Safety and Clinical Efficacy Outcomes From the Long-Term Extension Study of Tolebrutinib in Participants With Relapsing Multiple Sclerosis: 3-Year Results

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INTRODUCTION

- Tolebrutinib is an oral, central nervous system bioactive Bruton's tyrosine kinase (BTK) inhibitor that targets B cells and disease-associated microglia, and has the potential to mitigate the pathologic processes in MS leading to disability accumulation[1-3]
- In a Phase 2b trial (NCT03889639) of participants with relapsing MS, tolebrutinib 60 mg/day was well tolerated and reduced new gadolinium (Gd)-enhancing T1 lesions and new or enlarging T2 lesions by >85% versus placebo over 12 weeks[4]
- The 60 mg/day dose is being evaluated in four ongoing Phase 3 trials for relapsing forms of MS (NCT04410978, NCT04410991), non-relapsing secondary progressive MS (NCT04411641) and primary progressive MS (NCT04458051)
- LTS16004 (NCT03996291) is an ongoing long-term safety (LTS) extension study of tolebrutinib in participants who completed the Phase 2b trial

OBJECTIVE/AIM

- To report safety and efficacy data at Week 144 in the LTS extension of the Phase 2b tolebrutinib trial in participants with relapsing MS

Primary endpoint	Secondary endpoints
• Safety (includes treatment-emergent adverse event [TEAE] incidence)	• Annualised relapse rate (ARR) and relapse frequency on tolebrutinib 60 mg[a] • Mean Expanded Disability Status Scale (EDSS) score

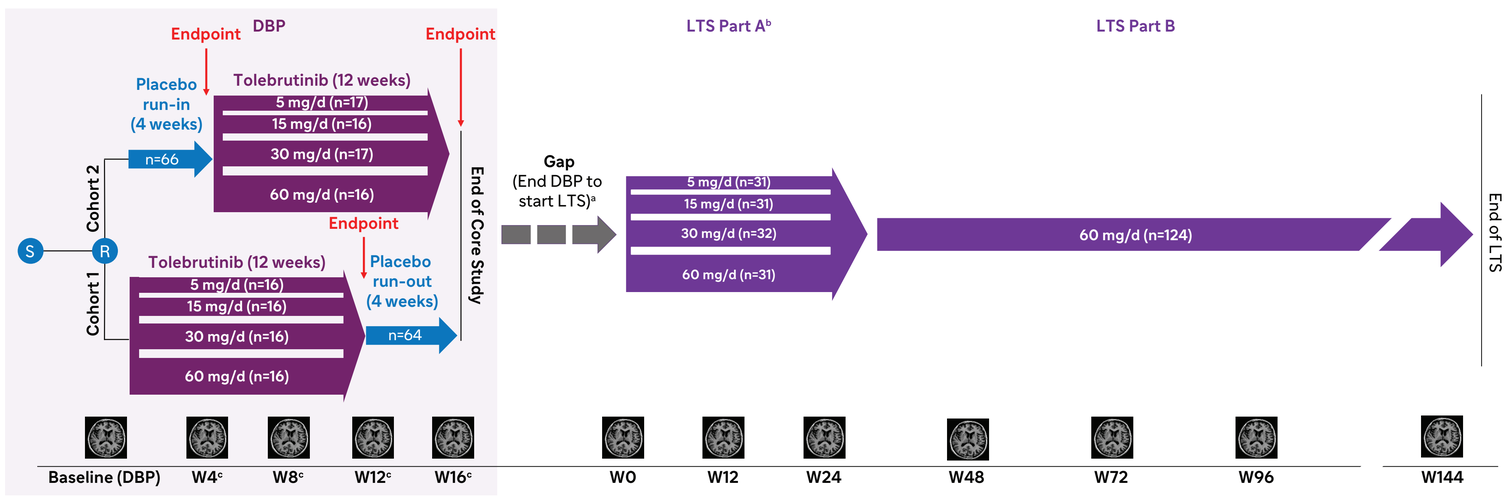
[a]ARR after ≥8 weeks of tolebrutinib 60 mg treatment in the LTS extension study (up to cut-off for analysis, 14 February 2023). For participants originally assigned to 5, 15 or 30 mg, only the participant years and relapses starting 8 weeks after the switch to Part B were included. For participants originally assigned to 60 mg, all data from the LTS extension study were included unless the sum of the Phase 2b trial placebo run-out period and any gap period to start of LTS Part A was >4 weeks, in which case only the participant years and relapses starting 8 weeks after re-initiation of treatment were included.

METHODS

In LTS Part A, participants who completed the Phase 2b trial double-blind period (DBP) continued on the originally assigned tolebrutinib dose (5, 15, 30 or 60 mg/day) from the core study in a double-blind manner until the Phase 3 trial dose selection (60 mg/day)

In open-label LTS Part B, all participants who completed LTS Part A were eligible to receive tolebrutinib 60 mg/day

Study design



[a]Gap period in the transition between last dose in the DBP and first dose in the LTS study was variable (mean ± SD, 7 ± 7.3 weeks; range, 0–21 weeks). [b]Duration of Part A of the LTS extension study was variable (mean ± SD, 27.4 ± 6.3 weeks; range, 15–47 weeks). [c]DBP MRI scans in this figure are labelled according to the week of the DBP.
D=Day; DBP=double-blind period; LTS=long-term safety; MRI=magnetic resonance imaging; R=randomisation; S=screening; SD=standard deviation; W=Week.

CONCLUSIONS

82% of participants with MS who enrolled in the tolebrutinib LTS extension study had ongoing treatment as of 14 February 2023

ARR in participants on 60 mg/day remained lower than baseline, and ~69% remained relapse-free

Safety data from the LTS extension study continue to show favourable tolerability

Ongoing follow-up in the LTS extension study, in addition to data from the Phase 3 trials, will continue to build on the safety and efficacy profile of tolebrutinib for people with MS

Through LTS Week 144, tolebrutinib 60 mg/day continues to demonstrate a favourable safety profile, with lower than baseline ARR and stable disability status

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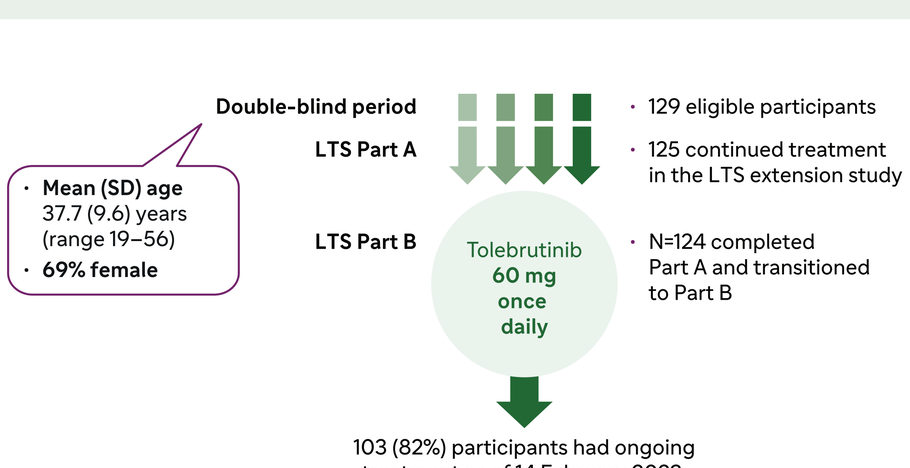
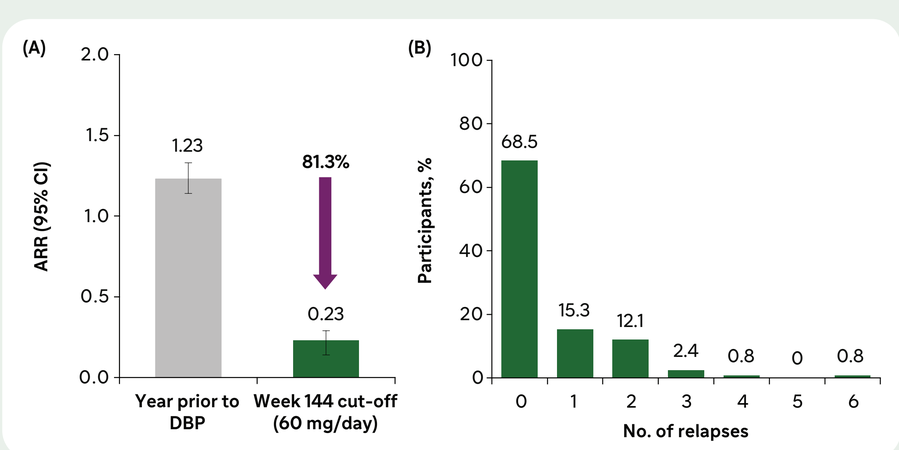
RESULTS

Participant disposition and baseline characteristics



LTS=long-term safety; SD=standard deviation.

ARR (A) and relapse frequency (B) up to the LTS extension study Week 144 cut-off[a]



- ARR for participants on tolebrutinib 60 mg was 0.23 (95% CI 0.17–0.32)
- 68.5% of participants remained relapse-free up to the LTS extension study Week 144 cut-off

[a]ARR after ≥8 weeks of tolebrutinib 60 mg treatment in the LTS extension study (up to cut-off for analysis, 14 February 2023). For participants originally assigned to 5, 15 or 30 mg, only the participant years and relapses starting 8 weeks after the switch to Part B are included. For participants originally assigned to 60 mg, all data from the LTS extension study are included unless the sum of the Phase 2b trial placebo run-out period and any gap period to start of LTS Part A was >4 weeks, in which case only the participant years and relapses starting 8 weeks after re-initiation of treatment are included.
ARR=annualised relapse rate; CI=confidence interval; DBP=double-blind period; LTS=long-term safety.

Mean EDSS score over time

DBP=double-blind period; EDSS=Expanded Disability Status Scale; LTS=long-term safety; SE=standard error; W=Week.

- Mean EDSS scores remained stable to LTS extension study Week 144

Most common TEAEs occurring in ≥5% of participants[a]

TEAE	Participants, n (%)
COVID-19[b]	43 (34)
Nasopharyngitis	20 (16)
Headache	17 (14)
Upper respiratory tract infection	14 (11)
Back pain	12 (10)
Arthralgia	9 (7)
Cystitis bacterial	9 (7)
Viral upper respiratory tract infection	9 (7)
Pharyngitis	8 (6)
Nausea	7 (6)
Increased ALT levels[c]	6 (5)[d]
Pain in extremity	6 (5)
Pyrexia	6 (5)

[a]All participants (N=125). [b]All cases of COVID-19 were mild (n=28) or moderate (n=14)[e] and resolved; and participants remained in the study. Three of the moderate COVID-19 cases were considered serious. Tolebrutinib treatment was interrupted temporarily in 3 participants. Five participants had COVID-19 twice during the study period. [c]Increased ALT levels was defined as ≥3 times the upper limit of normal. [d]No case met Hy's law, 1 case led to treatment discontinuation and all cases resolved. [e]One participant had missing data. [f]AEs leading to treatment discontinuation were headache, transaminase elevation and trichorrhexis (all n=1).
AE=adverse event; ALT=alanine aminotransferase; LTS=long-term safety; TEAE=treatment-emergent AE.

- The most common TEAEs were COVID-19, nasopharyngitis, headache, upper respiratory tract infection and back pain
- LTS Part A: No dose effects for TEAEs or serious adverse events (AEs) were observed
- LTS Part B: No new safety signals observed for participants who switched to the 60 mg dose
- A total of 22 participants discontinued treatment due to: participant decision (5%; n=6), perceived lack of efficacy (4%; n=5), progressive disease (3%; n=4), AEs (2%; n=3)[f], emigration (2%; n=2), planned pregnancy (1%; n=1) and site closure (1%; n=1)

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