ORIGINAL ARTICLE

Tolebrutinib in Nonrelapsing Secondary Progressive Multiple Sclerosis

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ABSTRACT

BACKGROUND

Throughout the course of multiple sclerosis, gradually progressive neurologic impairment can occur, which has been called disability accrual. Current disease-modifying therapies for multiple sclerosis have limited effects on disability accrual unrelated to relapses, which is thought to be partially caused by chronic, nonresolving neuroinflammation within the central nervous system. Tolebrutinib is an oral, brain-penetrant Bruton's tyrosine kinase inhibitor that targets myeloid cells (including microglia) and B cells in both the periphery and central nervous system. There are no approved treatments for nonrelapsing secondary progressive multiple sclerosis.

METHODS

In a phase 3, double-blind, placebo-controlled, event-driven trial, we randomly assigned participants with nonrelapsing secondary progressive multiple sclerosis, in a 2:1 ratio, to receive tolebrutinib (60 mg once daily) or matching placebo. The primary end point was confirmed disability progression that was sustained for at least 6 months, assessed in a time-to-event analysis.

RESULTS

A total of 1131 participants underwent randomization: 754 were assigned to receive tolebrutinib and 377 to receive placebo. The median follow-up was 133 weeks. A smaller percentage of participants in the tolebrutinib group than in the placebo group had confirmed disability progression sustained for at least 6 months (22.6% vs. 30.7%; hazard ratio, 0.69; 95% confidence interval, 0.55 to 0.88; P=0.003). Serious adverse events occurred in 15.0% of the participants in the tolebrutinib group and in 10.4% of those in the placebo group. A total of 4.0% of the participants in the tolebrutinib group and 1.6% of those in the placebo group had increases in alanine aminotransferase levels to more than 3 times the upper limit of the normal range.

CONCLUSIONS

In participants with nonrelapsing secondary progressive multiple sclerosis, the risk of disability progression was lower among those who received treatment with tolebrutinib than among those who received placebo. (Funded by Sanofi; HERCULES ClinicalTrials.gov number, NCT04411641.)

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*A full list of the HERCULES Trial Group members is provided in the Supplementary Appendix, available at NEJM.org.

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Current disease-modifying therapies for multiple sclerosis largely target lymphocyte activity in the periphery to effectively reduce the incidence of focal inflammation in the central nervous system (CNS), which is the pathophysiological basis of lesion formation detected on magnetic resonance imaging (MRI) and acute relapse.[1] Throughout the course of multiple sclerosis, gradually progressive neurologic impairment can occur, which has been called disability accrual. Current disease-modifying therapies have limited effects on disability accrual, especially progression that is independent of relapse activity, which is thought to be caused largely by chronic neuroinflammation within the CNS involving myeloid cells (including macrophages and CNS-resident microglia) and CNS-compartmentalized B cells.[2,3] Bruton's tyrosine kinase (BTK) is a key signaling element implicated in neuroinflammation that is expressed in microglial cells and CNS-resident and peripheral B lymphocytes and therefore participates in both innate and adaptive immunity.[4,5] In multiple sclerosis, myeloid cells and B cells interact to drive neuroinflammation and injury,[6,7] as evidenced by chronic active white-matter lesions in the brain[6,8,9] and leptomeningeal tertiary lymphoid structures.[8,10,11] Therefore, a BTK inhibitor that targets both myeloid cells and B cells in the periphery and CNS may have a greater effect on CNS neuroinflammation and neurodegeneration than existing therapies.

Tolebrutinib is an oral, brain-penetrant, and bioactive BTK inhibitor intended to target disease-associated microglia and B cells within the CNS in addition to their counterparts in the periphery.[4,12,13] With the sole exception of ocrelizumab, which is indicated for primary progressive disease,[14] currently approved disease-modifying therapies are limited to relapsing forms of multiple sclerosis, including active secondary progressive disease. No treatment has shown efficacy in slowing disability accrual in persons with secondary progressive multiple sclerosis without relapses. We conducted the phase 3 HERCULES trial to assess whether tolebrutinib affects disease progression that is independent of relapse activity in participants with nonrelapsing secondary progressive multiple sclerosis.

Methods

Trial Oversight

The trial was sponsored and designed by Sanofi in consultation with the trial steering committee. The sponsor managed the conduct of the trial, provided the trial agents as well as drug-safety management and medical monitoring, and performed the statistical analyses. Data were collected by trial-site investigators and analyzed under the supervision of the sponsor. Before the unblinding of the trial (August 26, 2024), the investigators, steering committee, sponsor, site personnel, and participants were unaware of the trial-group assignments and efficacy outcomes throughout the trial. An independent data monitoring committee reviewed safety data during the trial, including guidance from an independent hepatology assessment committee, and made nonbinding recommendations regarding the conduct of the trial and whether the trial should be stopped for futility. The authors had access to the data necessary to serve as authors and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). Confidentiality agreements were in place between the sponsor and the authors who were not employed by the sponsor. The manuscript was developed with medical writing assistance funded by the sponsor. All the authors agreed to submit the manuscript for publication. The sponsor could not delay or interdict the publication of the results.

The trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board or independent ethics committee at each trial site. All the participants provided written informed consent before starting trial-related procedures.

Participants

Eligible participants were 18 to 60 years of age and had a current diagnosis of secondary progressive multiple sclerosis according to the 2017 revised McDonald criteria, with no superimposed clinical relapses in the 24 months before screening.[15] At screening, the participants were required

to have documented evidence of disability progression in the previous 12 months and a score of 3.0 to 6.5 on the Expanded Disability Status Scale (EDSS; scores range from 0 to 10.0, with higher scores indicating greater disability[16]). Before randomization, an adjudication committee evaluated anonymized participant data to endorse the diagnosis of nonrelapsing secondary progressive multiple sclerosis and the presence of disability progression in the previous 12 months. Details regarding eligibility criteria are provided in the protocol and in the Supplementary Appendix (available at NEJM.org).

TRIAL DESIGN

This phase 3, event-driven, double-blind, randomized, placebo-controlled trial was designed to continue until approximately 288 disability-progression events had occurred across both trial groups. Participants were screened for eligibility at 264 sites in 31 countries (Table S1 in the Supplementary Appendix). Eligible participants were randomly assigned in a 2:1 ratio to receive 60 mg of oral tolebrutinib or a matching placebo tablet once daily with a meal (Fig. S1). Randomization was performed centrally with the use of an interactive Web-response system and was stratified according to age at screening (≤40 or >40 years) and geographic region (U.S. region or non-U.S. region).

Participants were required to discontinue therapies for multiple sclerosis before randomization, although short-term use (3 to 5 days) of glucocorticoids was permitted. Participants with confirmed disability progression sustained for at least 6 months were offered open-label treatment with tolebrutinib or could change to another disease-modifying therapy for multiple sclerosis, if available.

END POINTS

The primary end point was confirmed disability progression, defined as an increase from baseline in the EDSS score of 1.0 or more points (if the baseline score was ≤5.0) or 0.5 or more points (if the baseline score was >5.0), that was sustained for at least 6 months. Only confirmed disability-progression events with onset and confirmation more than 90 days after relapses were counted as events for the primary end point and were therefore considered to be independent of relapses (additional details are provided in the Supplementary Appendix).

The trial used six hierarchically ordered secondary end points: confirmed disability progression that was sustained for at least 3 months; the number of new or enlarging lesions on T2-weighted MRI per year; a 20% increase in the score on the nine-hole peg test[17] that was sustained for at least 3 months; a 20% increase in the score on the timed 25-foot walk[18] that was sustained for at least 3 months; confirmed lessening of disability (disability improvement, defined as a ≥1.0-point decrease from baseline in the EDSS score) that was sustained for at least 6 months; and the percentage change in brain volume from month 6 to the end-of-trial visit (Fig. S2). The annualized adjudicated relapse rate was a tertiary end point.

Adverse events were recorded at each visit. Vital signs and findings from 12-lead electrocardiography were assessed, and clinical laboratory tests (including hematologic and liver-function assessments) and pregnancy tests were conducted.

STATISTICAL ANALYSIS

We planned to screen approximately 1700 persons to ensure that up to 1290 participants underwent randomization. We estimated that 288 primary end-point events would provide the trial with more than 80% power (with a two-sided type I error rate of 0.05) to detect a 30% relative lower risk of disability progression with tolebrutinib than with placebo. The sample-size calculation was based on the assumption that 23.6% of the participants in the placebo group would have confirmed disability progression sustained for at least 6 months at 2 years (on the basis of previous data in a similar population[19]), the hazard rates (determined with the use of a log-rank test) would be constant, 10% of the participants would prematurely discontinue the trial each year, and the estimated enrollment period would be approximately 24 months, with the last participant being followed for 24 months.

The efficacy analyses were performed according to the intention-to-treat principle and included all the participants who had undergone randomization, including those who had discontinued the trial prematurely. The time to onset of confirmed disability progression sustained for at

least 6 months was analyzed with the use of a Cox proportional-hazards model that included terms for trial group, age at screening (≤40 or >40 years), and geographic region (U.S. region or non-U.S. region). Data were censored at the date of the last EDSS assessment for participants who completed the trial without initial disability progression or discontinued before confirmed disability progression that was sustained for at least 6 months had occurred. Confirmed disability-progression event status was imputed for participants who completed the trial, met the criteria for confirmed disability progression sustained for at least 3 months, and continued to meet the criteria for disability progression according to the EDSS score through the final trial assessment but did not reach the 6-month confirmation visit. Because in this context the partial missing data can reasonably be assumed to be missing at random, this approach leverages the partial information and adheres to the intention-to-treat principle. The methods used for the analyses of the secondary end points are described in the Supplementary Appendix.

The overall type I error rate was controlled at a two-sided alpha level of 0.05 for the key secondary end points with the use of a prespecified, sequential, hierarchical testing procedure. If significance for the primary end point was shown, each hierarchically ordered secondary end point would be tested in the order described above when each preceding end point was significant. A nonbinding interim futility analysis was performed by the independent statistical group and reviewed by the data monitoring committee on July 5, 2023. No alpha was spent on the futility analysis because it did not increase the risk of a type I error. For the primary end point, missing data for 6-month confirmation of disability progression owing to the end of the trial were imputed for the participants who had confirmed disability progression sustained for at least 3 months and continued to meet the criteria for disability progression through the final trial assessment. All other efficacy analyses were based on observed data without imputation. The widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer treatment effects.

The safety analyses included all the participants who had undergone randomization and received at least one dose of tolebrutinib or placebo and included all the data acquired from the time of the first dose to 10 days after the last dose, the date of death, or the last date of contact, whichever occurred first. Safety data were summarized with the use of descriptive statistics (see the Supplementary Appendix).

RESULTS

PARTICIPANTS

Of the 1438 persons who were screened, 1131 underwent randomization between October 23, 2020, and January 12, 2023: 754 participants were assigned to receive tolebrutinib and 377 to receive placebo. A total of 76.9% of the participants in the tolebrutinib group and 76.7% of those in the placebo group completed the trial (Fig. S3). The primary reason for early trial discontinuation in both groups was participant decision (18.7% of the participants in the tolebrutinib group and 19.4% of those in the placebo group). The median overall follow-up was 133 weeks — 133.1 weeks (interquartile range, 108.3 to 156.4) in the tolebrutinib group and 133.6 weeks (interquartile range, 108.4 to 156.9) in the placebo group.

The demographic and disease characteristics were similar in the two groups. The mean (±SD) time since the diagnosis of secondary progressive multiple sclerosis was 7.9±7.3 years in the tolebrutinib group and 8.4±7.8 years in the placebo group, and the time since the most recent clinical relapse was 7.4±5.3 years in the tolebrutinib group and 7.6±5.5 years in the placebo group (Table 1). During the trial, the adjusted annualized adjudicated relapse rate was 0.033 (95% confidence interval [CI], 0.024 to 0.045) in the tolebrutinib group and 0.032 (95% CI, 0.021 to 0.049) in the placebo group. Most of the participants (74.0%) had previously received one or more disease-modifying therapies, and 12.7% had gadolinium-enhancing lesions on T1-weighted MRI at baseline. Details regarding the representativeness of the trial population relative to the general population of persons with secondary progressive multiple sclerosis are provided in Table S2.

EFFICACY

Primary End Point

The percentage of participants with confirmed disability progression sustained for at least 6 months

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Tolebrutinib (N=754)	Placebo (N=377)
Age — yr	48.9±8.0	48.9±8.0
Female sex — no. (%)	454 (60.2)	242 (64.2)
Race — no. (%)†		
White	703 (93.2)	348 (92.3)
Black	6 (0.8)	4 (1.1)
Asian	36 (4.8)	19 (5.0)
Other, unknown, or not reported	9 (1.2)	6 (1.6)
EDSS score‡	5.5±1.0	5.6±0.9
Time since onset of symptoms of relapsing–remitting multiple sclerosis — yr	17.1±8.3	17.6±8.4
Time since diagnosis of secondary progressive multiple sclerosis — yr	7.9±7.3	8.4±7.8
Time since most recent clinical relapse — yr§	7.4±5.3	7.6±5.5
No. of previous disease-modifying therapies received — no. (%)		
0	205 (27.2)	89 (23.6)
1	200 (26.5)	102 (27.1)
≥2	349 (46.3)	186 (49.3)
Previous disease-modifying therapies received — no. (%)¶		
Interferons‖	354 (46.9)	177 (46.9)
Glatiramer acetate	176 (23.3)	99 (26.3)
Fingolimod	113 (15.0)	66 (17.5)
Dimethyl fumarate	93 (12.3)	61 (16.2)
Ocrelizumab	89 (11.8)	48 (12.7)
Teriflunomide	82 (10.9)	49 (13.0)
Natalizumab	72 (9.5)	42 (11.1)
Rituximab	47 (6.2)	23 (6.1)
Other	115 (15.3)	66 (17.5)
≥1 Gadolinium-enhancing lesion on T1-weighted MRI — no./total no. (%)	93/742 (12.5)	49/373 (13.1)
No. of gadolinium-enhancing lesions on T1-weighted MRI**	0.4±2.0	0.6±3.5
Median volume of lesions on T2-weighted MRI (IQR) — cm^3††	15.3 (7.2–25.8)	14.9 (7.6–28.3)

* Plus–minus values are means ±SD. The intention-to-treat population included all the participants who had undergone randomization, including those who had discontinued the trial prematurely. IQR denotes interquartile range, and MRI magnetic resonance imaging.
† Race was reported by the participants.
‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10.0, with higher scores indicating greater disability. The values are the average of the scores at the time of screening and the time of randomization.
§ Data were missing for 2 participants in the tolebrutinib group.
¶ A participant could be counted in more than one category. Disease-modifying therapies used by less than 5% of the participants in either group are not shown. A washout period was required for participants who received certain previous disease-modifying therapies (Table S3).
‖ Interferon therapies included interferon beta-1a, interferon beta-1b, and peginterferon beta-1a.
** Data were missing for 12 participants in the tolebrutinib group and 4 participants in the placebo group.
†† Data were missing for 7 participants in the tolebrutinib group.

Table 2. Primary and Secondary End Points (Intention-to-Treat Population).*

End Point	Tolebrutinib (N=754)	Placebo (N=377)
Primary end point		
Confirmed disability progression sustained for ≥6 mo†		
No. of events/no. of participants evaluated (%)‡	171/754 (22.6)	116/377 (30.7)
Kaplan–Meier estimate at 24 mo — % (95% CI)	21.9 (18.8 to 25.1)	30.2 (25.3 to 35.1)
Hazard ratio (95% CI)	0.69 (0.55 to 0.88)	
P value	0.003	
Secondary end points§		
Confirmed disability progression sustained for ≥3 mo†		
No. of events/no. of participants evaluated (%)	208/754 (27.6)	129/377 (34.2)
Kaplan–Meier estimate at 24 mo — % (95% CI)	26.7 (23.5 to 30.2)	33.3 (28.5 to 38.7)
Hazard ratio (95% CI)	0.76 (0.61 to 0.94)	
P value	0.01	
Annualized rate of new or enlarging lesions on T2-weighted MRI		
No. of participants evaluated	719	361
Mean estimate (95% CI)	1.84 (1.44 to 2.34)	2.95 (2.24 to 3.88)
Relative rate (95% CI)	0.62 (0.43 to 0.90)	
P value	0.01	
20% Increase in the score on the nine-hole peg test sustained for ≥3 mo		
No. of events/no. of participants evaluated (%)	143/754 (19.0)	74/377 (19.6)
Kaplan–Meier estimate at 24 mo — % (95% CI)	17.1 (14.5 to 20.2)	16.4 (12.9 to 20.8)
Hazard ratio (95% CI)	0.97 (0.74 to 1.29)	
P value	0.84¶	
20% Increase in the score on the timed 25-ft walk sustained for ≥3 mo		
No. of events/no. of participants evaluated (%)	310/754 (41.1)	187/377 (49.6)
Kaplan–Meier estimate at 24 mo — % (95% CI)	36.9 (33.4 to 40.7)	46.9 (41.7 to 52.4)
Hazard ratio (95% CI)	0.77 (0.64 to 0.92)	
Confirmed disability improvement sustained for 6 mo‖		
No. of events/no. of participants evaluated (%)	65/754 (8.6)	17/377 (4.5)
Kaplan–Meier estimate at 24 mo — % (95% CI)	8.3 (6.5 to 10.7)	4.3 (2.6 to 7.1)
Hazard ratio (95% CI)	1.88 (1.10 to 3.21)	
Percentage change in brain volume from mo 6 to end-of-trial visit		
No. of participants evaluated	451	223
Least-squares mean change (±SE)	–0.69±0.03	–0.78±0.05
Least-squares mean difference, tolebrutinib vs. placebo (95% CI)	0.08 (–0.03 to 0.20)	

* A total of 26 participants in the tolebrutinib group and 13 participants in the placebo group had missing baseline data for the nine-hole peg test and the timed 25-foot walk; 12 participants in the tolebrutinib group and 4 participants in the placebo group had missing baseline data for the presence of gadolinium-enhancing lesions at baseline, which was a covariate used in the Cox proportional-hazards models for the analyses of the primary end point and disability-related secondary end points; 7 participants in the tolebrutinib group had missing baseline data for the number of lesions on T2-weighted MRI, which was a covariate in the negative binomial regression model for the annualized rate of new or enlarging lesions on T2-weighted MRI; 79 participants in the tolebrutinib group and 41 participants in the placebo group had missing data for brain volume at month 6, which was a covariate in the mixed-effect model with repeated measures for the percentage change in brain volume from month 6 to the end-of-trial visit.

† Confirmed disability progression was defined as an increase from baseline in the EDSS score of at least 1.0 point if the baseline score was 5.0 or less, or an increase from baseline of at least 0.5 points if the baseline score was greater than 5.0.

‡ The percentages were calculated on the basis of the number of events after multiple imputations.

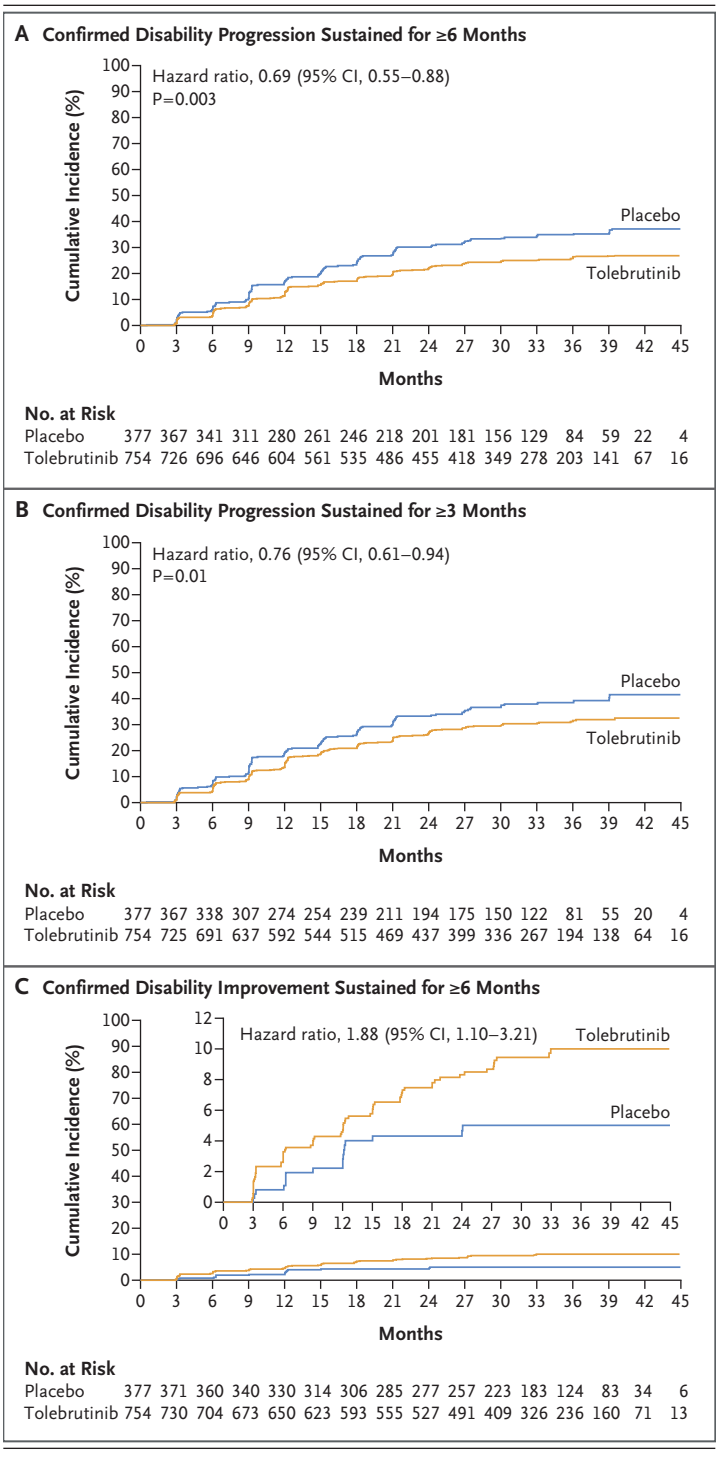
§ The secondary end points are ordered hierarchically. The widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer treatment effects.

¶ Because this P value is greater than 0.05, the results for all hierarchically lower secondary end points are reported as point estimates with 95% confidence intervals only.

‖ Confirmed lessening of disability (disability improvement) was defined as a decrease in the EDSS score of at least 1.0 point from baseline.

Figure 1. Primary and Key Secondary End Points (Intention-to-Treat Population).

The intention-to-treat population included all the participants who had undergone randomization, including those who had discontinued the trial prematurely. The primary end point was confirmed disability progression that was sustained for at least 6 months (Panel A). Confirmed disability progression that was sustained for at least 3 months (Panel B) and confirmed lessening of disability (disability improvement) that was sustained for at least 6 months (Panel C) were key secondary end points. The inset in Panel C shows the same data on an enlarged y axis.



during the trial was 22.6% in the tolebrutinib group and 30.7% in the placebo group (hazard ratio, 0.69; 95% CI, 0.55 to 0.88; P=0.003) (Table 2 and Fig. 1A). The corresponding Kaplan–Meier estimates at 24 months were 21.9% in the tolebrutinib group and 30.2% in the placebo group.

Disability-Related Secondary End Points

The percentage of participants with confirmed disability progression sustained for at least 3 months during the trial was 27.6% in the tolebrutinib group and 34.2% in the placebo group (hazard ratio, 0.76; 95% CI, 0.61 to 0.94; P=0.01) (Table 2 and Fig. 1B). The percentage of participants with a 20% increase in the score on the nine-hole peg test that was sustained for at least 3 months was 19.0% in the tolebrutinib group and 19.6% in the placebo group (hazard ratio, 0.97; 95% CI, 0.74 to 1.29; P=0.84) (Table 2 and Fig. S4); because this result was not significant, the results for all hierarchically lower secondary end points are reported as point estimates with 95% confidence intervals only. The percentage of participants with a 20% increase in the score on the timed 25-foot walk that was sustained for at least 3 months was 41.1% in the tolebrutinib group and 49.6% in the placebo group (hazard ratio, 0.77; 95% CI, 0.64 to 0.92) (Table 2 and Fig. S5). The percentage of participants with confirmed disability improvement sustained for at least 6 months was 8.6% in the tolebrutinib group and 4.5% in the placebo group (hazard ratio, 1.88; 95% CI, 1.10 to 3.21) (Table 2 and Fig. 1C).

MRI-Related Secondary End Points

The mean annualized rate of new or enlarging lesions on T2-weighted MRI was 1.84 in the tolebrutinib group and 2.95 in the placebo group (relative rate, 0.62; 95% CI, 0.43 to 0.90; P=0.01) (Table 2). The least-squares mean percentage change in brain volume at the end-of-trial visit as compared with month 6 was −0.69 in the

Table 3. Adverse Events and ALT Levels (Safety Population).*

Event	Tolebrutinib (N=752)	Placebo (N=375)
	no./total no. (%)	
Any adverse event	613/752 (81.5)	293/375 (78.1)
Adverse events occurring in ≥10% of participants in either group		
Covid-19	192/752 (25.5)	85/375 (22.7)
Urinary tract infection	85/752 (11.3)	49/375 (13.1)
Fall	72/752 (9.6)	41/375 (10.9)
Adverse event leading to discontinuation of tolebrutinib or placebo	29/752 (3.9)	11/375 (2.9)
Any serious adverse event	113/752 (15.0)	39/375 (10.4)
Serious infection	39/752 (5.2)	13/375 (3.5)
Death†	2/752 (0.3)	1/375 (0.3)
Increase in ALT level to >3× ULN	30/741 (4.0)	6/372 (1.6)
>3–5× ULN	15/741 (2.0)	3/372 (0.8)
>5–10× ULN	8/741 (1.1)	2/372 (0.5)
>10–20× ULN	3/741 (0.4)	1/372 (0.3)
>20× ULN	4/741 (0.5)	0
ALT level >3× ULN and total bilirubin level >2× ULN‡	3/752 (0.4)	0

* The safety population included all the participants who received at least one dose of tolebrutinib or placebo. ALT denotes alanine aminotransferase, Covid-19 coronavirus disease 2019, and ULN upper limit of the normal range.
† The deaths that occurred in the tolebrutinib group were due to postoperative complications after a liver transplantation (assessed as being related to tolebrutinib) and physician-assisted suicide (assessed as being unrelated to tolebrutinib). The death in the placebo group was due to cerebral edema and hemorrhage from a fall.
‡ In one participant, the ALT level of more than 3 times the ULN and total bilirubin level of more than 2 times the ULN occurred as a result of herpes simplex virus infection.

tolebrutinib group and −0.78 in the placebo group (least-squares mean difference, 0.08; 95% CI, −0.03 to 0.20) (Table 2 and Fig. S6).

SAFETY

Adverse Events

During the double-blind treatment period, adverse events were reported in 613 of 752 participants (81.5%) who received tolebrutinib and in 293 of 375 participants (78.1%) who received placebo (Table 3). Adverse events that were reported in at least 10% of the participants who received tolebrutinib were coronavirus disease 2019 (Covid-19) and urinary tract infections; adverse events that were reported in at least 10% of the participants who received placebo were Covid-19, urinary tract infection, and falls (Table 3 and Table S4). Respiratory infections were more common in the tolebrutinib group than in the placebo group, including Covid-19 (25.5% vs. 22.7%), nasopharyngitis (9.3% vs. 6.9%), and influenza (5.6% vs. 3.5%). Serious adverse events occurred in 15.0% of the participants who received tolebrutinib and in 10.4% of those who received placebo (Table 3). The most common serious adverse events with tolebrutinib were Covid-19 pneumonia (1.1%), relapse of multiple sclerosis (1.1%), Covid-19 (0.9%), and pneumonia (0.7%). The most common serious adverse events with placebo were pneumonia (0.8%) and urosepsis (0.8%). The incidence of death was similar in the two groups. In the tolebrutinib group, one participant had liver failure that was assessed as being related to tolebrutinib; this participant died as a result of postoperative complications related to a liver transplantation. One participant died by means of physician-assisted suicide; this death was assessed as being unrelated to tolebrutinib. In the placebo group, one participant died from cerebral edema and hemorrhage due to a fall.

Liver Safety

Increased alanine aminotransferase levels to more than 3 times the upper limit of the normal range were reported in 30 of 741 participants (4.0%) in the tolebrutinib group and in 6 of 372 participants (1.6%) in the placebo group (Table 3 and Fig. S7). Alanine aminotransferase level increases to more than 20 times the upper limit of the normal range were reported in 4 participants (0.5%) in the tolebrutinib group and in no participants in the placebo group. All the cases occurred within 90 days after the first dose of tolebrutinib or placebo, and all but one occurred before implementation of a protocol revision that included more frequent liver monitoring. Three of 752 participants (0.4%) in the tolebrutinib group had alanine aminotransferase levels greater than 3 times the upper limit of the normal range and total bilirubin levels greater than 2 times the upper limit of the normal range. The participant who died due to postoperative complications related to a liver transplantation, with the underlying liver failure assessed as being related to tolebrutinib, showed an increased alanine aminotransferase level before implementation of the revised schedule for liver monitoring. After weekly liver monitoring was implemented, all the cases of elevated liver-enzyme levels resolved without sequelae.

DISCUSSION

In this trial, the risk of confirmed disability progression sustained for at least 6 months among participants with nonrelapsing secondary progressive multiple sclerosis was lower with tolebrutinib than with placebo. All disability-progression events were independent of relapse activity. Tolebrutinib treatment was also associated with fewer new or enlarging brain lesions on MRI than placebo, a finding that is consistent with the effect of tolebrutinib on peripheral B lymphocytes.[13]

Tolebrutinib effectively penetrates the CNS, reaching cerebrospinal fluid concentrations that exceed the 90% inhibitory concentration.[13] This feature has not been observed for other tested BTK inhibitors,[13] including evobrutinib, which was not associated with a lower risk of disability worsening than teriflunomide in two phase 3, randomized trials involving participants with relapsing multiple sclerosis.[20] Additional analyses will evaluate the effect of tolebrutinib on pathophysiological substrates of chronic CNS neuroinflammation, including disease-associated microglial activity around chronic active lesions.[3,6]

The liver-enzyme elevations that were observed with tolebrutinib have also been reported with other BTK inhibitors that are in development for the treatment of multiple sclerosis.[20,21] Most of the increases in alanine aminotransferase level that were observed in this trial were mild to moderate, and the majority resolved without sequelae. In the single participant who received a liver transplant, the initial abnormal liver-enzyme level occurred before a protocol amendment that increased the frequency of liver monitoring to occur weekly for the first 12 weeks of the treatment period.

In this trial involving participants with nonrelapsing secondary progressive multiple sclerosis, tolebrutinib treatment resulted in a lower risk of disability progression than placebo. These results support the role of tolebrutinib in slowing disability accrual in persons with nonrelapsing secondary progressive multiple sclerosis, a population with an unmet need for treatments that delay disability.

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