ORIGINAL ARTICLE

Inebilizumab for Treatment of IgG4-Related Disease

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ABSTRACT

BACKGROUND

IgG4-related disease is a multiorgan, relapsing, fibroinflammatory, immune-mediated disorder with no approved therapy. Inebilizumab targets and depletes CD19+ B cells and may be effective for treating patients with IgG4-related disease.

METHODS

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, adults with active IgG4-related disease underwent randomization in a 1:1 ratio to receive inebilizumab (300-mg intravenous infusions on days 1 and 15 and week 26) or placebo for a 52-week treatment period. Participants in both groups received identical glucocorticoid tapers. Glucocorticoids were allowed to treat disease flares, but background immunosuppressants were not permitted. The primary end point was the first treated, adjudicated disease flare during the treatment period, assessed in a time-to-event analysis. Key secondary end points were the annualized flare rate and treatment-free and glucocorticoid-free complete remission.

RESULTS

A total of 135 participants with IgG4-related disease underwent randomization: 68 participants were assigned to receive inebilizumab and 67 were assigned to receive placebo. Treatment with inebilizumab reduced flare risk; 7 participants (10%) in the inebilizumab group had at least one flare, as compared with 40 participants (60%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.06 to 0.28; P<0.001). The annualized flare rate was lower with inebilizumab than with placebo (rate ratio, 0.14; 95% CI, 0.06 to 0.31; P<0.001). More participants in the inebilizumab group than in the placebo group had flare-free, treatment-free complete remission (odds ratio, 4.68; 95% CI, 2.21 to 9.91; P<0.001) and flare-free, glucocorticoid-free complete remission (odds ratio, 4.96; 95% CI, 2.34 to 10.52; P<0.001). Serious adverse events occurred during the treatment period in 12 of the participants (18%) who received inebilizumab and 6 of the participants (9%) who received placebo.

CONCLUSIONS

Inebilizumab reduced the risk of flares of IgG4-related disease and increased the likelihood of flare-free complete remission at 1 year, confirming the role of CD19-targeted B-cell depletion as a potential treatment for IgG4-related disease. (Funded by Amgen; MITIGATE ClinicalTrials.gov number, NCT04540497.)

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*The full list of the MITIGATE Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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IgG4-related disease is a rare, chronic, relapsing, immune-mediated fibroinflammatory disorder with a reported prevalence in the United States of 5.3 persons per 100,000.[1] IgG4-related disease is characterized by the development of mass lesions rich in CD19+ B cells that may drive inflammation and fibrosis directly by means of cytokines or indirectly by the activation of pathogenic T cells.[2-4] IgG4-related disease can affect nearly any organ system; multiorgan involvement is typical.[5-8] Disease flares — periods of recurrent active disease associated with inflammation and fibrosis — may lead to progressive organ dysfunction and failure.[9,10] The pathophysiological features of IgG4-related disease involve antigen-driven interactions between B-cell subsets and various CD4+ and CD8+ T lymphocytes[11,12] that drive tissue injury and fibrosis and are associated with striking oligoclonal expansions of plasmablasts and increased levels of serum IgG4.[13]

There are no approved pharmacotherapies for IgG4-related disease. Glucocorticoid agents are recommended for remission induction and flare prevention.[7,14] Although patients typically have improvement while receiving glucocorticoid therapy,[15,16] disease control is not maintained in most patients when glucocorticoids are tapered or discontinued.[15,17,18] Moreover, the toxic effects of glucocorticoids are of great concern,[19,20] because IgG4-related disease frequently affects middle-aged and older patients with coexisting conditions that are exacerbated by glucocorticoid use.[6,8,15]

In addition, IgG4-related disease frequently impairs pancreatic function, heightening the risk of glucocorticoid-induced hyperglycemia and diabetes complications.[21,22] Immunosuppressant agents are often used as glucocorticoid-sparing maintenance therapy, but their usefulness has yet to be shown in randomized, placebo-controlled trials.[14,21] Thus, IgG4-related disease presents a high unmet need for therapies that can sustain remission, preserve organ function, and minimize the adverse effects of glucocorticoids.[7]

B-cell–targeted treatments offer potential benefits in the treatment of IgG4-related disease,[7] but supporting data are derived exclusively from case reports and open-label studies.[23-25] In an open-label study involving 30 patients, rituximab, a CD20-targeted, B-cell–depleting agent, appeared to induce remission,[26] but data from randomized, controlled trials of rituximab for the treatment of persons with IgG4-related disease are lacking.[26] CD19 expression appears earlier than CD20 expression in B-cell development and persists later, notably on plasmablasts and some plasma cells.[7] Therefore, therapies targeting CD19 may be effective in the treatment of IgG4-related disease and may offer advantages over anti-CD20 strategies by means of targeting broader ranges of B cells that drive IgG4-related disease.

Inebilizumab, a humanized, afucosylated IgG1 kappa monoclonal antibody, specifically targets CD19 and results in rapid, deep, and durable B-cell depletion.[27-30] Here, we report the results of MITIGATE, a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of inebilizumab in reducing the risk of disease flares among participants with active IgG4-related disease.

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

Details of the MITIGATE trial design have been published previously.[10] This phase 3, multicenter, parallel-cohort, double-blind, randomized, placebo-controlled trial was conducted at 80 sites in 22 countries (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. The trial was designed by several of the authors, including employees of the sponsor (Amgen).

The manuscript was written by the first and penultimate authors, and all the authors contributed to the collection and interpretation of the data, vouch for the completeness and accuracy of the data and the fidelity of the trial to the protocol, and participated in the decision to submit the manuscript for publication. The protocol (available with the statistical analysis plan at NEJM.org) was approved by the institutional review board or independent ethics committee at each site. All the participants provided written, informed consent before beginning any trial-related procedures. Members of the steering committee and the authors signed confidentiality agreements.

Participants

Persons who were at least 18 years of age, met the 2019 IgG4-related disease classification criteria of the American College of Rheumatology–

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European League against Rheumatism,[9] and had a diagnosis of IgG4-related disease with a history of involvement of at least two organs were eligible. All the participants had a current IgG4-related disease flare that resulted in initiation or continuation of glucocorticoid treatment. Full eligibility criteria are provided in Section S2 of the Supplementary Appendix.

TREATMENT AND RANDOMIZATION

All the participants received glucocorticoid treatment for 3 to 8 weeks before undergoing randomization. The dose of prednisone or equivalent was reduced to 20 mg per day on the day preceding randomization. Eligible participants were stratified according to whether they had newly diagnosed or recurrent disease at baseline and then were randomly assigned, in a 1:1 ratio, to receive inebilizumab or placebo. Randomization was performed with the use of an interactive voice-response or Web-response system (Fig. S1). Inebilizumab (at a dose of 300 mg) or placebo was administered intravenously on days 1 and 15 and at week 26 during the 52-week treatment period. Before each dose administration, all the participants were scheduled to receive standard prophylactic treatment against infusion reactions (intravenous methylprednisolone at a dose of 100 mg or equivalent, an antihistamine, and an antipyretic). Glucocorticoid doses were tapered by 5 mg per day every 2 weeks until discontinuation after 8 weeks. Concomitant use of immunosuppressants or glucocorticoids for flare prevention was prohibited; glucocorticoids were allowed for treatment of IgG4-related disease flares.

END POINTS

The primary end point was the first treated disease flare positively adjudicated by the adjudication committee during the treatment period, assessed in a time-to-event analysis. The date of the disease flare was the date of initiation of any therapy deemed to be necessary by the investigator to treat active disease. A flare was defined as new or worsening clinical features of IgG4-related disease that met organ-specific flare criteria and for which there was no clear alternative diagnosis. Flare criteria encompassing symptoms, physical examination, imaging, and laboratory and pathological findings were developed for the trial by a multinational panel of experts on IgG4-related disease (Section S3). All potential flares were evaluated by a central expert adjudication committee.[10]

Key secondary end points were the annualized flare rate for treated and adjudicated IgG4-related disease flares during the treatment period; flare-free, treatment-free complete remission at week 52; and flare-free, glucocorticoid-free complete remission at week 52 (Section S4). Flare-free complete remission was defined as the absence of any adjudicated disease flare, no flare treatment, and the absence of disease activity confirmed by a score of 0 on the IgG4-Related Disease Responder Index or attestation by the investigator that there was no clinical evidence of active disease. Other secondary efficacy end points are described in Section S5. Safety end points included adverse events and changes in clinical laboratory values. Adverse events were categorized according to severity, seriousness, and relation to inebilizumab or placebo (as determined by the investigator in a blinded manner).

STATISTICAL ANALYSIS

We determined that a sample size of 160 participants would result in 39 disease flares, which would provide the trial with 90% power to detect a relative reduction in the risk of disease flare by 65% during the 52-week treatment period, with a two-sided alpha level of 0.05. This calculation was based on the probability of 0.35 for an adjudicated disease flare in the placebo group. Details regarding the sample-size calculations are provided in Section 9 of the protocol.

Flares were analyzed with the use of a Cox proportional-hazards model with placebo recipients as the reference group and treatment and stratification as explanatory factors. Additional details about the assessment of the proportional-hazards assumption are provided in Section S6. The statistical calculations were performed with the use of SAS software, version 9.4 or higher (SAS Institute).

Efficacy was analyzed in the full analysis population, which included all the participants who underwent randomization and received any dose of inebilizumab or placebo. Participants were assessed on an intention-to-treat basis. The primary analysis, conducted after the 52-week treatment period was completed, was tested at a two-sided alpha level of 0.05 with the use of a Cox proportional-hazards model. No imputation was applied to the primary analysis; missing pri-

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Table 1. Characteristics of the Participants at Baseline (Full Analysis Population).*

Characteristic	Inebilizumab (N=68)	Placebo (N=67)	Overall (N=135)
Age — yr	58.2±11.5	58.2±12.2	58.2±11.8
Male sex — no. (%)	39 (57)	49 (73)	88 (65)
Race or ethnic group — no. (%)†			
Asian	38 (56)	25 (37)	63 (47)
White	21 (31)	32 (48)	53 (39)
Other	9 (13)	10 (15)	19 (14)
Region — no. (%)‡			
United States	7 (10)	14 (21)	21 (16)
European Union	20 (29)	26 (39)	46 (34)
Asia	34 (50)	18 (27)	52 (38)
IgG4-related disease manifestation			
Recurrent — no. (%)	37 (54)	36 (54)	73 (54)
Newly diagnosed — no. (%)	31 (46)	31 (46)	62 (46)
Disease duration — yr§	2.6±3.7	2.5±3.1	2.6±3.4
Median among patients with recurrent disease (range)	3.6 (0.2–20.5)	3.6 (0.1–12.5)	3.6 (0.1–20.5)
Median among patients with newly diagnosed disease (range)	0.2 (0.1–3.8)	0.1 (0.1–7.3)	0.2 (0.1–7.3)
Median ACR–EULAR score (IQR)¶	38.7 (31.0–46.5)	36.3 (29.2–44.7)	36.7 (30.0–46.2)
No. of organs ever affected by IgG4-related disease — no. of participants (%)‖			
2	15 (22)	7 (10)	22 (16)
3 or 4	24 (35)	34 (51)	58 (43)
>4	29 (43)	26 (39)	55 (41)
Previous surgery or medical procedure, other than biopsy, associated with IgG4-related disease — no. (%)**	14 (21)	19 (28)	33 (24)
Previous treatments for IgG4-related disease — no. (%)			
Immunosuppressants other than glucocorticoids for treatment of disease flare	6 (9)	11 (16)	17 (13)
Maintenance therapy††	11 (16)	12 (18)	23 (17)

* Plus–minus values are means ±SD. The full analysis population included all participants who underwent randomization and received any dose of inebilizumab or placebo in the trial. IQR denotes interquartile range.
† Race or ethnic group was reported by the participants. The "other" category included participants who reported their race as American Indian or Alaska Native, Black or African American, Native Hawaiian or other Pacific Islander, other, multiple, unknown, or not reported.
‡ Only regions with the highest enrollment are shown.
§ Disease duration is defined as the time between the date of diagnosis of IgG4-related disease (as reported by the investigator) and the start of inebilizumab or placebo.
¶ Scores on the American College of Rheumatology–European League against Rheumatism (ACR–EULAR) classification system range from 0 to 101, with higher scores indicating more severe disease.
‖ The median number of organs ever affected by IgG4-related disease was four in both the inebilizumab and placebo groups.
** Surgical and medical procedures are listed in Section S8 in the Supplementary Appendix.
†† Maintenance therapy included azathioprine, methotrexate, mycophenolate mofetil, leflunomide, abatacept, or rituximab.

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mary end-point data were censored in the Cox proportional-hazards model. The key secondary end points were evaluated only if the between-group difference with regard to the primary end point was significant, and the fallback method was used for trial-wise type I error control.[31]

The remaining secondary end points were not adjusted for multiplicity, and estimates are presented with 95% confidence intervals; the widths of the intervals have not been adjusted and should not be used in place of a hypothesis test (details regarding the multiplicity adjustment are provided in Section S7). Among the participants who were in flare-free, treatment-free, or glucocorticoid-free complete remission at week 52, those who did not complete the treatment period or who were missing assessments of IgG4-related disease activity at week 52 were considered to have had treatment failure with regard to the primary end point at week 52. Between-group differences in flare-free remission and annualized flare rate were assessed with the use of a logistic-regression model and a negative binomial model, respectively. Safety data were examined according to trial group with the use of the safety analysis population, which was made up of all the participants who received any dose of inebilizumab or placebo.

RESULTS

PARTICIPANTS

Between September 2020 and April 2023, a total of 227 participants underwent screening. Of the total, 135 underwent randomization: 68 to the inebilizumab group and 67 to the placebo group (Fig. S2). Overall, 127 (94.1%) completed the 52-week treatment period. The trial population reflected the general population of patients with IgG4-related disease (Table S2) — most of the participants were men (88 participants [65.2%]), and the mean age was 58.2 years, findings consistent with participants in large, single-center studies from different countries.[32,33] The demographic and clinical characteristics of the participants at baseline were generally balanced between the groups, with some disparities with regard to sex, race, and geographic region despite randomization (Table 1 and Table S3). At screening, 62 participants (45.9%) had newly diagnosed disease, and 73 participants (54.1%) had recurrent IgG4-related disease.

EFFICACY

Inebilizumab reduced the risk of treated and adjudicated IgG4-related disease flares by 87% as compared with placebo (hazard ratio, 0.13; 95%

Table 2. Primary and Key Secondary Efficacy End Points (Full Analysis Population).

End Point	Inebilizumab (N=68)	Placebo (N=67)	Effect vs. Placebo (95% CI)	P Value
Primary: time to first treated and adjudicated IgG4-related disease flare — no. (%)	7 (10.3)	40 (59.7)	0.13 (0.06–0.28)*	<0.001
Key secondary				
Annualized flare rate: treated and adjudicated IgG4-related disease flares — no. (95% CI)	0.10 (0.05–0.21)	0.71 (0.53–0.94)	0.14 (0.06–0.31)†	<0.001
Flare-free, treatment-free complete remission at wk 52 — no. (%)‡	39 (57.4)	15 (22.4)	4.68 (2.21–9.91)§	<0.001
Flare-free, glucocorticoid-free complete remission at wk 52 — no. (%)¶	40 (58.8)	15 (22.4)	4.96 (2.34–10.52)§	<0.001

* The hazard ratio for disease flare was based on the Cox regression method with IgG4-related disease manifestation (newly diagnosed vs. recurrent disease) as the stratification factor, with placebo as the reference group. The proportional-hazards assumption was met on the basis of the Grambsch and Therneau test of the Schoenfeld residuals.

† The rate ratio was estimated from the negative binomial regression.

‡ Flare-free, treatment-free complete remission was defined as the lack of evident disease activity at week 52, no flare (as determined by the adjudication committee) during the treatment period, and no treatment for flare or disease control except the required 8-week glucocorticoid taper. Participants who did not complete the treatment period or who missed the IgG4-related disease activity assessment at week 52 were considered to have not had complete remission at week 52.

§ The odds ratio was based on the logistic-regression model, with placebo recipients as the reference group.

¶ Flare-free, glucocorticoid-free complete remission was defined as the lack of evident disease activity at week 52, no flare (as determined by the adjudication committee) during the treatment period, and no glucocorticoid treatment for flare or disease control except the required 8-week glucocorticoid taper.

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confidence interval [CI], 0.06 to 0.28; P<0.001) (Fig. 1 and Table 2). Only 7 participants (10%) in the inebilizumab group had disease flares, as compared with 40 participants (60%) in the placebo group (Table 2), and there was a substantial delay in the time to disease flare with inebilizumab as compared with placebo (Fig. 1). The annualized flare rate for treated, adjudicated IgG4-related disease flares was reduced by 86% with inebilizumab therapy (hazard ratio for flare, 0.10; 95% CI, 0.05 to –0.21) as compared with placebo (hazard ratio for flare, 0.71; 95% CI, 0.53 to 0.94) (rate ratio, 0.14; 95% CI, 0.06 to 0.31; P<0.001) (Table 2). The percentage of participants who had flare-free, treatment-free complete remission was higher in the inebilizumab group (39 participants [57%]) than in the placebo group (15 participants [22%]) (odds ratio, 4.68; 95% CI, 2.21 to 9.91; P<0.001) (Table 2). The percentage of participants who had flare-free, glucocorticoid-free complete remission was higher in the inebilizumab group (40 participants [59%]) than in the placebo group (15 participants [22%]) (odds ratio, 4.96; 95% CI, 2.34 to 10.52; P<0.001) (Table 2).

Similar results regarding the primary and key secondary end points were obtained both with the inclusion of all treated flares regardless of the decision of the adjudication committee and with the inclusion of all adjudicated flares, whether treated or not (Table S4). Efficacy outcomes were also similar in the subgroups defined according to newly diagnosed disease and recurrent disease (Table S5). Concordance between the investigators' flare determinations and the adjudication committee's determination of these events was high (Table S6).

Excluding the 8-week glucocorticoid taper in all participants, the mean total glucocorticoid use per participant for IgG4-related disease (flare treatment or maintenance) during the treatment period was 118.3 mg of prednisone or equivalent in the inebilizumab group and 1384.5 mg in the placebo group (least-squares mean difference, –1264.2 mg; 95% CI, –1689.2 to –839.2) (Table S4). Overall, 61 participants (90%) in the inebilizumab group discontinued glucocorticoid treatment entirely during the treatment period, as compared with 25 participants (37%) in the placebo group. Inebilizumab treatment resulted in rapid, deep, and sustained peripheral CD20 B-cell depletion and IgG4 reduction during the treatment period (Fig. 2).

SAFETY

The number of participants who had at least one adverse event during the treatment period was

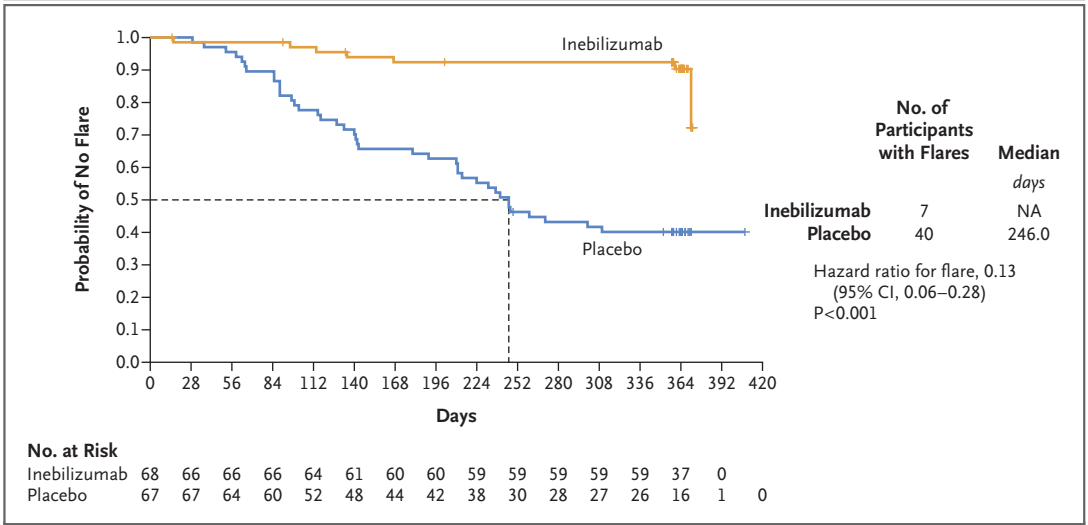

Figure 1. Time to First Treated and Adjudicated IgG4-Related Disease Flare (Full Analysis Population).

The full analysis population included all the participants who underwent randomization and received any dose of inebilizumab or placebo. Tick marks indicate censored data. The dashed lines indicate the median; estimated median time to event in the inebilizumab group could not be determined because less than 50% of the participants had an event by the end of the treatment period. The nominal day-365 visit occurred after day 365 in some participants for safety reasons or owing to the visit window specified in the protocol. CI denotes confidence interval, and NA not available.

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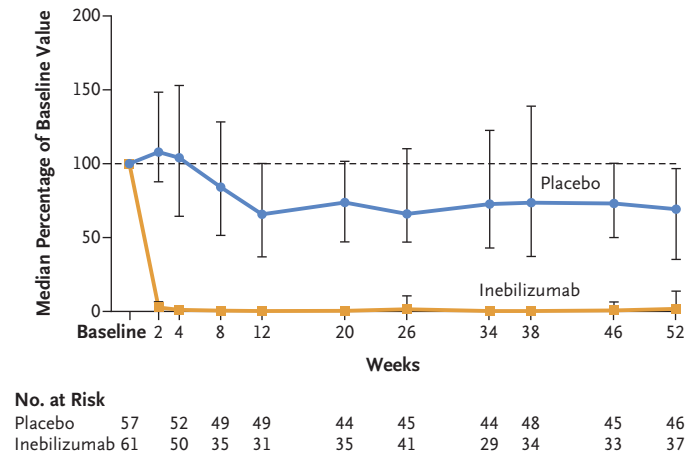

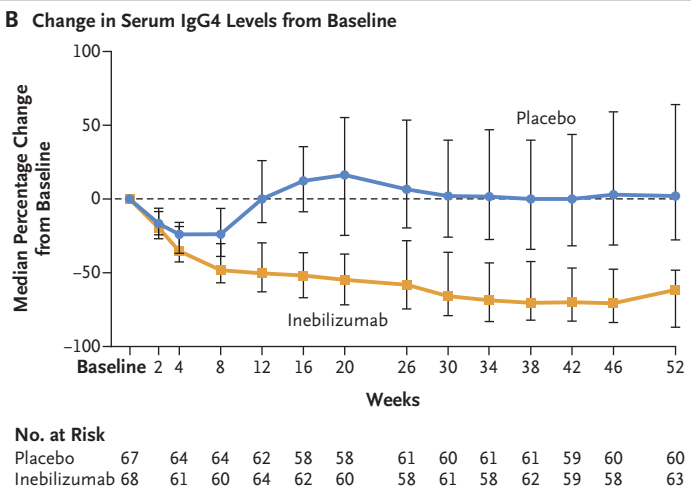

Figure 2. CD20+ B-Cell and IgG4 Levels over Time during the Treatment Period (Full Analysis Population).

CD20+ B-cell counts were the primary pharmacodynamic assay owing to potential CD19+ assay interference by inebilizumab. Dashed lines indicate levels at baseline, and I bars represent the interquartile range.

similar in the two groups — 66 participants (97%) in the inebilizumab group and 66 participants (98%) in the placebo group. Adverse events of grade 3 or higher occurred in 12 participants (18%) in the inebilizumab group and 8 participants (12%) in the placebo group, and serious adverse events occurred in 12 participants (18%) and 6 participants (9%), respectively. No serious adverse event occurred in more than one participant (Table S7). No deaths were reported.

Adverse events led to withdrawal from the trial by 6 participants (9%) in the inebilizumab group and 3 participants (4%) in the placebo group. Infusion-related reactions were reported in 3 participants (4%) and 5 participants (7%), respectively. A single serious adverse event involving anaphylaxis occurred in a participant in the inebilizumab group who did not receive full protocol-specified preinfusion medication. Inebilizumab treatment was withdrawn and the participant recovered, with no resumption of inebilizumab. Adverse events that occurred in more than 10% of participants in the inebilizumab group were coronavirus disease 2019 in 16 participants (24%), lymphopenia in 11 (16%), and urinary tract infection in 8 (12%). Lymphopenia was the most common adverse event of special interest observed in both groups (Table 3).

DISCUSSION

The MITIGATE trial showed the efficacy of CD19-targeted B-cell depletion by inebilizumab for the treatment of IgG4-related disease. Inebilizumab reduced the risk of disease flares and the annualized flare rate relative to placebo over the 52-week treatment period. More participants who received inebilizumab had treatment-free and glucocorticoid-free complete remission than did participants who received placebo. Participants who received inebilizumab required lower cumulative glucocorticoid exposure to induce remission and maintain disease control during the treatment period than participants who received placebo. The incidence of adverse events was similar in the two groups, although there was a higher incidence of adverse events of grade 3 or higher, serious adverse events, adverse events of special interest, and adverse events that led to discontinuation of the trial regimen in the inebilizumab group than in the placebo group.

Disease flares were chosen as the basis for the primary end point owing to their effect on the health and well-being of patients.[4,7,9,10,34] IgG4-related disease flares represent periods of inflammation and fibrosis in affected organs that, if unchecked, can lead to permanent damage and disability.[4,9] Reduction of flare risk and maintenance of a quiescent disease state without glucocorticoids are the principal goals in the management of IgG4-related disease.[14]

The trial design led to enrollment of a cohort of participants similar to the overall population

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of persons with IgG4-related disease, which supports the generalizability of the results. Our trial evaluated inebilizumab in the absence of other immunosuppressive medications for the treatment of IgG4-related disease; therefore, effects can be directly attributable to inebilizumab alone. Although the glucocorticoid taper in both groups was appropriate to ensure that participants in the placebo group received treatment that was aligned with standard care, the trial results suggest the potential for the use of inebilizumab as a standalone therapy for remission maintenance in IgG4-related disease.

Our trial has certain limitations. First, a single trial of modest size may not accurately predict the safety or efficacy of inebilizumab when administered to a much larger number of patients. However, the safety data complement and add to the safety profile of inebilizumab use in the treatment of other conditions.[27-30] Second, the number of participants with previous IgG4-related disease treatment as reported by investigators was low, although there is no reason to suspect an effect of previous medications on the safety and efficacy outcomes reported. Third, although the median disease duration in the trial population overall was relatively short, the median duration was 3.6 years among the 54% of participants with recurrent disease at baseline, and it appeared that participants with recurrent disease and those with newly diagnosed disease derived similar clinical benefits. Fourth, although randomization resulted in some imbalances between the groups with regard to certain baseline characteristics, these imbalances did not appear to affect the overall trial results. Fifth, the inclusion criterion of a history of involvement of at least two organs may have excluded some patients with single-organ disease. However, numerous large-cohort studies have shown that multiorgan disease is the rule, with median organ involvement ranging from two to four or more.[33,35]

A trial of 52 weeks is not sufficient to fully understand the long-term risks and benefits of inebilizumab as treatment in IgG4-related disease. Long-term CD20 B-cell depletion has resulted in an increased incidence of infection,[1,36-38] a concern that could be shared by CD19 B-cell depletion. The incidence of infection in a trial involving participants with neuromyelitis optica spectrum disorder was similar in the inebilizumab and placebo

Table 3. Common Adverse Events Occurring during Treatment Period and Adverse Events of Special Interest (Safety Analysis Population).*

Event	Inebilizumab (N=68)	Placebo (N=67)
	no. of participants (%)	
Event occurring during treatment period†		
Covid-19	16 (24)	13 (19)
Lymphopenia	11 (16)	6 (9)
Urinary tract infection	8 (12)	4 (6)
Headache	6 (9)	7 (10)
Abdominal pain	4 (6)	7 (10)
Arthralgia	4 (6)	7 (10)
Upper respiratory tract infection	4 (6)	8 (12)
Diarrhea	3 (4)	9 (13)
Asthenia	2 (3)	8 (12)
Serious event occurring during treatment period	12 (18)	6 (9)
Event of special interest occurring in ≥1 participant	23 (34)	15 (22)
Cytopenia	17 (25)	9 (13)
Lymphopenia‡	13 (19)	6 (9)
Neutropenia	4 (6)	2 (3)
Anemia§	2 (3)	2 (3)
Cytopenia	1 (1)	0
Leukopenia	1 (1)	1 (1)
Thrombocytopenia¶	1 (1)	2 (3)
Serious or opportunistic infection	6 (9)	2 (3)
Herpes zoster‖	2 (3)	2 (3)
Appendicitis	1 (1)	0
Covid-19**	2 (3)	0
Diverticulitis	1 (1)	0
Infusion-related reaction	3 (4)	5 (7)
Anaphylaxis and serious hypersensitivity reactions	1 (1)	0
Anaphylactic reaction	1 (1)††	0

* The safety analysis population included all the participants who received any dose of inebilizumab or placebo during the treatment period. Covid-19 denotes coronavirus disease 2019.
† Shown are adverse events that occurred during the treatment period in at least 10% of participants in either group, listed according to the preferred term in the *Medical Dictionary for Regulatory Activities* (version 26.1).
‡ Lymphopenia includes decreased lymphocyte count.
§ Anemia includes iron-deficiency anemia.
¶ Thrombocytopenia includes decreased platelet count.
‖ Herpes zoster includes varicella zoster virus infection.
** Covid-19 includes Covid-19 pneumonia.
†† An anaphylactic reaction occurred in a participant who did not receive protocol-specified prophylactic premedication.

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groups during a 28-week treatment period (most infections in participants treated with inebilizumab were minor),[27] and the incidence of infection did not increase over a 4-year open-label period.[28] In our trial, more participants who received inebilizumab had infection-related adverse events than participants who received placebo. Longer-term data are needed to establish the safety profile of inebilizumab in the treatment of IgG4-related disease and to characterize the patterns of B-cell and immunoglobulin changes; for these reasons, a 3-year open-label period is ongoing.

The MITIGATE trial established the efficacy of CD19-targeted B-cell depletion with inebilizumab in the treatment of IgG4-related disease. The magnitude and consistency of the efficacy results suggest inebilizumab as a treatment option for patients with IgG4-related disease.

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