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Inhibition of CD40L with Frexalimab in Multiple Sclerosis

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ABSTRACT

BACKGROUND

The CD40–CD40L costimulatory pathway regulates adaptive and innate immune responses and has been implicated in the pathogenesis of multiple sclerosis. Frexalimab is a second-generation anti-CD40L monoclonal antibody being evaluated for the treatment of multiple sclerosis.

METHODS

In this phase 2, double-blind, randomized trial, we assigned, in a 4:4:1:1 ratio, participants with relapsing multiple sclerosis to receive 1200 mg of frexalimab administered intravenously every 4 weeks (with an 1800-mg loading dose), 300 mg of frexalimab administered subcutaneously every 2 weeks (with a 600-mg loading dose), or the matching placebos for each active treatment. The primary end point was the number of new gadolinium-enhancing T1-weighted lesions seen on magnetic resonance imaging at week 12 relative to week 8. Secondary end points included the number of new or enlarging T2-weighted lesions at week 12 relative to week 8, the total number of gadolinium-enhancing T1-weighted lesions at week 12, and safety. After 12 weeks, all the participants could receive open-label frexalimab.

RESULTS

Of 166 participants screened, 129 were assigned to a trial group; 125 participants (97%) completed the 12-week double-blind period. The mean age of the participants was 36.6 years, 66% were women, and 30% had gadolinium-enhancing lesions at baseline. At week 12, the adjusted mean number of new gadolinium-enhancing T1-weighted lesions was 0.2 (95% confidence interval [CI], 0.1 to 0.4) in the group that received 1200 mg of frexalimab intravenously and 0.3 (95% CI, 0.1 to 0.6) in the group that received 300 mg of frexalimab subcutaneously, as compared with 1.4 (95% CI, 0.6 to 3.0) in the pooled placebo group. The rate ratios as compared with placebo were 0.11 (95% CI, 0.03 to 0.38) in the 1200-mg group and 0.21 (95% CI, 0.08 to 0.56) in the 300-mg group. Results for the secondary imaging end points were generally in the same direction as those for the primary analysis. The most common adverse events were coronavirus disease 2019 and headaches.

CONCLUSIONS

In a phase 2 trial involving participants with multiple sclerosis, inhibition of CD40L with frexalimab had an effect that generally favored a greater reduction in the number of new gadolinium-enhancing T1-weighted lesions at week 12 as compared with placebo. Larger and longer trials are needed to determine the long-term efficacy and safety of frexalimab in persons with multiple sclerosis. (Funded by Sanofi; ClinicalTrials.gov number, NCT04879628.)

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A Quick Take is available at NEJM.org

The CD40–CD40L (CD154) costimulatory pathway regulates the initiation of adaptive and innate immune responses.[1,2] Clinical and pathological observations have indicated the involvement of the CD40–CD40L pathway in multiple sclerosis and its association with disease progression,[3-8] with possible links to peripheral immune tolerance[9] and Epstein–Barr virus infection, which has been shown to induce CD40L expression.[10] Persons with multiple sclerosis have elevated levels of CD40L expression on activated T cells that result in high levels of soluble CD40L, which broadly correlate with disability assessed according to the Expanded Disability Status Scale (EDSS).[4,6,8] Genetic associations between single-nucleotide polymorphisms on *CD40* and the risk of multiple sclerosis have been identified.[11-13] Infiltrating CD40L+ T cells act as drivers of CD40-mediated inflammatory responses and activate CD40+ monocytes, macrophages, B cells, endothelial cells, and central nervous system–resident immune cells, potentiating multiple sclerosis lesions and disease progression. These effects support the inhibition of the CD40–CD40L pathway as a potential therapeutic strategy in multiple sclerosis.

In a small, phase 1 study, a first-generation anti-CD40L monoclonal antibody was investigated in persons with multiple sclerosis.[14] However, this study was terminated early owing to thromboembolic events that were reported with other first-generation antibodies in other indications, such as proliferative lupus nephritis and systemic lupus erythematosus.[14-16]

Frexalimab is a second-generation anti-CD40L humanized IgG1 monoclonal antibody that has been Fc-engineered to overcome the risk of thromboembolic events. The Fc engineering abrogates the platelet activation that is triggered by FcγRIIa stimulation by immune complexes.[17] Frexalimab targets CD40L, which is expressed on a variety of cells, including activated T cells. Inhibition of the binding of CD40L to CD40 expressed on the surface of antigen-presenting cells disrupts the CD40–CD40L signaling pathway and can prevent T-cell–mediated immune response. Here, we report the efficacy and safety results of a phase 2, double-blind, randomized, placebo-controlled trial of frexalimab in participants with relapsing multiple sclerosis.

METHODS

TRIAL DESIGN AND PARTICIPANTS

We screened participants for eligibility at 38 sites in 10 countries. The trial consisted of two parts: a 12-week, double-blind, randomized, placebo-controlled period (part A), followed by an open-label extension period lasting 212 to approximately 280 weeks (part B) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Key eligibility criteria were an age of 18 to 55 years; a diagnosis of relapsing multiple sclerosis meeting the 2017 revised McDonald criteria[18]; at least one relapse within the previous year, at least two relapses in the previous 2 years, or at least one active gadolinium-enhancing lesion in the 6 months before screening; and an EDSS score of no more than 5.5 (on a scale from 0 [normal neurologic examination] to 10 [death due to multiple sclerosis]). Key exclusion criteria were a diagnosis of primary or nonrelapsing secondary progressive multiple sclerosis,[18,19] current receipt of disease-modifying therapy for multiple sclerosis or immunosuppressive or chemotherapeutic agents within the prespecified washout periods, relapse within 30 days before randomization, any medical or clinical condition or situation that could adversely affect trial participation (e.g., infections and thromboembolic events), pregnancy, and use of certain concomitant medications, including systemic glucocorticoids. The inclusion and exclusion criteria were meant to identify patients with active multiple sclerosis, as judged on the basis of clinical or imaging findings. Persons with secondary progressive multiple sclerosis who were having relapses were permitted to enroll in the trial (see the protocol, available at NEJM.org, and the Supplementary Appendix).

After a 4-week screening period, participants were randomly assigned in a 4:4:1:1 ratio by means of interactive response technology to receive 1200 mg of frexalimab administered intravenously every 4 weeks (with an 1800-mg loading dose on day 1), 300 mg of frexalimab administered subcutaneously every 2 weeks (with a 600-mg loading dose on day 1), intravenously administered matching placebo, or subcutaneously administered matching placebo. Frexalimab and placebo were administered for 12 weeks in a double-blind fash-

ion, although the route of administration was not blinded. After 12 weeks, all the participants could receive open-label frexalimab. Participants in the intravenous-placebo and subcutaneous-placebo groups were switched to receive the corresponding frexalimab treatment — that is, the 1200-mg dose administered intravenously every 4 weeks (after an 1800-mg loading dose at week 12) or the 300-mg dose administered subcutaneously every 2 weeks (after a 600-mg loading dose at week 12), respectively.

TRIAL OVERSIGHT

The trial was sponsored and designed by Sanofi. The sponsor was involved in the collection, analysis, and interpretation of the data. The trial protocol was approved by relevant institutional review boards. There was no data and safety monitoring board. 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. All the participants provided written informed consent; they were informed that disease-modifying therapy for multiple sclerosis would be withheld during the trial.

The manuscript was developed with medical writing assistance that was funded by the sponsor. The authors contributed to the trial design, data acquisition, and data analysis. All the authors, five of whom were employees of the sponsor, drafted the initial version of the manuscript, reviewed it critically for important intellectual content, and approved the final version to be submitted for publication. There were confidentiality agreements in place between the authors and the sponsor. The sponsor could not delay or interdict the publication of the trial results. The authors vouch for the fidelity of the trial to the protocol, for the completeness and accuracy of the data, and for the complete reporting of adverse events.

END POINTS AND ASSESSMENTS

The primary end point was the number of new gadolinium-enhancing T1-weighted lesions at week 12 relative to week 8, as determined on magnetic resonance imaging (MRI). In assessments of scans, the total number of gadolinium-enhancing lesions and the number of lesions that were not present on the previous scan were counted. Secondary end points included the number of new or enlarging T2-weighted lesions at week 12 relative to week 8, the total number of gadolinium-enhancing T1-weighted lesions at week 12, pharmacokinetics, and safety. MRI assessments were performed at screening, at weeks 8 and 12 during the double-blind period, and at weeks 20 and 24 and every 6 months thereafter during the open-label period. Imaging review was performed by a central reading site (NeuroRx) by persons who were unaware of the trial-group assignments.

Exploratory end points included the number of relapses during the 12-week double-blind period, the change from baseline to week 12 in the EDSS score, the changes from baseline to week 12 in the Multiple Sclerosis Impact Scale (MSIS-29) domain scores (range, 0 to 100, with higher scores indicating a greater effect of multiple sclerosis from the patient's perspective[20]), and levels of circulating biomarkers of neuroaxonal damage and inflammatory activity (plasma neurofilament light chain [NfL] and chemokine [C-X-C motif] ligand 13 [CXCL13], respectively). We used the MSIS-29 to assess patient-reported outcomes in the physical domain (20 items) and psychological domain (9 items). A complete list of the trial end points as specified in the protocol and statistical analysis plan is provided in Table S1.

Safety was monitored by the recording of adverse events by site investigators who were unaware of the trial-group assignments. Prespecified adverse events of special interest included severe infections (including opportunistic infections), severe acute respiratory syndrome coronavirus 2 infection (coronavirus disease 2019 [Covid-19]), arterial or venous thrombotic or embolic events, severe infusion-related or injection-related reactions, an increase in the alanine aminotransferase level of more than three times the upper limit of the normal range, pregnancy in participants with exposure to frexalimab, and overdose of frexalimab that was associated with symptoms (serious or nonserious; see Section 8.3.7 of the protocol). Results on clinical laboratory tests, such as hematologic tests, chemical analysis, pregnancy tests, 12-lead electrocardiography, and vital signs, were recorded.

STATISTICAL ANALYSIS

We derived the sample size by applying the quantitative decision-making method[21] (see the Statistical Considerations section of the Supplementary Appendix) and assuming a negative binomial distribution and a 90% reduction in the mean count of gadolinium-enhancing T1-weighted lesions in either of the frexalimab groups as compared with the pooled placebo group, for a probability of 0.71 that the conclusion would be positive, with no adjustment for multiplicity. We estimated that we would need to screen approximately 160 potential participants in order for 120 to undergo randomization (assuming that 25% of the persons screened would have screening failure) and for 100 participants to have evaluable data (assuming withdrawal by 15%). To limit the number of participants receiving a placebo, a randomization

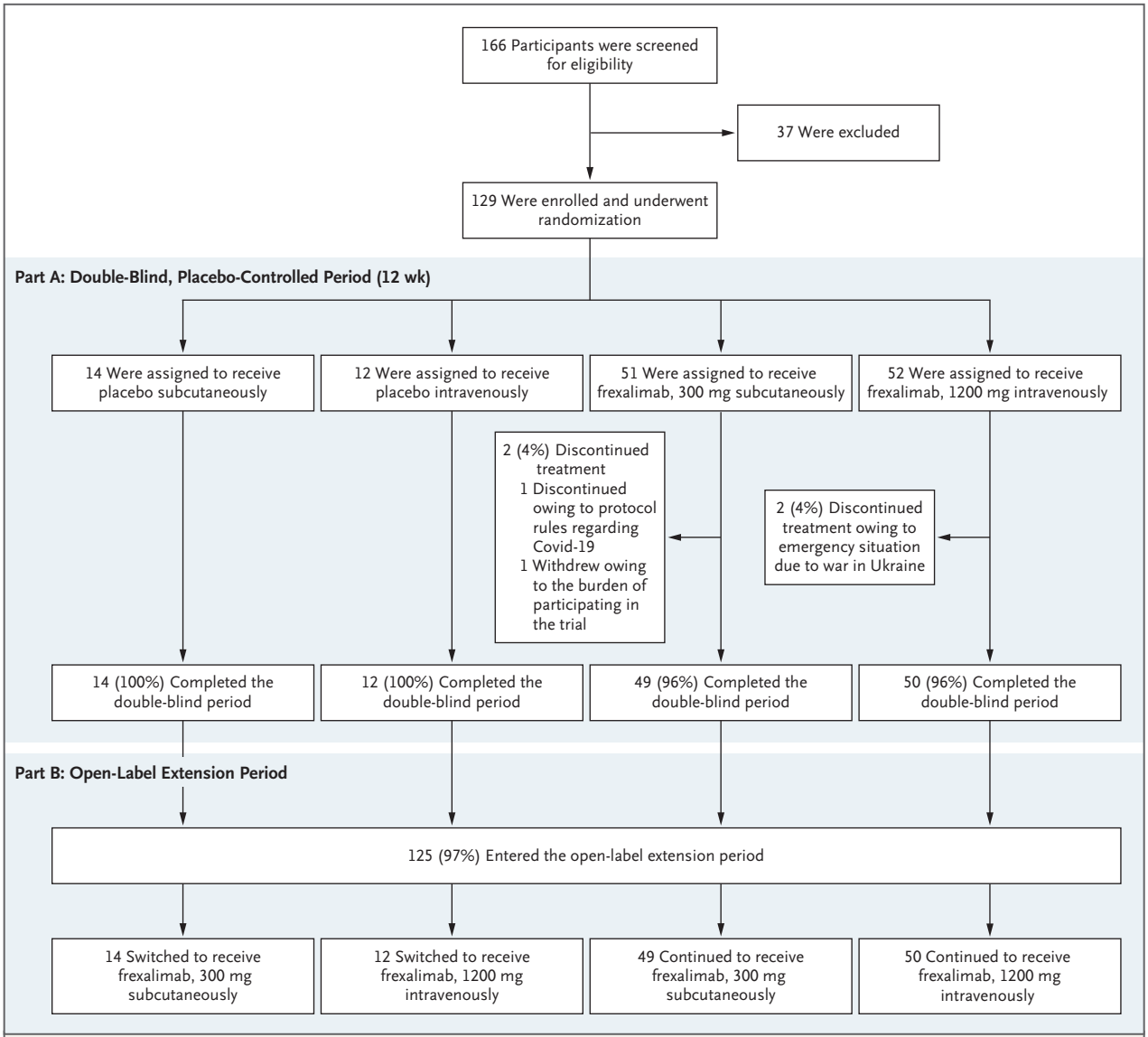

Figure 1. Randomization and Follow-up of the Participants.

Participants in the placebo groups switched to the corresponding frexalimab treatment at week 12 (either 300 mg subcutaneously every 2 weeks or 1200 mg intravenously every 4 weeks, depending on whether they had received placebo subcutaneously or intravenously). Participants who had been receiving frexalimab continued their assigned regimen. The percentages of participants are based on the original number of participants who underwent random assignment to each trial group. Covid-19 denotes coronavirus disease 2019.

ratio of 4:1 (active treatment to placebo) was applied, and the two placebo groups were pooled for the main analyses.

The primary end point was analyzed by means of a negative binomial regression model with the gadolinium-enhancing T1-weighted lesion activity (presence or absence) at baseline as a covariate and trial group as a factor and with the duration (in months) between the week 12 MRI and the previous MRI as an offset variable after natural logarithm transformation. Lesion counts that were unadjusted or that were adjusted for the baseline number of lesions were calculated from the model. The relative reduction in each frexalimab group as compared with the pooled placebo group was estimated, with a 95% confidence interval. The widths of the 95% confidence intervals for the primary and secondary end points were not adjusted for multiplicity; these intervals may not be used in place of hypothesis testing, and no definite conclusions can be drawn from these results. The goodness of fit of the negative binomial regression model that was used for the primary end point was assessed with the use of the Pearson chi-square statistic, which was calculated as follows: for each participant, the squared difference between the observed number of lesions and the value predicted by the model was calculated and then divided by the variance of the predicted value. We then summed all these values to obtain the Pearson chi-square statistic, which was used to estimate the distance between the observed data and the predicted values for the whole trial.

Analysis of the primary end point was performed in the efficacy population, which included all the participants who had undergone randomization, had received all Part A doses of frexalimab or placebo (skipping one subcutaneous dose was allowed), and had evaluable data for the primary end point. No imputation was made for missing primary end-point results, and participants with-

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Randomized Population).*

Characteristic	All Participants (N=129)	Pooled Placebo (N=26)	Frexalimab, 300 mg Subcutaneous (N=51)	Frexalimab, 1200 mg Intravenous (N=52)
Age — yr	36.6±9.4	31.9±9.4	38.2±8.9	37.3±9.3
Female sex — no. (%)	85 (66)	17 (65)	31 (61)	37 (71)
Race — no. (%)†				
White	128 (99)	26 (100)	50 (98)	52 (100)
Black	1 (1)	0	1 (2)	0
Type of multiple sclerosis — no. (%)				
Relapsing–remitting	121 (94)	24 (92)	47 (92)	50 (96)
Secondary progressive	8 (6)	2 (8)	4 (8)	2 (4)
Time since symptom onset — yr	7.7±7.2	7.0±6.8	7.9±7.6	7.9±7.0
No. of relapses in the previous yr	1.2±0.5	1.1±0.6	1.2±0.5	1.3±0.6
Median EDSS score (interquartile range)‡	2.5 (2.0–3.5)	2.8 (2.0–4.5)	2.5 (2.0–3.5)	2.5 (1.5–3.5)
≥1 Gadolinium-enhancing T1-weighted lesion — no. (%)	39 (30)	10 (38)	16 (31)	13 (25)
No. of gadolinium-enhancing T1-weighted lesions	1.0±2.7	1.6±3.5	0.9±2.5	0.8±2.4
Any previous disease-modifying treatment — no. (%)§	25 (19)	5 (19)	9 (18)	11 (21)

* Plus–minus values are means ±SD. All the participants from the screened population who underwent randomization by means of interactive response technology were included in the randomized population. Data from the intravenous and subcutaneous placebo groups were pooled.
† Race was reported by the participant.
‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 (no disability) to 10 (death).
§ Previous disease-modifying treatments included injectable agents (glatiramer acetate and interferons) and oral agents (teriflunomide, dimethyl fumarate, and fingolimod).

out evaluable data for the primary end point were not included in the main analysis. Potential reasons for the lack of evaluable data for the primary end point included MRI assessments in participants who received systemic glucocorticoids within 30 days before the MRI assessment date, as well as missing blinded MRI central assessment of the primary end point (see the Supplementary

Table 2. Primary, Secondary, and Selected Exploratory End Points.*

End Point	Pooled Placebo (N=22)	Frexalimab, 300 mg Subcutaneous (N=45)	Frexalimab, 1200 mg Intravenous (N=47)
Primary end point			
No. of new gadolinium-enhancing T1-weighted lesions at wk 12			
Unadjusted mean (95% CI)	3.0 (1.2–7.3)	0.4 (0.2–0.9)	0.2 (0.1–0.4)
Adjusted mean (95% CI)†	1.4 (0.6–3.0)	0.3 (0.1–0.6)	0.2 (0.1–0.4)
Adjusted rate ratio vs. placebo (95% CI)	—	0.21 (0.08–0.56)	0.11 (0.03–0.38)
Secondary end points			
No. of new or enlarging T2-weighted lesions at wk 12			
Unadjusted mean (95% CI)	4.3 (1.8–10.2)	0.6 (0.3–1.3)	0.4 (0.2–0.8)
Adjusted mean (95% CI)	3.5 (1.6–7.9)	0.5 (0.2–1.0)	0.3 (0.1–0.6)
Adjusted rate ratio vs. placebo (95% CI)	—	0.14 (0.05–0.41)	0.08 (0.03–0.26)
Total no. of gadolinium-enhancing T1-weighted lesions at wk 12			
Unadjusted mean (95% CI)	3.7 (1.6–8.8)	0.5 (0.2–1.0)	0.2 (0.1–0.5)
Adjusted mean (95% CI)	1.7 (0.8–3.7)	0.3 (0.2–0.7)	0.2 (0.1–0.5)
Adjusted rate ratio vs. placebo (95% CI)	—	0.20 (0.07–0.53)	0.12 (0.04–0.36)
Selected exploratory end points			
Relapse during 12-wk period — no./total no. (%)	1/26 (4)	2/51 (4)	0/52
Plasma NfL level‡			
At baseline			
No. of participants with data	26	50	51
Geometric mean — pg/ml	12.33±1.86	12.99±1.79	12.04±2.01
At wk 12			
No. of participants with data	26	49	48
Geometric mean — pg/ml	13.75±1.93	11.56±1.66	10.29±1.91
Adjusted geometric mean analysis			
No. of participants with data for adjusted analyses	26	48	47
Adjusted geometric mean of NfL value — pg/ml	13.8	11.2	10.5
Adjusted geometric mean of the reduction ratio§	1.12	0.91	0.85
Adjusted geometric mean ratio (95% CI)	—	0.82 (0.67–0.99)	0.76 (0.63–0.93)
Plasma CXCL13 level‡			
At baseline			
No. of participants with data	25	51	52
Geometric mean — pg/ml	87.73±2.05	110.74±3.12	95.18±2.51
At wk 12			
No. of participants with data	26	49	50
Geometric mean — pg/ml	102.52±2.32	79.16±2.75	81.37±2.88

Table 2. (Continued.)

End Point	Pooled Placebo (N=22)	Frexalimab, 300 mg Subcutaneous (N=45)	Frexalimab, 1200 mg Intravenous (N=47)
Adjusted geometric mean analysis			
No. of participants with data for adjusted analyses	25	49	50
Adjusted geometric mean of CXCL13 value — pg/ml	106.2	74.0	83.5
Adjusted geometric mean of the reduction ratio§	1.08	0.75	0.85
Adjusted geometric mean ratio (95% CI)	—	0.70 (0.49–1.00)	0.79 (0.55–1.12)

* Plus–minus values are means ±SD. The efficacy population included all the participants who had undergone randomization, had received all part A doses of frexalimab or placebo (skipping one subcutaneous dose was allowed), and had evaluable data for the primary end-point analysis. The primary end point could be evaluated when the following conditions were met: availability of the blinded MRI central assessment of the primary end point and no systemic glucocorticoid administration within 30 days before the MRI assessment at baseline and during the 12-week double-blind period (part A). Primary or secondary end-point results were not adjusted for multiple comparisons. No imputation was made for participants with missing or incomplete data. Data from the intravenous and subcutaneous placebo groups were pooled. CXCL13 denotes chemokine (C-X-C motif) ligand 13, and NfL neurofilament light chain.
† The adjusted mean was calculated by a negative binomial regression model, with and without adjustment for the number of lesions at baseline.
‡ The safety population included all the participants who had undergone randomization and had received at least one dose (regardless of the amount) of frexalimab or placebo. Data were analyzed according to the intervention that the participants actually received.
§ The reduction ratio refers to the value at week 12 divided by the value at baseline.

Appendix). Analyses of the secondary MRI end points were performed in a manner similar to that for the primary end point. A prespecified sensitivity analysis of the primary end point was performed, with the gadolinium-enhancing T1-weighted lesion count at baseline as a continuous covariate.

For the NfL and CXCL13 levels, we calculated geometric mean estimates and ratios. For the MSIS-29 scores, a post hoc analysis was performed with the use of an analysis of covariance to estimate the difference in the change from baseline among the trial groups with the baseline value as a covariate. Safety was reported with descriptive statistics (see the Supplementary Appendix). All the safety analyses (adverse events, laboratory variables, vital signs, and electrocardiograms) were performed in the safety population, which included all the participants who had undergone randomization and received at least one dose of frexalimab or placebo (regardless of the amount).

RESULTS

PARTICIPANTS

Between June 7, 2021, and September 21, 2022, a total of 166 persons underwent screening, of whom 37 did not meet the screening criteria. The most common reasons for screening failure were abnormal laboratory tests at screening and the exclusion of persons in Ukraine and Russia on the basis of the sponsor's decision after the start of the war. A total of 129 participants were randomly assigned to a trial group: 52 to the group that received 1200 mg of frexalimab intravenously, 51 to the group that received 300 mg of frexalimab subcutaneously, 12 to the group that received intravenous placebo, and 14 to the group that received subcutaneous placebo.

Of the 129 participants, 125 (97%) completed the 12-week double-blind period and entered the open-label period. The cutoff date for the data reported here was 24 weeks after baseline for the last participant who had undergone randomization. During the double-blind period, 2 participants receiving 1200 mg of frexalimab intravenously discontinued treatment owing to an emergency situation as a result of the war in Ukraine. In the group that received 300 mg of frexalimab subcutaneously, 1 participant discontinued treatment because of protocol rules regarding Covid-19, and 1 withdrew owing to the burden of participating in the trial (Fig. 1). A total of 15 participants (12%) were excluded from the analysis: 13 participants (5 in the 1200-mg group, 4 in the 300-mg group, and 4 in the pooled placebo group) because data regarding the primary end point were missing, and 2 participants (in the

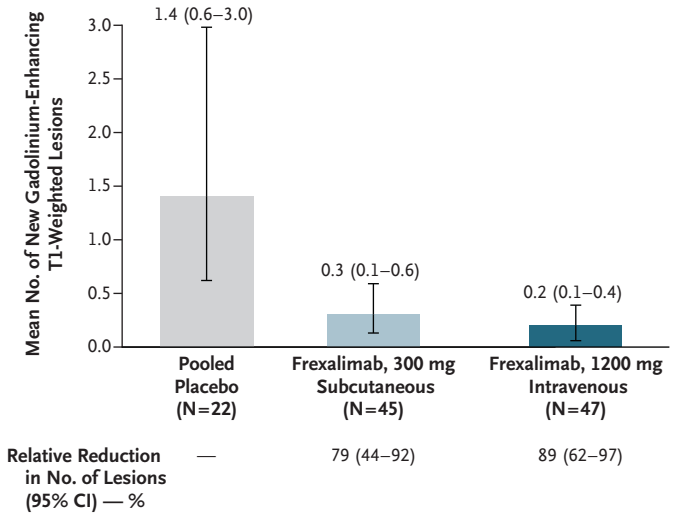

Figure 2. Number of New Gadolinium-Enhancing T1-Weighted Lesions at Week 12 (Efficacy Population).

The efficacy population included all the participants who had undergone randomization, received all part A doses of frexalimab or placebo (skipping one subcutaneous dose was allowed), and had evaluable data for the primary end point (the number of new gadolinium-enhancing T1-weighted lesions at week 12 relative to week 8). The primary end point could be evaluated when the following conditions were met: availability of the blinded MRI central assessment of the primary end point and no administration of systemic glucocorticoids 30 days before the baseline MRI and during the 12-week double-blind period (part A). Of the 129 participants who had undergone randomization, 15 (12%) were excluded from the analysis: 13 participants (5 in the 1200-mg group, 4 [8%] in the 300-mg group, and 4 [15%] in the pooled placebo group) because data regarding the primary end point were missing, and 2 participants (in the 300-mg group) because they had received glucocorticoids within 30 days before their MRI assessment. The results of the primary analysis were not adjusted for multiple comparisons, and no imputation was made for missing or incomplete data. I bars indicate 95% confidence intervals.

300-mg group) because they had received glucocorticoids within 30 days before their MRI assessment.

The demographic and disease characteristics of the participants at baseline were generally similar among the trial groups, except that the participants in the pooled placebo group were younger than the participants in the frexalimab groups and had a higher total number of gadolinium-enhancing T1-weighted lesions (1.6 in the placebo group vs. 0.9 in the 300-mg group and 0.8 in the 1200-mg group) (Table 1). All the participants (except one in the 300-mg frexalimab group) were White. The mean age of the participants was 36.6 years, and 66% were women. A total of 94% of the participants had relapsing–remitting multiple sclerosis; the remainder had secondary progressive multiple sclerosis with relapses. The representativeness of the trial population with respect to the general population of persons with multiple sclerosis is shown in Table S2.

PRIMARY END POINT

Lesion counts at week 12 that were unadjusted for the number of lesions at baseline are provided in Table 2. The adjusted mean number of new gadolinium-enhancing T1-weighted lesions at week 12 relative to week 8 was 0.2 (95% confidence interval [CI], 0.1 to 0.4) in the group that received 1200 mg of frexalimab intravenously and 0.3 (95% CI, 0.1 to 0.6) in the group that received 300 mg of frexalimab subcutaneously, as compared with 1.4 (95% CI, 0.6 to 3.0) in the pooled placebo group (Fig. 2). The rate ratios from the model, as compared with placebo, were 0.11 (95% CI, 0.03 to 0.38) in the 1200-mg group and 0.21 (95% CI, 0.08 to 0.56) in the 300-mg group (Table 2). At week 12, a total of 85% of the participants in the 1200-mg group and 84% of those in the 300-mg group had no new gadolinium-enhancing lesions, as compared with 50% of the participants in the pooled placebo group (Fig. S2).

The results of the prespecified sensitivity analysis of the primary end point, with baseline gadolinium-enhancing T1-weighted lesion activity as a continuous covariate, and a post hoc sensitivity analysis that excluded one participant in the pooled placebo group who had an outlier result were similar to those for the primary analysis (Table S3). Post hoc analyses during the open-label period until week 24 showed that the number of new gadolinium-enhancing T1-weighted lesions remained low among participants who continued to receive frexalimab and appeared to decrease among participants in the placebo groups after they switched to frexalimab treatment at week 12 (Fig. S3A). The unadjusted mean number of new gadolinium-enhancing T1-weighted lesions in the group that received 1200 mg of frexalimab intravenously was 0.1 (95% CI, 0.02 to 0.2) at week 24, and 96% of the participants had no new gadolinium-enhancing T1-weighted lesions, but no definite conclusions can be drawn from this nonprespecified analysis.

Table 3. Adverse Events at 12 Weeks (Safety Population).*

Event	Pooled Placebo (N=26)	Frexalimab, 300 mg Subcutaneous (N=51)	Frexalimab, 1200 mg Intravenous (N=52)
	no. of participants with event (percent)		
Any adverse event	8 (31)	23 (45)	15 (29)
Any serious adverse event	0	0	0
Adverse event leading to death	0	0	0
Adverse event leading to permanent discontinuation of frexalimab or placebo†	0	1 (2)	0
Adverse event of special interest	0	5 (10)	1 (2)
Increased alanine aminotransferase level‡	0	0	1 (2)
Covid-19§	0	5 (10)	0
Infection or infestation	1 (4)	12 (24)	4 (8)
Most common adverse events¶			
Covid-19	0	5 (10)	0
Headache	0	1 (2)	3 (6)

* The safety population included all the participants who had undergone randomization and received at least one dose (regardless of the amount) of frexalimab or placebo. The numbers and percentages of participants with at least one adverse event (according to the *Medical Dictionary for Regulatory Activities*, version 25.0) that occurred during the double-blind period are shown. Data from the subcutaneous and intravenous placebo groups were pooled. A complete list of the adverse events that were reported during the double-blind period is provided in Table S5. Covid-19 denotes coronavirus disease 2019.

† Covid-19 led to the discontinuation of frexalimab in one participant in the 300-mg group.

‡ During the 12-week double-blind period, one participant in the 1200-mg group had an alanine aminotransferase level that increased to 5.9 times the upper limit of the normal range, at 1 month 26 days after starting treatment, with a slight elevation in the aspartate aminotransferase and alkaline phosphatase levels and no concomitant increase in the bilirubin level. The increase in the alanine aminotransferase level resolved while the participant continued to receive frexalimab. During the open-label period until a cutoff at week 24, two participants who continued receiving 1200 mg of frexalimab intravenously had an increase in the alanine aminotransferase level (with no associated increase in the bilirubin level); the participants recovered while continuing to receive frexalimab.

§ Five participants in the 300-mg group had Covid-19. One case led to treatment discontinuation. All five cases were of mild or moderate intensity.

¶ Shown are the adverse events that were reported in at least 5% of the participants in any group. In the open-label period until a cutoff at week 24, a total of 10 participants had Covid-19 (all the cases were considered by the investigator to be nonserious), 6 had nasopharyngitis, and 12 had headaches.

SECONDARY MRI END POINTS

The baseline unadjusted numbers of lesions in the secondary end-point analyses are shown in Table 2. The adjusted mean number of new or enlarging T2-weighted lesions at week 12 was 0.3 (95% CI, 0.1 to 0.6) in the group that received 1200 mg of frexalimab intravenously, 0.5 (95% CI, 0.2 to 1.0) in the group that received 300 mg of frexalimab subcutaneously, and 3.5 (95% CI, 1.6 to 7.9) in the pooled placebo group (Table 2). The adjusted mean total number of gadolinium-enhancing T1-weighted lesions at week 12 was 0.2 (95% CI, 0.1 to 0.5) in the 1200-mg group and 0.3 (95% CI, 0.2 to 0.7) in the 300-mg group, as compared with 1.7 (95% CI, 0.8 to 3.7) in the pooled placebo group (Table 2). At week 24, the counts of gadolinium-enhancing T1-weighted lesions and new and enlarging T2-weighted lesions remained low among participants who continued receiving frexalimab treatment and appeared to decrease among participants in the placebo groups after they switched to frexalimab treatment (in analyses that were not adjusted for multiplicity) (Fig. S3B and S3C).

EXPLORATORY CLINICAL END POINTS

Three protocol-confirmed relapses (in two participants [4%] in the 300-mg group and in 1 [4%] in the pooled placebo group) were reported over the 12-week double-blind period; there were no protocol-confirmed relapses in the 1200-mg group (Table 2). The MSIS-29 physical domain scores at week 12 were 24 in the group that received 1200 mg of frexalimab intravenously, 25 in the group that received 300 mg of frexalimab subcutaneously, and 32 in the pooled placebo group. There was no meaningful difference in the MSIS-29 psychological domain score between either frexalimab group and the pooled placebo group. There was no substantial change from baseline in the median change in the EDSS score at week 12 in any trial group. Data on the exploratory clinical end points are shown in Table S4.

PLASMA NFL AND CXCL13 LEVELS IN EXPLORATORY ANALYSES

At week 12, the mean NfL levels appeared to decrease from baseline in the two frexalimab groups as compared with the pooled placebo group, with a 24% reduction in the 1200-mg group and an 18% reduction in the 300-mg group (Table 2 and Fig. S4A). At week 12, the CXCL13 levels appeared to decrease from baseline in the two frexalimab groups as compared with the pooled placebo group, with a 21% reduction in the 1200-mg group and a 30% reduction in the 300-mg group (Table 2 and Fig. S4B).

SAFETY

During the 12-week double-blind period, at least one adverse event occurred in 29% of the participants (15 of 52) in the group that received 1200 mg of frexalimab intravenously, in 45% of those (23 of 51) in the group that received 300 mg of frexalimab subcutaneously, and in 31% of those (8 of 26) in the pooled placebo group. The most common adverse events (those that occurred in ≥5% of the participants in any group) were Covid-19 and headaches (Table 3). The adverse events included five mild-to-moderate cases of Covid-19 (in 10% of the participants) in the group that received 300 mg of frexalimab subcutaneously; one case led to permanent treatment discontinuation owing to protocol rules. No cases of Covid-19 were reported in the 1200-mg group or the placebo groups. One or more infections or infestations during the double-blind period were reported in 4 participants (8%) in the 1200-mg group, in 12 (24%) in the 300-mg group, and in 1 (4%) in the pooled placebo group. All the cases of infection or infestation were rated by the investigators as being mild or moderate in severity.

One participant who received 1200 mg of frexalimab intravenously had an isolated asymptomatic elevation in the alanine aminotransferase level (to 5.9 times the upper limit of the normal range) on day 57 (i.e., at 1 month 26 days after frexalimab treatment began), with no concomitant increase in the bilirubin level and with slight elevations in the levels of aspartate aminotransferase (to 2.0 times the upper limit of the normal range) and alkaline phosphatase. This event resolved, with the level reaching the normal range on day 85, while the participant continued to receive frexalimab. Two participants who received 300 mg of frexalimab subcutaneously and one who received the 1200-mg dose intravenously had neutropenia; all the participants recovered while continuing to receive frexalimab. No participant had a thromboembolic event. No serious or severe adverse events or deaths were reported during the double-blind period.

A complete list of the adverse events that were reported during the open-label period, until a cutoff at week 24 after baseline (after the last participant had undergone randomization), is provided in Table S6. All 10 cases of Covid-19 that were reported during the open-label period were considered by the investigators to be nonserious, and the participants recovered; one case led to treatment discontinuation. Two participants who continued intravenous treatment with 1200 mg of frexalimab had an elevation in the alanine aminotransferase level (with no associated elevation in the bilirubin level); the highest value was 9.2 times the upper limit of the normal range, which resolved back to the normal range while the patient continued to receive frexalimab.

DISCUSSION

Frexalimab treatment resulted in an effect generally favoring a reduction, as compared with placebo, in the number of new gadolinium-enhancing T1-weighted lesions at week 12. Results regarding the secondary imaging end points were generally similar to those regarding the primary end point.

Frexalimab treatment lowered plasma levels of NfL, a biomarker of neuroaxonal damage in multiple sclerosis.[22-24] Plasma levels of CXCL13, a biomarker of inflammatory activity, were decreased in participants who received frexalimab. Studies have shown high serum levels of CXCL13 in patients with active disease.[25-27]

The potential risks that have been associated with blocking CD40L include thromboembolic events (on the basis of data regarding first-generation compounds),[15,16] increased susceptibility to infection (including opportunistic infection), and hypersensitivity reactions. An elevated thromboembolic risk that had been seen with first-generation anti-CD40L antibodies resulted from platelet activation triggered by FcγRIIa stimulation by CD40L-mediated immune complexes; second-generation anti-CD40L therapies such as frexalimab have been engineered to lack an Fc or to contain a modified Fc with low FcγRIIa binding in order to eliminate the Fc-mediated thromboembolic risk.[17,28-32] In the present trial, no thromboembolic events were reported.

A small immunologic study involving patients with relapsing–remitting multiple sclerosis showed no depletion of major peripheral lymphocyte subsets during treatment with an anti-CD40L antibody that is different from the one used in our trial; instead, an increase in regulatory T cells and a shift toward an antiinflammatory cytokine response were observed, findings that implicated a potential induction of tolerance mechanisms.[14] In the present trial, depletion of lymphocytes was not observed. More infections were observed with active treatment than with placebo, but no serious infections occurred during 24 weeks of frexalimab treatment. All the reported cases of Covid-19 were uncomplicated and were mild to moderate in severity as evaluated by the investigators.[33]

The trial was too brief and small for conclusions regarding clinical outcomes, but over the 12-week double-blind period, no relapses occurred in the group that received 1200 mg of frexalimab intravenously, and relapses occurred in approximately 4% of the participants in the group that received 300 mg of frexalimab subcutaneously and in the pooled placebo group. There was no change from baseline in the EDSS median scores at week 12 in any trial group. Limitations of this phase 2 trial include its small sample size, the short duration of the double-blind period, and the use of imaging end points for the main analyses.

In this phase 2 trial involving participants with relapsing multiple sclerosis, treatment with the anti-CD40L monoclonal antibody frexalimab had a generally favorable effect, as compared with placebo, on the number of new gadolinium-enhancing T1-weighted lesions at week 12. Larger and longer trials are needed to determine the long-term efficacy and safety of frexalimab in persons with relapsing multiple sclerosis.

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APPENDIX

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