phase 3 HERCULES Trial

Robert J. Fox[1], Amit Bar-Or[2], Anthony Traboulsee[3], Celia Oreja-Guevara[4], Gavin Giovannoni[5], Patrick Vermersch[6], Sana Syed[7], Ye Li[8], Wendy S. Vargas[8], Timothy J. Turner[7], Erik Wallstroem[7], Daniel S. Reich[9] on behalf of the Tolebrutinib Phase 3 HERCULES Trial Group

[1]Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, USA; [2]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, University of Pennsylvania, Philadelphia, USA; [3]Division of Neurology, The University of British Columbia, Vancouver, Canada; [4]Multiple Sclerosis Center, University Hospital San Carlos, Madrid, Spain; [5]Queen Mary University London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; [6]University of Lille, Inserm U1172, CHU Lille, FHU Precise, Lille, France; [7]Sanofi, Cambridge, USA; [8]Sanofi, Bridgewater, USA; [9]Translational Neuroradiology Section, National Institutes of Health, Bethesda, USA

Disclosures and Acknowledgements

- **Robert J. Fox:** Consulting (AB Science, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Greenwich Biosciences, Immunic, INmune Bio, Eli Lilly and Company, Janssen, Novartis, Sanofi, Siemens, TG Therapeutics) and research support (Biogen, Novartis, Sanofi)
- **Amit Bar-Or**: Grant support to the University of Pennsylvania (Biogen Idec, EMD Serono, Novartis, Roche Genentech); speaking and/or consulting (Accure, Atara Biotherapeutics, Biogen, Bristol-Myers Squibb, EMD Serono, GlaxoSmithKline, Gossamer, Janssen, MedImmune, Novartis, Roche Genentech, Sanofi)
- **Anthony Traboulsee**: Consulting and/or speaking and grant/research support (Biogen, EMD Serono, Roche, Sanofi)
- **Celia Oreja-Guevara**: Speaking and/or consultancy (Bayer, Biogen, Merck Serono, Novartis, Roche, Sanofi, Teva)
- **Gavin Giovannoni**: Consulting/speaking and/or research support (Astoria Biologica, Aurinia Pharmaceuticals, Biogen, BMS-Celgene, GSK, Janssen/J&J, Japanese Tobacco, Merck KGaA/EMD Serono, Moderna, Novartis, Roche/Genentech, Sandoz, Sanofi, Vir Biotechnology, Viracta)
- **Patrick Vermersch**: Honoraria or consulting (AB Science, Ad Scientiam, Biogen, Celgene-BMS, Imcyse, Merck, Novartis, Roche, Sanofi); research support (Biogen, F. Hoffmann-La Roche, Merck, Novartis, Sanofi)
- **Sana Syed, Ye Li, Wendy S. Vargas, Timothy J. Turner, Erik Wallstroem**: Employees of Sanofi (may hold shares and/or stock options in the company)
- **Daniel S. Reich**: Grant/research support (Abata, Sanofi)

- Trial registration: NCT04411641
- This research was funded by Sanofi
- We thank Rebecca Zhou, PharmD, of Sanofi, for contributions to the planning, review and coordination of this presentation
- Editorial support for this presentation was provided by Meenakshi Subramanian, PhD, and Renee E. Granger, PhD, of Envision Pharma Group and was funded by Sanofi

We thank the participants and their families for their involvement in the HERCULES trial

We also thank the participating centres and investigators for their commitment to this trial

Background and Objective

- Disability accumulation starts early in MS and is thought to be driven by chronic smoldering neuroinflammation
- 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 placebo in participants with non-relapsing secondary progressive MS (nrSPMS)

Potential Implications of Tolebrutinib in MS Pathophysiology

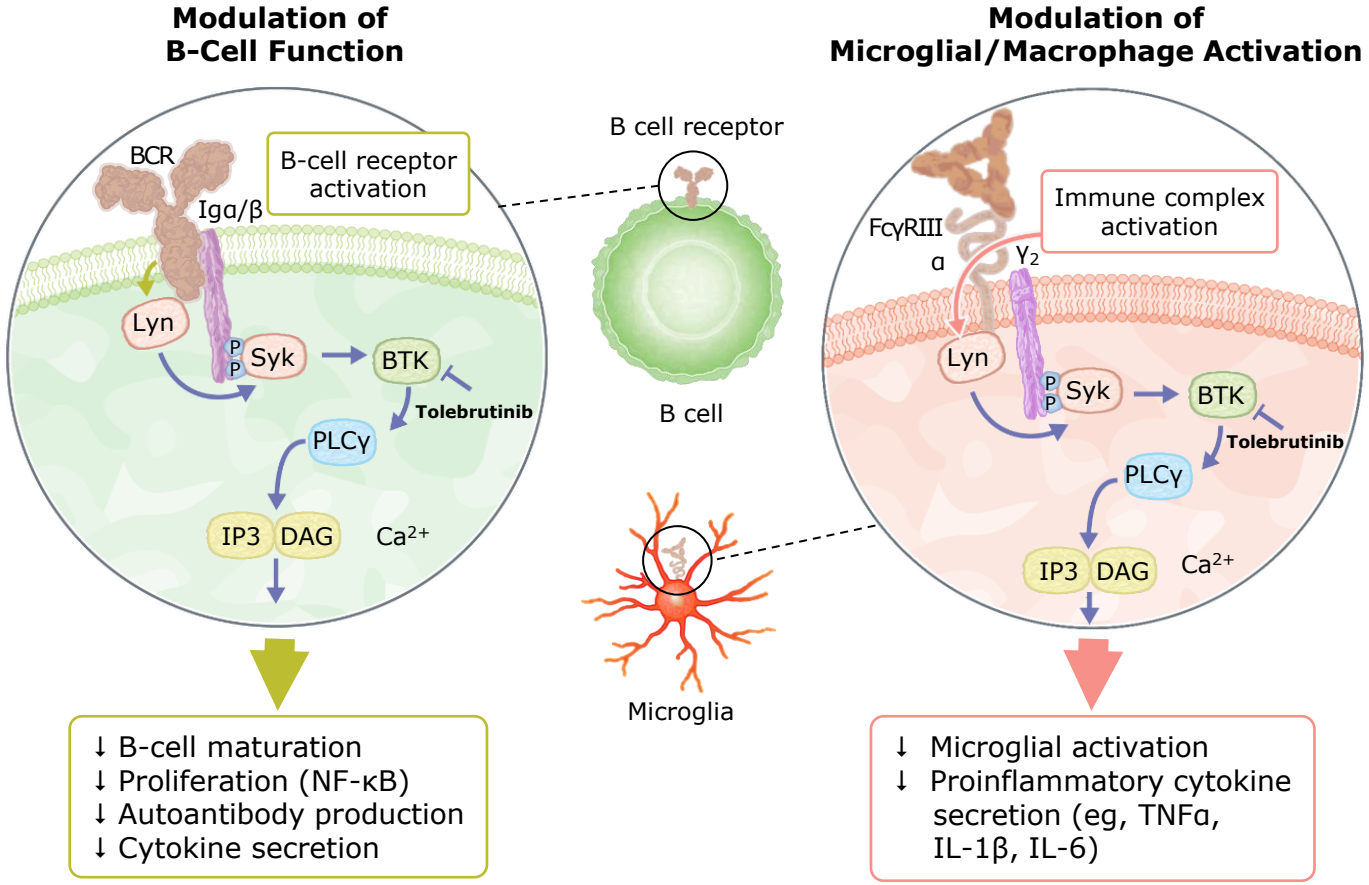
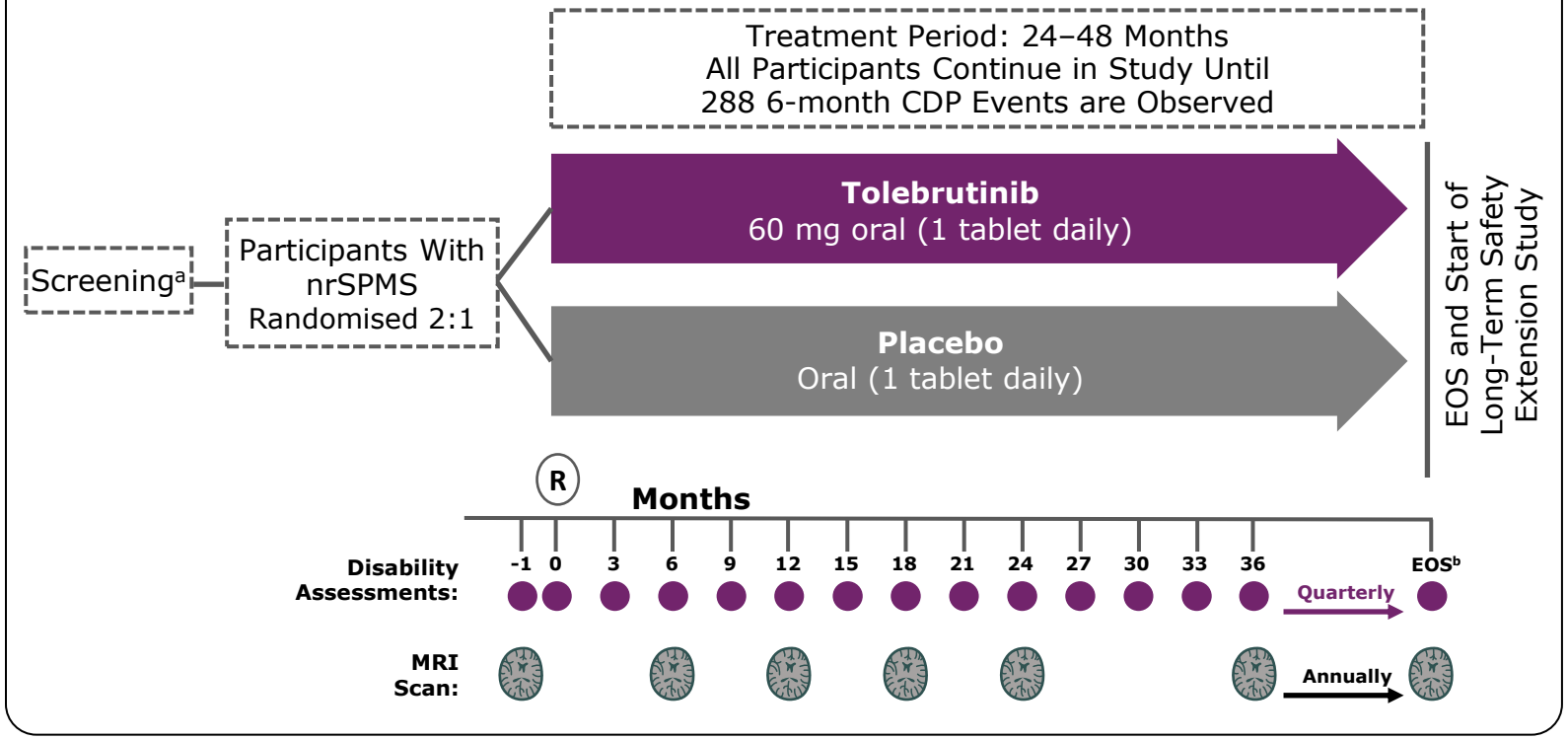


Figure adapted from Hendricks RW, et al. *Nature Chem Biol.* 2011;7:4-5. Tolebrutinib is investigational and has not been approved by the US Food and Drug Administration or any other regulatory agency worldwide. BCR=B cell receptor; DAG=diacylglycerol; FcγR=Fc gamma receptor; Ig=immunoglobulin; IL=interleukin;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

HERCULES: Study Design

Phase 3, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Event-Driven, Trial in Participants With nrSPMS



Key Eligibility Criteria

- Age 18–60 years
- Diagnosis of SPMS
- Absence of clinical relapses in the 24 months before screening
- Documented evidence of disability progression in the 12 months before screening
- EDSS score ≥3.0 and ≤6.5 at screening

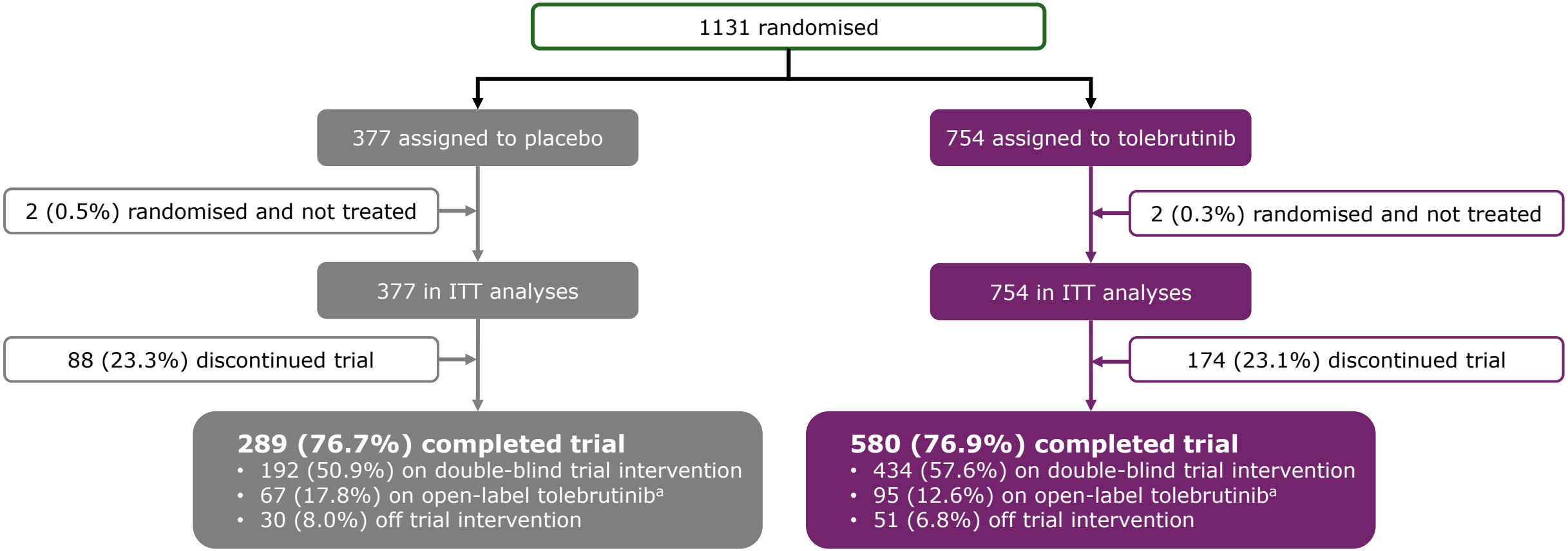
[a]The 28-day screening period was considered Month –1. [b]EOS safety follow-up visit occurred 4 weeks after the last dose of study treatment for participants not entering the long-term safety study.
CDP=confirmed disability progression; EDSS=Expanded Disability Status Scale; EOS=end of study; MRI=magnetic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

Main Endpoints

Trial Endpoints	
Primary endpoint	• Time to onset of 6-month CDP
Secondary endpoints include:[a]	• Time to onset of 3-month CDP • Time to onset of 6-month CDI • Total number of new or enlarging T2 lesions • % change in brain volume
Safety and tolerability	• Adverse events

[a]Secondary endpoints also include time to onset of sustained 20% increase in 9-hole peg test and time to onset of sustained 20% increase in Timed 25-Foot Walk, which are currently being analysed.
CDI=confirmed disability improvement; CDP=confirmed disability progression.

Participant Disposition



[a]Participants who experienced 6-month CDP were offered rescue treatment with open-label tolebrutinib.
CDP=confirmed disability progression; ITT=intent to treat.

Baseline Characteristics

Characteristic	Placebo (N=377)	Tolebrutinib (N=754)
Age, years	48.9 (8.0)	48.9 (8.0)
Female, n (%)	242 (64.2)	454 (60.2)
EDSS score[a]		
Mean (SD)	5.59 (0.94)	5.49 (0.99)
Median (IQR)	6.0 (5.0–6.3)	6.0 (4.8–6.3)
Time since relapsing remitting MS symptom onset, years	17.6 (8.4)	17.1 (8.3)
Time since most recent relapse, years	7.6 (5.5)	7.4 (5.3)
Participants with ≥1 Gd-enhancing T1 lesions, n (%)	49 (13.1)	93 (12.5)
Number of T2 lesions, median (IQR)	49 (33–75)	50 (35–73)
T2 lesion volume, cm^3, median (IQR)	14.9 (7.5–28.3)	15.3 (7.2–25.8)
Participants with ≥1 prior DMTs, n (%)	288 (76.4)	549 (72.8)

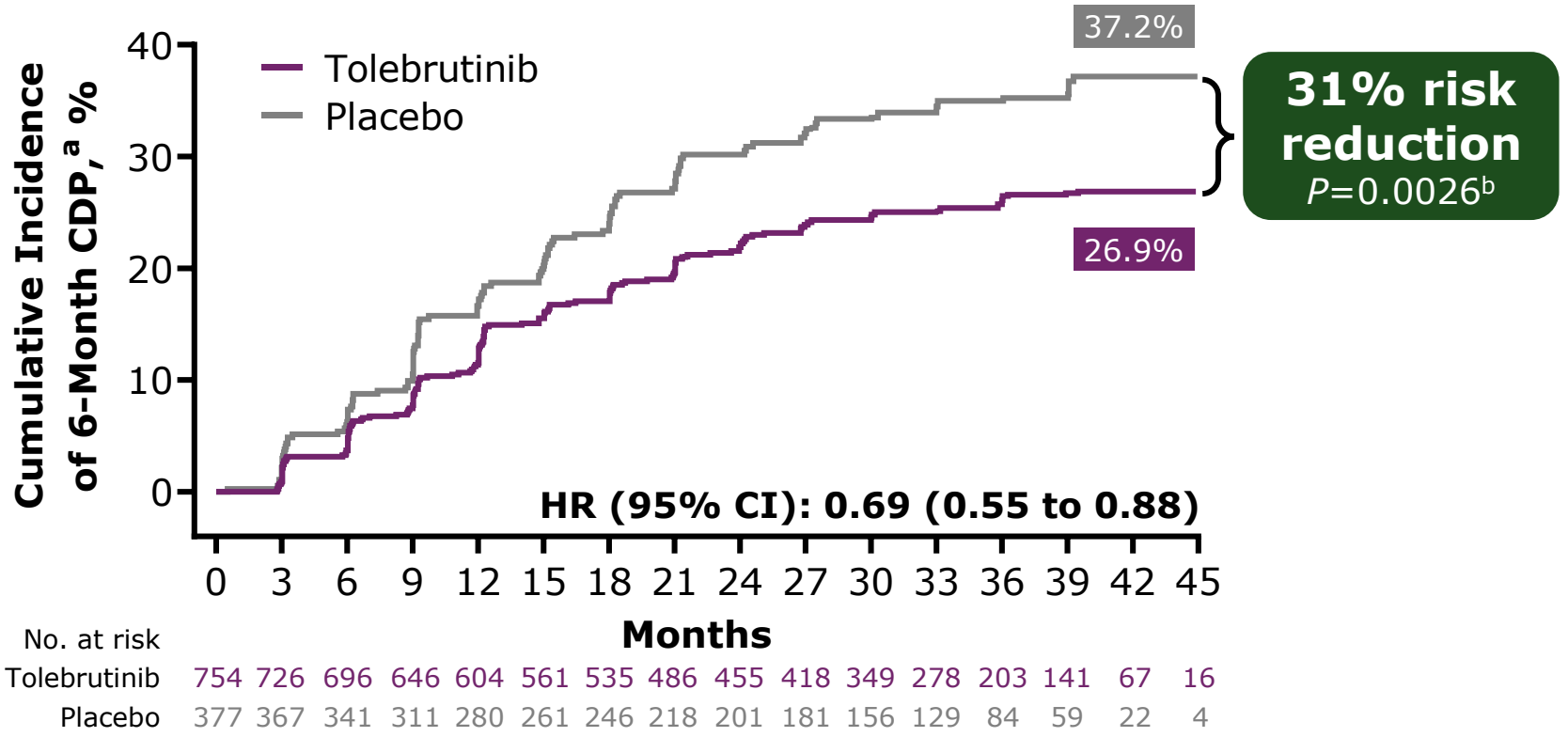
~50% of participants were ≤50 years

40% of participants had EDSS ≤5.5

- Baseline characteristics were well-balanced across both treatment arms

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

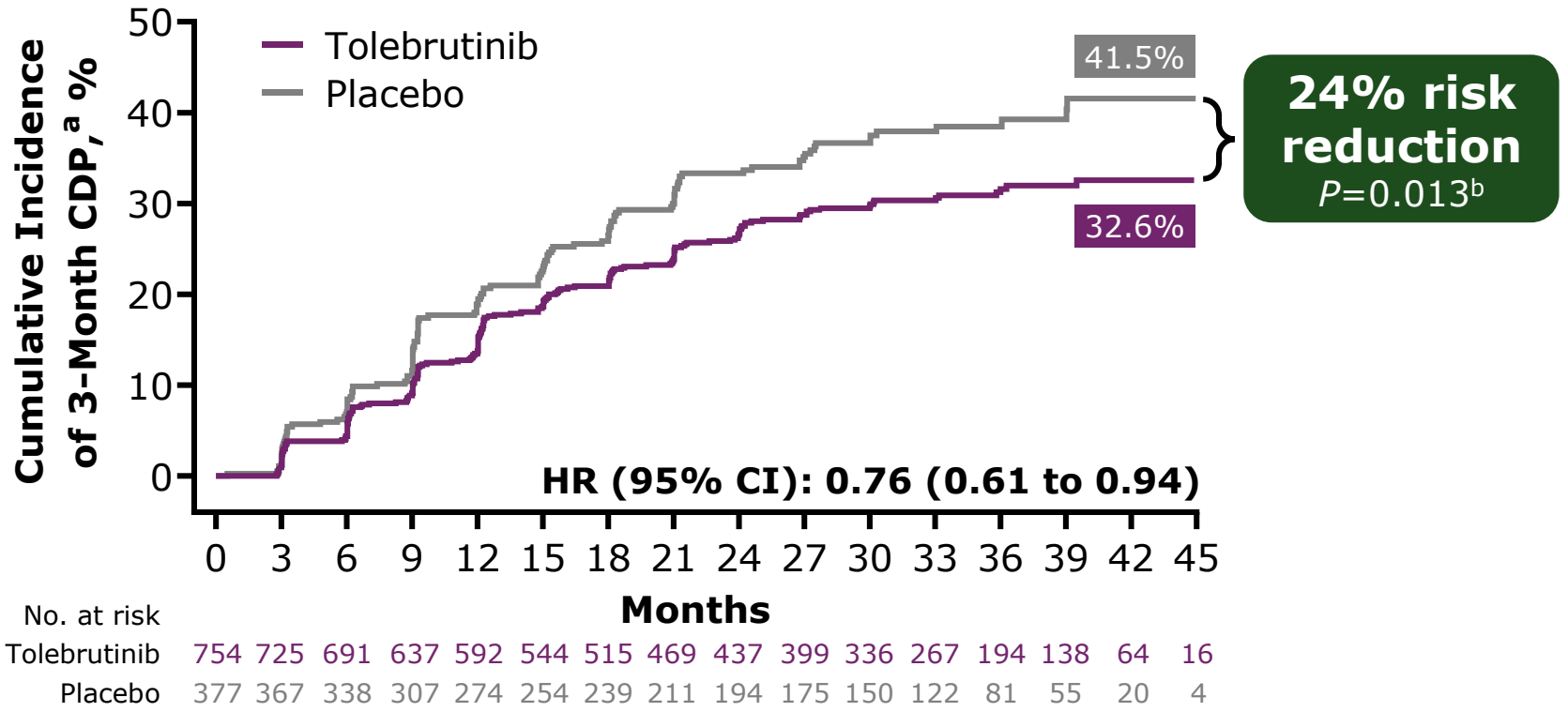
Primary Endpoint: Time to 6-Month CDP



- Tolebrutinib demonstrated a significant effect on disability accumulation in a non-relapsing SPMS population

[a]6-month CDP is defined as an increase of ≥1.0 point from baseline EDSS score when baseline score is ≤5.0 or an increase of ≥0.5 points when baseline score is >5.0, confirmed over ≥6 months. [b]P-value is from Cox proportional hazards model.
CDP=confirmed disability progression; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

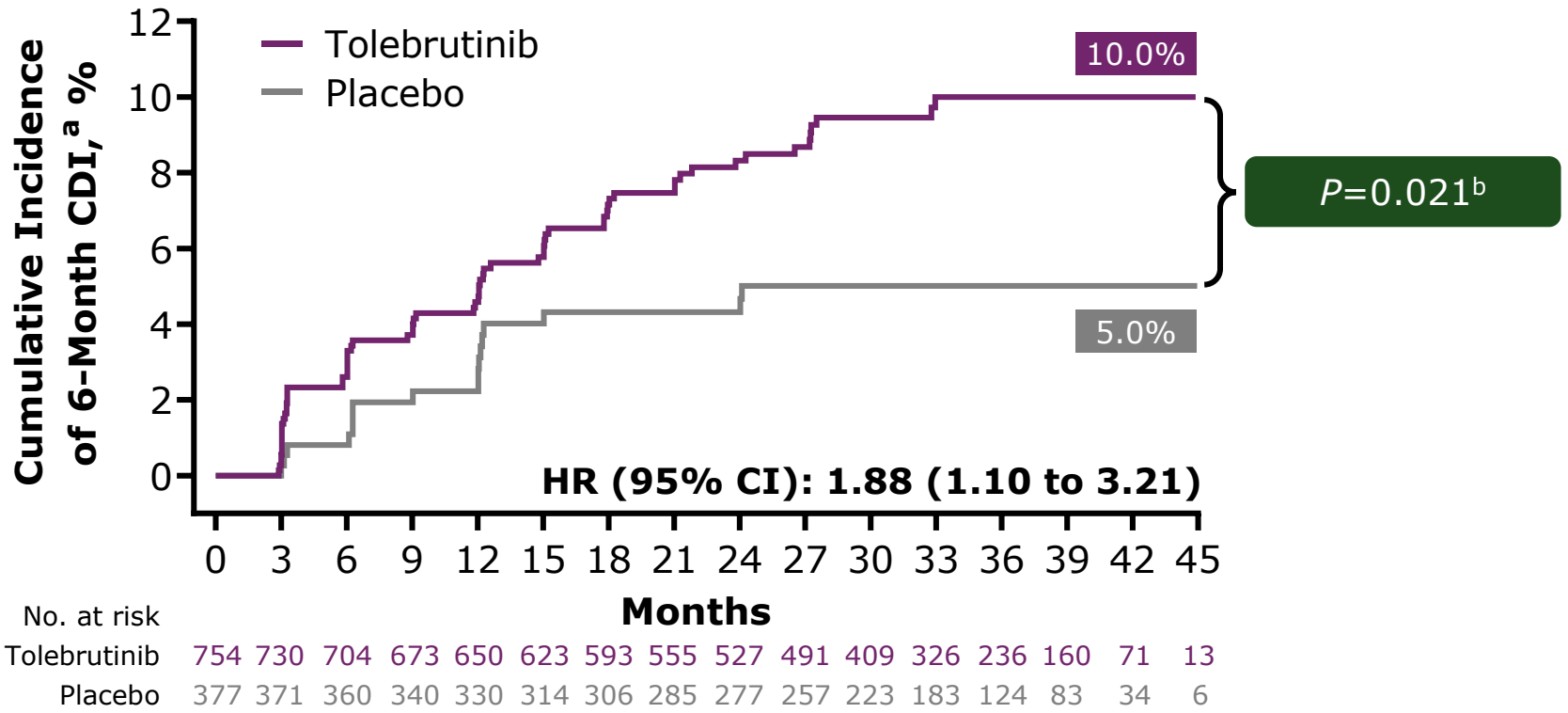
Secondary Endpoint: Time to 3-Month CDP



- Tolebrutinib demonstrated a significant effect on time to 3-month CDP

[a]3-month CDP is defined as an increase of ≥1.0 point from baseline EDSS score when baseline score is ≤5.0 or an increase of ≥0.5 points when baseline score is >5.0, confirmed over ≥3 months. [b]P-value is from Cox proportional hazards model.
CDP=confirmed disability progression; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

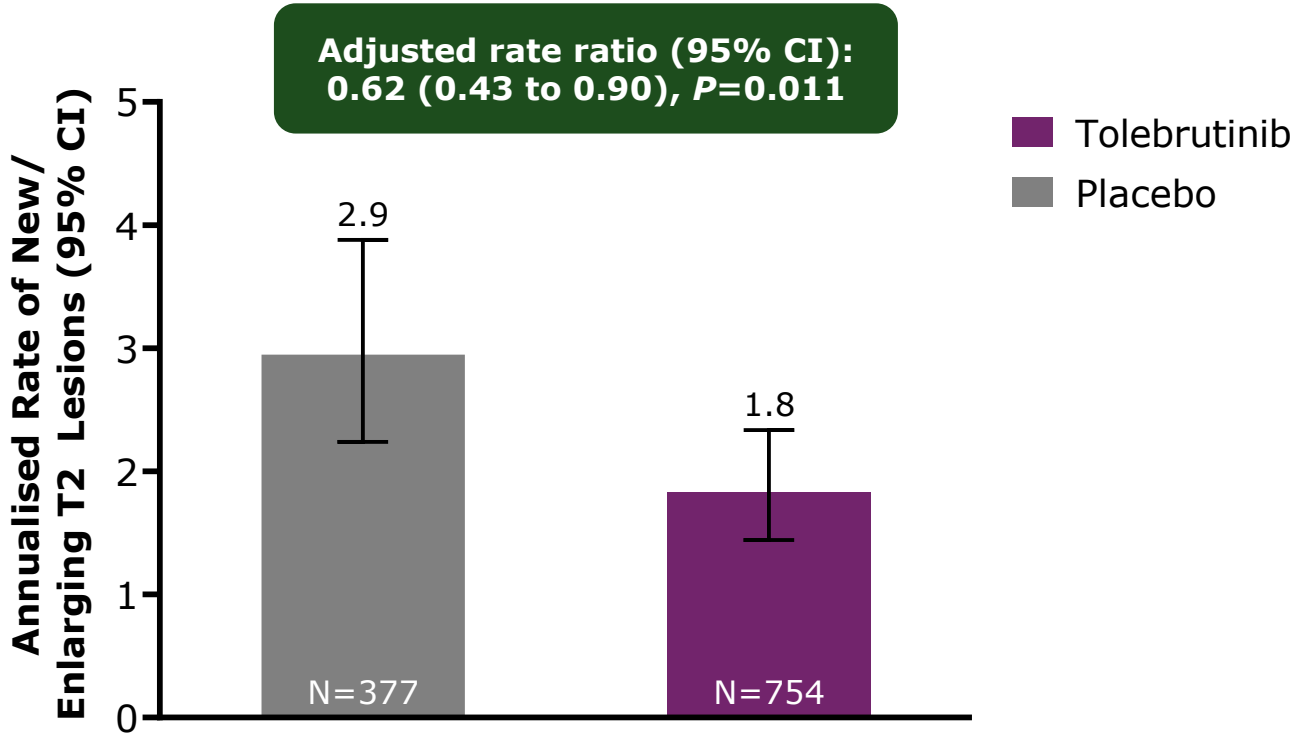
Secondary Endpoint: Time to 6-Month CDI



- Proportionally more participants experienced CDI on tolebrutinib vs. placebo

[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 from Cox proportional hazards model.
CDI=confirmed disability improvement; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

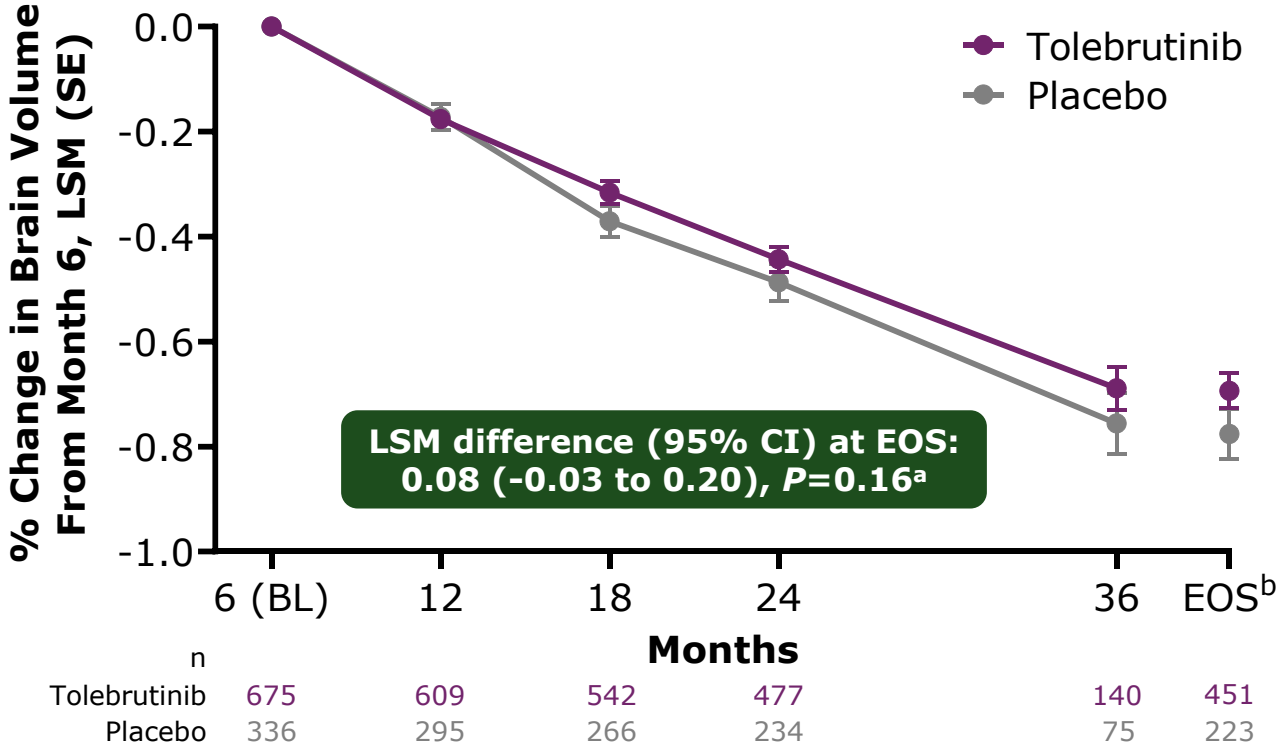
Secondary Endpoint: New/Enlarging T2 Lesions



- Tolebrutinib significantly lowered the annualised rate of new/enlarging T2 lesions vs. placebo

CI=confidence interval.

Secondary Endpoint: Brain Volume Loss (BVL)



- BVL from Month 6 to EOS was low for both tolebrutinib and placebo groups

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 27 months.
BL=baseline; EOS=end of study; LSM=least squares mean; SE=standard error.

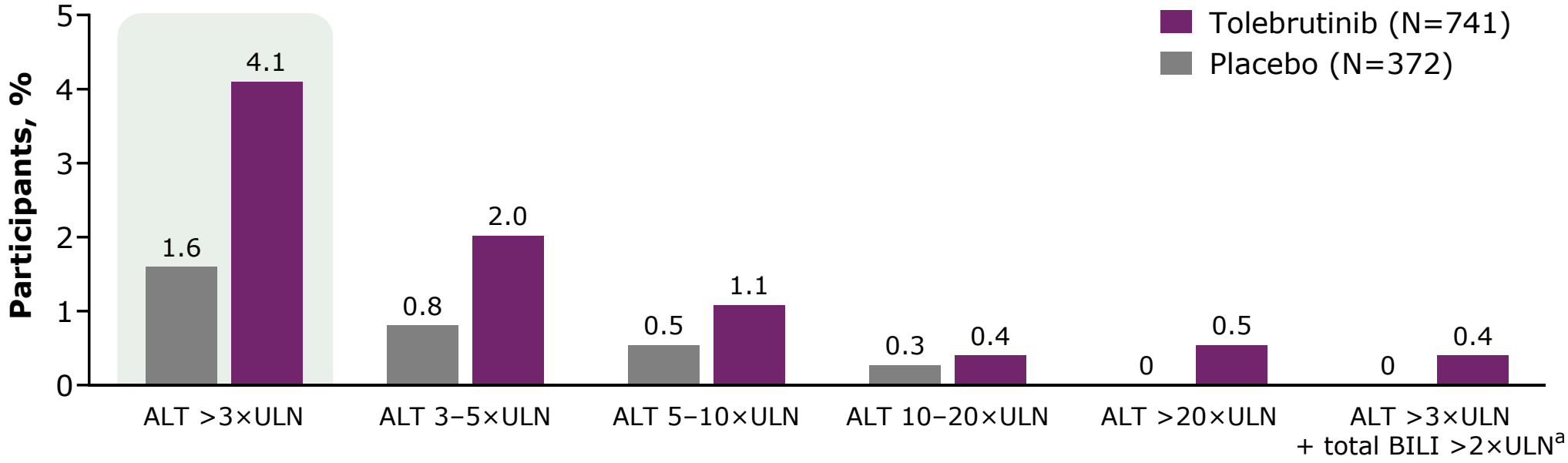
Adverse Events

Event, n (%)	Placebo (N=375)	Tolebrutinib (N=752)
Any TEAE	293 (78.1%)	613 (81.5%)
Any serious TEAE	39 (10.4%)	113 (15.0%)
Any TEAE leading to treatment discontinuation	11 (2.9%)	29 (3.9%)
Deaths[a]	1 (0.3%)	2 (0.3%)
Most common TEAEs (≥5% in the tolebrutinib arm)		
COVID-19 infection	85 (22.7%)	192 (25.5%)
Urinary tract infection	49 (13.1%)	85 (11.3%)
Fall	41 (10.9%)	72 (9.6%)
Nasopharyngitis	26 (6.9%)	70 (9.3%)
Headache	27 (7.2%)	54 (7.2%)
Arthralgia	19 (5.1%)	49 (6.5%)
Back pain	24 (6.4%)	47 (6.3%)
Influenza	13 (3.5%)	42 (5.6%)
Hypertension	11 (2.9%)	38 (5.1%)

- Based on preliminary analysis, there was a slight increase in the tolebrutinib arm in some adverse events, including respiratory infections, compared to placebo

[a]In the placebo arm, 1 participant died from cerebral oedema and haemorrhage due to a fall (assessed as unrelated to the placebo intervention by the investigator). In the tolebrutinib arm, 1 participant died due to post-operative complications of a liver transplant (assessed as related to tolebrutinib) and 1 participant completed assisted suicide (assessed as unrelated to tolebrutinib).
TEAE=treatment-emergent adverse event.

Liver Safety



- 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 and most resolving without sequelae

[a]One participant on tolebrutinib received a liver transplant and died due to post-operative complications. This case occurred prior to the implementation of a revised protocol with more stringent monitoring.
ALT=alanine aminotransferase; BILI=bilirubin; ULN=upper limit of normal.

Conclusions

- Tolebrutinib showed a 31% risk reduction in time to 6-month CDP vs. placebo (*P*=0.0026)
- Tolebrutinib increased the probability of achieving 6-month CDI vs. placebo
- Tolebrutinib significantly lowered the annualised rate of new/enlarging T2 lesions vs. placebo
- Liver enzyme elevations (>3x ULN) were observed in 4.1% of tolebrutinib participants, a signal reported with other BTK inhibitors in MS
  - The vast majority of cases resolved without sequelae
  - Frequent liver monitoring in the first 90 days has been implemented

HERCULES is the first trial to show a significant slowing of disability progression in people with nrSPMS – a population with a large unmet need

The totality of data from HERCULES and GEMINI indicate that tolebrutinib has a consistent impact on disability accumulation that may be largely driven by effects on smoldering neuroinflammation

BTK=Bruton's tyrosine kinase; CDI=confirmed disability improvement; CDP=confirmed disability progression; nrSPMS=non-relapsing secondary progressive MS; ULN=upper limit of normal.