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STUDY PROTOCOL

Efficacy and Safety of Inebilizumab in IgG4-Related Disease: Protocol for a Randomized Controlled Trial

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ABSTRACT

Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a debilitating multiorgan disease characterized by recurring flares leading to organ dysfunction, decreased quality of life, and mortality. Glucocorticoids, the standard of care for IgG4-RD, are associated with substantial treatment-related toxicity. Inebilizumab, an antibody directed against CD19, mediates the rapid and durable depletion of $CD19^+$ B cells thought to be involved in IgG4-RD pathogenesis. We describe the first international, prospective, double-blind, placebo-controlled trial to evaluate the safety and efficacy of B-cell depletion for flare prevention in IgG4-RD (MITIGATE).

Methods: The study was designed by an international panel of physicians with expertise in IgG4-RD. Critical trial design decisions included the selection of participants, definition of clinically meaningful primary and secondary endpoints, accommodation of standard of care, and development of flare diagnostic criteria. The study is approved for conduct in 22 countries.

Planned Outcomes: The primary efficacy endpoint is time from randomization to the

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occurrence of the first centrally adjudicated and investigator-treated disease flare during the 1-year randomized controlled period. A set of novel, organ-specific flare diagnostic criteria were developed specifically for this trial, incorporating symptoms and signs, laboratory findings, imaging study results, and pathology data. MITIGATE aims to accrue 39 flares for the primary endpoint, which provides sufficient power to detect a relative risk reduction of 65% in the inebilizumab group. It is anticipated that enrollment of 160 participants will achieve this goal. Additional endpoints include safety, annualized flare rate, flare-free complete remission, quality-of-life measures, and cumulative glucocorticoid use. MITIGATE represents the first randomized, double-blind, placebo-controlled trial of any treatment strategy conducted in IgG4-RD. Data from this study will provide insights into the natural history and pathophysiology of IgG4-RD and the efficacy and safety of B-cell depletion as a therapeutic avenue.
Trial Registration: NCT04540497.

Keywords: Anti-CD19 monoclonal antibody; B-cell depletion; Clinical trial; IgG4-RD; IgG4-related disease; Inebilizumab; Trial design

Key Summary Points

Immunoglobulin G4-related disease (IgG4-RD) is a debilitating, multiorgan disease with few long-term treatment options, which have limited data supporting their efficacy and/or substantial toxicity.

Inebilizumab is a monoclonal antibody that depletes $CD19^+$ B cells, which are thought to be involved in IgG4-RD pathogenesis.

MITIGATE is the first randomized, double-blind, placebo-controlled trial for any treatment strategy in IgG4-RD.

This study seeks to investigate the safety and efficacy of B-cell depletion by inebilizumab in preventing IgG4-RD flares.

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INTRODUCTION

Background

Immunoglobulin G4-related disease (IgG4-RD) is a chronic, immune-mediated, fibrotic disease characterized by fibroinflammatory lesions in affected organs [1, 2]. The range of potential organ involvement is broad, but manifestations typically occur within approximately a dozen organs [3, 4]. These include the lacrimal glands, major salivary glands (submandibular, parotid), thyroid gland, lungs, aorta, liver, bile ducts, pancreas, kidneys, retroperitoneal tissues, meninges, and lymph nodes. Consistent histologic and immunologic findings within the affected organs include a prominent infiltrate of plasma cells and lymphocytes, fibrosis in a storiform pattern, luminal obliteration of venules, and disproportionate IgG class-switching to IgG4 [5, 6]. IgG4-RD is therefore a discrete, unique multiorgan disease that is likely mediated through autoimmune mechanisms including aberrant $CD19^+$ B-cell activity [1–3].

The disease is insidious, generally developing over a period of months to years and causing organ damage, dysfunction, and even death [7]. Disease exacerbations (flares) occur in a high percentage of patients either during taper or after discontinuation of the glucocorticoids (GCs) typically used as initial disease treatment. The medical consequences of flares include

increasing organ dysfunction, the potential need for medical procedures such as biliary stents, and the possibility of irreversible disease progression or death [8].

Glucocorticoids are widely used for the initial treatment of IgG4-RD [7–9], and experts in the field agree that GCs are efficacious for the induction of remission in active IgG4-RD [10–13]. Indeed, a lack of responsiveness to GCs calls into question the diagnosis of IgG4-RD and comprises an important exclusion criterion in the classification criteria for IgG4-RD developed by the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) [3].

Although nearly all patients with IgG4-RD respond to GCs, approximately 40% either fail to achieve complete remission or relapse within 1 year despite the use of maintenance prednisone [14–18]. Moreover, the potential for GC toxicity is increased in IgG4-RD because these patients are typically middle-aged or older and frequently have comorbidities such as hypertension, glucose intolerance, and obesity. The potential for GC-related toxicity is heightened further by the tendency of IgG4-RD to cause damage in both the endocrine and exocrine pancreas. The major deficits in glucose tolerance acquired by many patients with IgG4-RD are compounded substantially by GC treatment. Thus, there is a clear need for effective GC-sparing treatment options in IgG4-RD.

In contrast to the general agreement on the efficacy of GCs as remission induction therapy for IgG4-RD, there is no consensus about the optimal approach to remission maintenance with GC-sparing agents [19]. The literature supporting the use of traditional disease-modifying antirheumatic drugs (DMARDs) such as mycophenolate mofetil, azathioprine, tacrolimus, low-dose cyclophosphamide, methotrexate, and hydroxychloroquine is limited [17, 18, 20–23], and there have been no randomized, double-blind, placebo-controlled trials testing the efficacy of any agent purporting to be a "GC-sparing" drug.

Based on the involvement of B cells in disease processes, rituximab (a CD20-targeted B-cell–depleting agent) is often used to prevent flares in IgG4-RD. Unfortunately, efficacy data for CD20-mediated B-cell depletion in IgG4-RD are limited, consisting mainly of case series/reports and open-label studies [24–29]. In one prospective, open-label phase 2 study, 97% of patients experienced an improvement in disease activity with rituximab, but complete remission was observed in only 40% of patients at 12 months [24], underscoring an unmet need for better remission maintenance strategies for most patients.

The rationale for a B-cell depletion by a $CD19^+$ targeted approach in IgG4-RD is strong [29]. Clonal expansions of activated $CD19^+$ B-cell populations such as plasmablasts have been observed consistently in IgG4-RD [30, 31]. Plasmablasts correlate highly with disease activity in untreated patients [32, 33]. Though plasmablasts decline following treatment with the CD20-targeted agent rituximab, complete depletion does not occur [31, 32]. Moreover, the expansion of $CD19^+$ plasmablasts in patients treated with rituximab is associated with a recurrence of disease activity [31]. Although the precise mechanisms by which $CD19^+$ B cells contribute to pathogenesis remain unproven, they have been shown to secrete autoantibodies [34, 35], to express profibrotic molecules [36], and are suspected to act as potential antigen-presenting cells to $CD4^+$ T cells [37, 38].

Inebilizumab is a humanized, affinity-optimized monoclonal antibody (mAb) that binds to the B-cell–specific surface antigen CD19, resulting in $CD19^+$ B-cell depletion. In contrast to the anti-CD20 mAb rituximab, inebilizumab is afucosylated to efficiently eliminate B cells exclusively via antibody-dependent cellular cytotoxicity and antibody-mediated cellular phagocytosis mechanisms, without activating complement [39].

Inebilizumab has been studied in several autoimmune inflammatory disorders, including phase 1 trials in systemic sclerosis [40] and multiple sclerosis [41], and a phase 2/3 trial in neuromyelitis optica spectrum disorder (NMOSD) [42]. Inebilizumab is now approved for the treatment of NMOSD. Inebilizumab achieved rapid and durable peripheral $CD19^+$ B-cell depletion that was sustained with every 6-month dosing and has demonstrated an

acceptable safety profile in the diseases studied to date.

Objectives

Given the unmet medical need and the established role of $CD19^+$ B cells in the pathophysiology of IgG4-RD, we designed a clinical trial framework to evaluate the efficacy of inebilizumab in reducing the risk of disease relapse in patients with this disease. Hurdles to clinical trial design in IgG4-RD include establishing appropriate entry criteria, defining clinically meaningful primary and secondary endpoints, and aligning the study design with current IgG4-RD management practices globally. The primary endpoint for the MITIGATE trial—time to first IgG4-RD flare—presents challenges due to the clinical heterogeneity of the disease. Investigators must differentiate between manifestations of active IgG4-RD and damage related to disease or treatment. The lack of widely accepted diagnostic criteria for flares represents another challenge. We describe the design of the MITIGATE trial and discuss how each of these hurdles was addressed.

Trial Design

IgG4-RD poses two major challenges in the design of a randomized, placebo-controlled trial. First, there remains a limited understanding of the natural history of IgG4-RD, due to the relative rarity of the disease and the fact that it was only described in the last two decades as a distinct, unified condition. The lack of clear understanding of the flare rate (on and off treatment) and the risk factors for relapse complicate the selection of the target population and derivation of sample size estimates. There have been no previous randomized controlled trials conducted on this disease to help guide design choices.

Second, the protean characteristics of IgG4-RD mean that investigators must be capable of identifying, evaluating, and treating disease in multiple organs. IgG4-RD often affects organs beyond the usual focus of subspecialists. The characteristics of disease flares are heterogeneous, often differing from patient to patient. Assessing the efficacy of any treatment, therefore, requires monitoring and evaluating all potentially involved organs.

The MITIGATE trial represents a groundbreaking effort to determine the efficacy and safety of CD19-targeted B-cell depletion with inebilizumab in reducing the risk of flare in IgG4-RD. Novel elements of the trial design mitigate the numerous risks and gaps in our knowledge of IgG4-RD. The findings of this study may lead to a new therapeutic option for patients with IgG4-RD, for whom no maintenance therapy has yet been proven safe and effective in a randomized controlled trial.

METHODS

Study Design and Sample Selection

The trial design is summarized in Fig. 1. The study seeks to enroll participants aged 18 years and older with a diagnosis of IgG4-RD. To ensure the accuracy of the diagnosis, eligible participants must fulfill the 2019 ACR/EULAR Classification Criteria for IgG4-RD with a score of ≥ 20, a threshold at which the classification criteria have a specificity of 99% and a sensitivity of 86% [3]. Screening data are reviewed by a central Eligibility Committee comprised of IgG4-RD experts to determine the classification criteria score prior to enrollment. Eligible patients must have recently experienced a disease flare requiring GC treatment. Participants are randomized 1:1 to placebo or inebilizumab treatment and then begin a protocol-mandated prednisone taper designed to discontinue GC 8 weeks after the baseline infusion. Participants are followed for 1 year in the randomized controlled period (RCP). Participants who complete the RCP and otherwise remain eligible may also participate in an optional 3-year open-label period (OLP) during which all participants receive inebilizumab. A 2-year safety follow-up period for participants who discontinue the study drug will monitor safety, recovery of B cells, and other measures.

A study population at risk of flare during the trial is needed to ensure the accrual of a

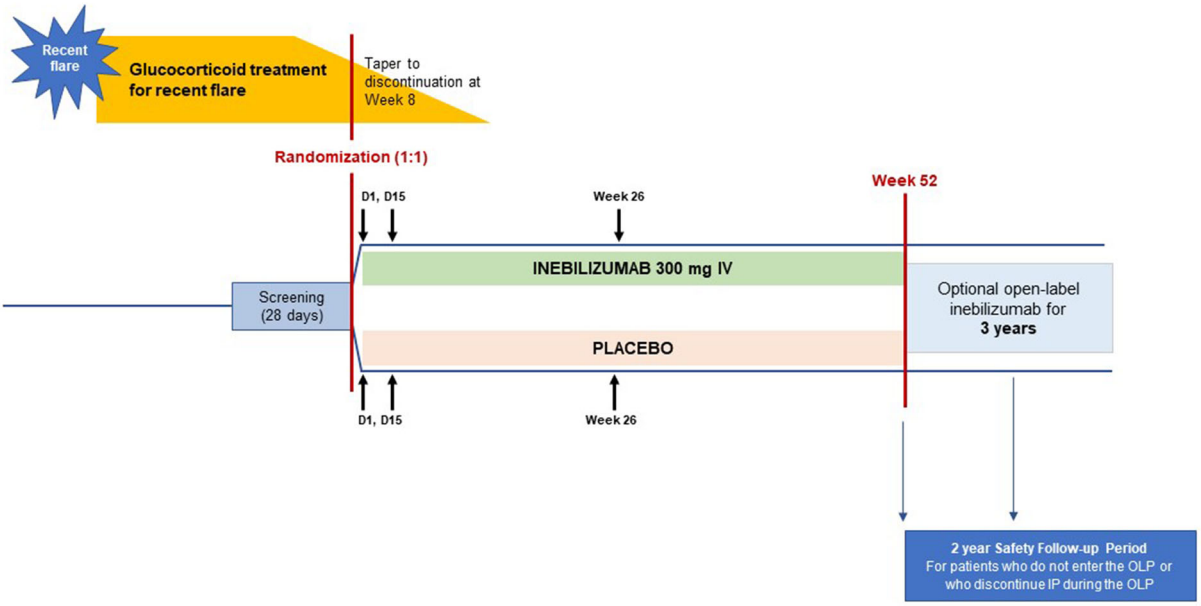

Fig. 1 MITIGATE study schema. *OLP* open-label period, *IP* investigational product

sufficient number of flares to achieve the goals of the study. Factors that predict relapse include multiorgan disease, serum IgG4 elevation at baseline, and the occurrence of previous flares [43–45]. Therefore, eligible participants must have a history of disease affecting ≥ 2 organ systems/sites and have experienced a recent flare in ≥ 1 organ or site. Many patients with IgG4-RD experience a disease flare when GC treatment is tapered or discontinued [23], so enrolling patients undergoing GC treatment at the time of enrollment—and tapering GCs to discontinuation during the trial—provides an opportunity to observe a period of heightened flare risk for the assessment of inebilizumab efficacy.

Eligible participants will have experienced an IgG4-RD flare prior to screening, and they must be undergoing GC treatment for this flare at the time of randomization. Typical treatment for flares, according to current treatment guidelines [23], consists of an induction period (1–2 weeks of 30 mg/day prednisone equivalent) followed by a gradual taper to discontinuation of steroids 3–6 months after initiation of therapy. In this study, eligible participants will have received 3–8 weeks of GC treatment for their recent flare at randomization. To establish a treatment baseline that allows a safe, uniform taper of GCs, participants must be on a dose of 20 mg/day prednisone equivalent the day prior to randomization. Once randomized, all participants begin a taper from 20 mg/day prednisone to discontinuation at 8 weeks following a regimen in which the dose is decreased by 5 mg/day every 2 weeks.

To ensure the safety of participants, investigators may institute GC treatment for disease activity (flares) during the trial at their discretion to control new or worsening IgG4-RD activity. Additionally, a carefully circumscribed amount of GC use is permitted for non-IgG4-RD indications (e.g., low-dose oral steroids for adrenal insufficiency, inhaled or topical steroids for allergic and respiratory conditions). Such quantities of GC are strictly limited to prevent any significant impact on the primary endpoint.

To assess the safety and efficacy of inebilizumab in IgG4-RD rigorously, the MITIGATE study is designed as a monotherapy trial. All maintenance therapy is discontinued prior to randomization into MITIGATE to avoid confounding effects on efficacy and safety. Nonbiological immunosuppressive agents (azathioprine, mycophenolate mofetil,

methotrexate, etc.) must be discontinued ≥ 4 weeks before screening. Rituximab and other B-cell–depleting agents must be discontinued ≥ 6 months before screening.

Participants are randomly assigned to one of two treatment groups (intravenous [IV] inebilizumab 300 mg or a matching IV placebo on day 1, on day 15, and at week 26) for the duration of the 1-year RCP of the trial. To account for potential differences in flare risk between newly diagnosed patients and those with recurrent disease, enrollment is stratified according to whether patients have newly diagnosed disease or have relapsing disease at screening. Stratification and randomization are performed via an interactive voice/web response system. All participants, in both the investigational treatment group and the placebo group, receive infusion reaction prophylaxis (100 mg of methylprednisolone, an antihistamine, and an antipyretic) prior to each infusion. During the RCP of the trial, neither the investigators nor the sponsor receives central laboratory measurements that have the potential to unblind treatment assignment. To provide long-term access to the study drug to participants and to collect additional safety data, eligible participants are offered the option to participate in a 3-year OLP in which all participants receive inebilizumab.

Measurements

Primary Outcome Measures

The primary endpoint for this study is time to disease flare, defined as the number of days from day 1 (dosing) to the date of the first flare in the RCP. An IgG4-RD flare is defined as new or worsening signs or symptoms of IgG4-RD activity that meet ≥ 1 of the organ-specific flare criteria. These criteria were developed specifically for this study and are described further below. Only those events that are positively adjudicated by the central Adjudication Committee (AC) and treated independently by the investigator will contribute to the primary endpoint. Although flares that do not require treatment occur, they have less clinical significance and do not contribute to the primary endpoint. IgG4-RD flares may develop gradually over time, and both patients and physicians are often challenged to identify the precise date of onset. Additionally, nonspecific symptoms are often the first clinically evident manifestations of important disease flares, such as those affecting the kidneys. Therefore, to assign an objective and accurate date to the timing of each flare for the primary analysis, we elected to use the date of initiation of flare treatment, which may be medical (e.g., GCs) or procedural (e.g., placement of a biliary stent).

Secondary and Exploratory Outcome Measures

The secondary endpoints of MITIGATE include the evaluation of the safety, tolerability, and immunogenicity of inebilizumab, and the assessment of other measures of disease activity to support the primary endpoint. The latter group includes annualized flare rate, GC use for disease control, and the proportion of participants achieving flare-free complete remission. Flare-free complete remission is defined as the absence of evident disease activity at week 52 (defined as an IgG4-RD Responder Index [46, 47] score of 0 or determination by the investigator that no disease activity is present on the basis of physical, laboratory, pathology, or other evidence), no AC-determined flare during the RCP of the trial, and no treatment for flare or disease control beyond the protocol-required prednisone taper.

Exploratory endpoints are intended to provide further insight into disease processes and the effects of treatment, specifically regarding drug effects on B cells, immunoglobulins, biomarkers related to IgG4-RD, gene expression, physician- and patient-reported health status, health-related quality of life, and disease-related health resource utilization.

Imaging

The protocol permits imaging to be performed for the assessment of potential disease flares or intercurrent occurrences as clinically appropriate. These studies are ordered at the discretion of the investigator, not at regular intervals written into the protocol.

Laboratory and Pathology Assessments

Serum IgG4 concentrations and all laboratory analyses performed in the context of this trial are performed at a central laboratory. All pathology assessments were conducted at the sites, without central review, with clinicopathologic correlation provided by the site investigators.

Ethics and Safety

The study protocol has been approved by health authorities in 22 countries around the world, and by institutional review boards at 80 sites (Supplementary Table S1). The study will be performed in line with the Helsinki Declaration and informed consent for participation will be received from all participants prior to the conduct of any study-related procedures.

The safe and ethical conduct of the study requires protection of participants from disease- and drug-related risks. Of particular concern are participants assigned to placebo and participants who experience multiple on-study flares despite study drug treatment. The risk of harm to patients in this placebo-controlled study is mitigated by the following measures:

- Investigators may institute flare treatment at their discretion, regardless of whether flare criteria have been met.
- Alternative maintenance therapy may be initiated if it is deemed by the investigator to be in the best interest of the participant, such as in the case of a participant experiencing multiple on-study flares, but requires discontinuation of investigational product.
- Monthly in-person study visits will be conducted, during which participants are evaluated for safety and disease activity.
- An independent Safety Data Monitoring Committee (SDMC) will be used to ensure participant safety and the ethical conduct of the study.

Data Collection and Analysis

Flare Diagnosis

Diagnosis of IgG4-RD flares is challenging due to the variety of organs involved and the diversity of manifestations. Disease flares may take the form of obstructive jaundice in a patient with IgG4-related autoimmune pancreatitis, rising biochemical abnormalities in a patient with IgG4-related cholangitis, proptosis in a patient with IgG4-related orbital disease, or extension of soft tissue inflammation evident on cross-sectional imaging in a patient with retroperitoneal fibrosis.

No widely accepted flare diagnostic criteria existed at the time of this study's design. Therefore, a set of 14 organ-specific flare criteria was developed for the trial to define events relevant to the primary endpoint. The flare criteria were developed with the input of a geographically diverse group of IgG4-RD expert physicians, representing the medical specialties that most often manage patients with IgG4-RD. The purpose of these criteria is to ensure the consistent and objective diagnosis of IgG4-RD flares by investigators around the world, recognizing that investigators likely have differing levels of familiarity with the diversity of disease manifestations. These criteria address the 13 organs most often affected by IgG4-RD and include one criterion suitable for all other organs affected less commonly. Representative data collection elements and flare criteria for the pancreas/common bile duct are shown in Fig. 2. Full flare criteria for all organs are presented in Supplementary Table S2.

Role of the Investigator

The investigator is responsible for recognizing, assessing, and treating IgG4-RD flares in enrolled participants (Fig. 3). If a participant's symptoms, physical examination, laboratory parameters, or other findings suggest that new or worsening disease activity may be occurring, the investigator will fully evaluate the participant by conducting appropriate assessments and reviewing all relevant data from the investigative site and any other facilities.

Assessments of potential disease flares are at the discretion of the investigator. To avoid conducting assessments that are not clinically warranted, there are no protocol-mandated flare assessment procedures. Furthermore, the protocol does not obligate the investigator to assess organs in which there is no suspicion of new or

worsening disease activity. Rather, the approach to flare assessment is determined by the investigator according to the patient's status, the investigator's clinical judgement, and the local standard of care.

Pancreas and Common Bile Duct
Symptom(s) or Finding(s)
Symptoms consistent with flare of pancreas/common bile duct
Pain (e.g., flank, back, abdominal), weight loss
Systemic/constitutional
Other (describe)
None
PE findings consistent with flare of pancreas/common bile duct
Abdominal tenderness, jaundice, palpable mass, weight loss
Other (describe)
None
Laboratory findings consistent with flare of pancreas/common bile duct
Elevated bilirubin, alk phos, GGT, amylase and/or lipase
Other, including low fecal elastase, high glucose/HbA1C (describe)
None
Imaging of pancreas/common bile duct
Consistent with pancreatic mass or diffuse pancreatic enlargement with loss of lobulations, diffuse pancreatic enlargement, pseudocapsule, pancreatic duct stricture, common bile duct abnormality
Other (describe)
None
Biopsy results consistent with flare of pancreas/common bile duct
Biopsy not done, unreadable, or report unavailable
Biopsy consistent with pancreatic/common bile duct flare
Biopsy not consistent with pancreatic/common bile duct flare
Criterion for Pancreatic Flare
Required to be present:
In a patient with a prior history of IgG4-related autoimmune pancreatitis EITHER:
New or worsening symptom and/or PE finding AND new or worsening laboratory finding consistent with flare in disease of pancreas/common bile duct OR
Imaging or endoscopic finding that confirms new or worsening involvement of pancreas/common bile duct
In a patient with no prior history of IgG4-related autoimmune pancreatitis:
New symptom, PE finding and/or laboratory finding consistent with involvement of the pancreas/common bile duct, AND EITHER
New imaging or endoscopic finding that confirms involvement of the pancreas/common bile duct, OR
Biopsy evidence of involvement of the pancreas
Required to be absent:
Alternative diagnosis or inconsistent biopsy findings

Investigator Conclusion—Pancreatic Flare

☐ Yes
☐ No

Why do you believe this patient is or is not having a pancreas/common bile duct disease flare?

Fig. 2 Data collection and diagnostic criteria for immunoglobulin G4-related disease (IgG4-RD) flare in the pancreas and common bile duct. *GGT* gamma-glutamyl transferase, *HbA1C* hemoglobin A1c, *PE* physical examination

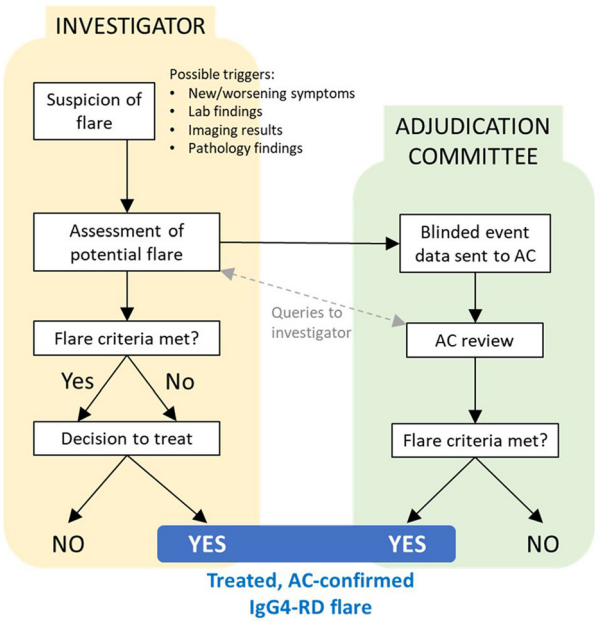

Fig. 3 Process for the identification, assessment, and adjudication of disease flares

Role of the Flare Adjudication Committee

To ensure uniformity in the application of the flare diagnostic criteria, an AC independent of the sponsor was created. This committee is composed of physicians with expertise in the care and treatment of patients with IgG4-RD. The committee members, trained on the study flare criteria, review all suspected flares evaluated by investigators during the trial (Fig. 3). The AC receives all data available to the investigator and operates independently. The AC is blinded to the treatment group of the participant experiencing the potential flare, the investigator's decision about whether or not to treat the event, and the participant's response to any treatment administered. Queries from the AC to the site are permitted to clarify or seek additional information. The AC determines, by majority vote, whether the event meets at least one of the organ-specific flare criteria.

Planned Outcomes

Sample Size and Power

MITIGATE is an event-driven trial. The enrollment target is based on estimates of the flare rate in the control arm and the treatment effect of inebilizumab. The sample size calculation, based on the desire to have 90% power, assumes a two-sided $\alpha = 0.05$, a 1:1 randomization ratio, and a log-rank test for comparing the two study groups. We anticipate that a total of 39 flares will be required to detect a relative reduction in the risk of flare by 65% during the RCP of the trial. Assuming the probability of having an AC-confirmed IgG4-RD flare during the RCP in the placebo group is 0.35 [17, 18, 48], a total of 160 participants (80 participants per treatment group) are expected to be enrolled.

To address uncertainty about the event rate in the study population, a blinded overall event-rate analysis will be conducted when the 50th participant completes the randomized portion of the trial. The sample size may be adjusted up to a maximum of 200 participants if needed to reach the target of 39 flares.

Strengths and Limitations

Challenges in Trial Design in IgG4-RD

MITIGATE is the first randomized, double-blind, placebo-controlled trial in IgG4-RD. The challenges addressed during the design of this trial include the selection of the target population, selection of the primary efficacy endpoint, and reconciliation of the needs of the study with current medical practices in this disease.

The development of a consistent approach to assessing disease flares posed a unique challenge, as no consensus definition of flare existed at the time the study was designed. A set of novel, organ-specific flare criteria was developed with input from expert specialists familiar with IgG4-RD from around the world. The use of strict flare criteria serves to minimize potential differences across individual investigators in the trial, whose familiarity with IgG4-RD and its varied manifestations may differ. Data collected by the investigators at times of potential flares, however, are reviewed by an independent, expert AC, ensuring uniformity in the interpretation of the data. Flare treatment is left entirely to the judgement of the treating investigator. Inclusion of only AC-determined, investigator-treated flares in the primary

endpoint ensures both uniformity in diagnosis and clinical significance of the events contributing to the primary outcome.

In the absence of any agent with clearly established efficacy in flare prevention for IgG4-RD, the trial was designed with a placebo control. Risks to patients are mitigated by allowing GC treatment for disease flares that occur during the trial, the ability to institute alternative maintenance therapy if needed, and review of emerging study data by the SDMC.

The eligibility criteria ensure the enrollment of a patient population with IgG4-RD by using the ACR/EULAR Classification Criteria [3]. Review of the classification criteria data and scoring for each patient is conducted by an independent Eligibility Committee before the patient is deemed eligible for the trial. To enrich for a study population at high risk for disease flares, the trial targets patients with a history of involvement of ≥ 2 organs, which is a strong risk factor for disease relapse [44, 45]. Additionally, eligible patients must have experienced a recent flare that requires GC treatment, as many patients experience a new flare when their GC treatment is tapered or discontinued [23].

Limitations and Uncertainties

There is considerable uncertainty about the sample size needed to achieve the 39 flares on which this event-based study is powered. Reviews of the literature guided sample-size calculations, but whether these published data are relevant to the patient population in this trial cannot be known with certainty beforehand. The preplanned blinded event-rate analysis is intended to attenuate this risk.

The use of novel endpoints also represents risk. In the absence of any precedent for such a study, a global panel of experts agreed that the MITIGATE primary endpoint—time to first flare—was meaningful and appropriate. Nevertheless, uncertainties remain about the treatment effect size, performance of the novel flare criteria, and regulatory acceptance of the selected endpoints.

There are no widely accepted definitions for remission or complete response in IgG4-RD. One of the MITGATE secondary endpoints, flare-free complete remission at 52 weeks, aims to capture complete response rate, but whether the definition used in this study is achievable and broadly relevant is not yet known.

It is possible that disease flares could be detected earlier in some cases if imaging were performed at some regular interval in the trial, e.g., every 6 months, regardless of whether patients had clinical evidence of active disease. We elected not to include regular, protocolized imaging for several reasons. First, there was concern about exposing patients to excessive ionizing radiation, as would be associated with the performance of computed tomography and other types of scans (e.g., positron emission tomography). Second, there is uncertainty about how extensive such protocolized imaging would need to be. In view of the radiation concerns, for example, if a patient has disease only involving the head and neck region at baseline, it seems imprudent and unnecessary to image the chest, abdomen, and pelvis in the absence of a clinical indication that there might be active disease in those regions. Finally, there is uncertainty about the interpretation of potentially equivocal findings on imaging.

Finally, there is uncertainty regarding the risk–benefit of long-term B-cell depletion in patients with IgG4-RD and how an agent such as inebilizumab would be incorporated into management practices. Some patients experience relatively benign disease manifestations, and some patients tolerate periodic treatment with GCs without serious adverse effects. Such patients may not require long-term maintenance therapy, and the risks of long-term B-cell depletion may not be appropriate in such cases. In many patients, however, the effects of organ dysfunction and damage can be life-threatening, and/or repeated courses of GCs for flare treatment are not acceptable. We envision that in these patients, long-term maintenance therapy with a B-cell-depleting agent at some interval might be an appropriate and acceptable strategy as it is in many other immune-mediated diseases.

ETHICS AND DISSEMINATION

The study protocol has been approved by health authorities in 22 countries around the world, and by institutional review boards at 80 sites (Supplementary Table S1). The study will be performed in line with the Helsinki Declaration and informed consent for participation will be received from all participants prior to the conduct of any study-related procedures. Trial results will be disseminated in the form of congress abstracts/presentations and peer-reviewed publication(s).

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Declarations

Conflict of Interest. Cory Perugino receives consulting fees from Horizon Therapeutics and funding from the National Institutes of Health (NIH/NIAMS K08AR079615). Emma L. Culver receives funding from the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) Oxford and receives consulting fees from Horizon Therapeutics. Arezou Khosroshahi has participated in advisory boards and served in a consulting role for Viela Bio, Horizon Therapeutics, and Sanofi, and has received grants from Pfizer unrelated to this manuscript. Wen Zhang received consulting fees from Horizon Therapeutics. Emanuel Della-Torre received consulting fees from Horizon Therapeutics. Kazuichi Okazaki has nothing to disclose. Yoshiya Tanaka has received speaking fees and/or honoraria from Behringer-Ingelheim, Eli Lilly, AbbVie, Gilead, AstraZeneca, Bristol-Myers, Chugai, Daiichi-Sankyo, Eisai, Pfizer, Mitsubishi-Tanabe, GlaxoSmithKline, received research grants from Asahi-Kasei, AbbVie, Chugai, Eisai, Takeda, Daiichi-Sankyo, Behringer-Ingelheim. Matthias Löhr has nothing to disclose. Nicolas Schleinitz has participated in advisory boards and received consulting fees from Viela Bio and Horizon Therapeutics. Judith Falloon is a former employee of Horizon Therapeutics and owns stock. Dewei She and Daniel Cimbora are employees of Horizon Therapeutics and own stock. John H. Stone has received consulting fees from Horizon Therapeutics, is the global Principal Investigator of the MITIGATE trial, and receives funding from the National Institutes of Health (NIH/NIAID UM1AI144295).

Ethical Approval. The study protocol has been approved by health authorities in 22 countries around the world, and by institutional review boards at 80 sites (Supplementary Table S1). The study will be performed in line with the Helsinki Declaration and informed consent for participation will be received from all participants prior to the conduct of any study-related procedures. Trial results will be disseminated in the form of congress abstracts/presentations and peer-reviewed publication(s).

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