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STUDY PROTOCOL

Efficacy and Safety of Obexelimab to Treat IgG4-Related Disease: Protocol for a Global, Randomized, Placebo-Controlled Trial

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ABSTRACT

Introduction: IgG4-related disease (IgG4-RD) is a chronic, multiorgan fibroinflammatory condition characterized by recurring flares that can lead to progressive organ damage and failure, impaired quality of life, and death. Glucocorticoids (GCs) remain the primary therapy despite their significant toxicity. Obexelimab is a humanized, bifunctional, monoclonal antibody designed to inhibit B cells by co-engaging CD19 and FcγRIIb (CD32b), mimicking natural inhibitory signaling triggered by antigen-antibody complexes. Following promising phase 2 results that demonstrated clinical improvement in 93% of patients with IgG4-RD, the phase 3 INDIGO trial was initiated.

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Methods: INDIGO is a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of obexelimab in patients with IgG4-RD. The trial has enrolled adult patients ≥ 18 years old with active IgG4-RD meeting the 2019 ACR/EULAR classification criteria (score ≥ 20). Following standardized GC induction, patients are randomized 1:1 to weekly subcutaneous obexelimab 250 mg or placebo for 52 weeks. An independent adjudication committee (AC) ensures consistent application of IgG4-RD classification and organ-specific flare criteria developed for the trial.
Planned Outcomes: The primary endpoint is time to first IgG4-RD flare requiring initiation of rescue therapy as determined by both the investigator and AC. Key secondary endpoints are time to first investigator-determined flare requiring rescue therapy, number of investigator- and AC-determined flares requiring rescue therapy, proportion of patients achieving complete remission, and cumulative dose of GC rescue therapy for active IgG4-RD through Week 52.
Conclusion: The INDIGO trial achieved its global enrollment goal with 194 patients, making it the largest phase 3 trial in IgG4-RD to date and providing 90% power to detect a clinically meaningful reduction in flare risk. This trial will provide critical evidence on B-cell inhibition as a treatment strategy for IgG4-RD and assess obexelimab as a potential steroid-sparing option to address significant unmet needs of this patient population.
Trial Registration: NCT05662241.

Keywords: B-cell inhibition; Clinical trial; IgG4-related disease; Obexelimab; Subcutaneous administration; Trial design

Key Summary Points

IgG4-related disease (IgG4-RD) is a chronic, multiorgan fibroinflammatory condition characterized by recurring flares that can lead to organ damage and impaired quality of life with limited long-term treatment options

Obexelimab is a bifunctional monoclonal antibody designed to inhibit B cells through co-engagement of CD19 and FcγRIIb

INDIGO is the largest phase 3 trial in IgG4-RD to date and the first to evaluate a subcutaneous formulation for this disease

This study seeks to evaluate the safety and efficacy of weekly obexelimab administration in reducing IgG4-RD flares

INTRODUCTION

Background

IgG4-related disease (IgG4-RD) is a rare, chronic, immune-mediated, fibroinflammatory disease. The histopathology of this condition is characterized by lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis that often leads to tumefactive mass formation mimicking malignancy [1, 2]. Any organ can be involved, with the pancreas, biliary tract, salivary and lacrimal glands, lymph nodes, retroperitoneum, aorta, kidneys, lungs, thyroid, and orbits among the most commonly affected sites [1–3]. IgG4-RD typically manifests as a multiorgan disorder, but a subset of patients presents with single-organ involvement at diagnosis [3–5]. Due to the often indolent progression of IgG4-RD, nearly 60% of patients present with irreversible organ damage [2, 6]. IgG4-RD predominantly affects male patients, with an estimated male-to-female ratio of 2:1 across global cohorts, and typically occurs in middle-aged to older adults [4, 7, 8].

Due to its recent recognition as a distinct disease and variable clinical presentation, the incidence and prevalence of IgG4-RD are likely

underestimated [4, 7]. In the US, prevalence estimates more than doubled between 2014 and 2019, increasing from 2.4 to 5.3 cases per 100,000 people [9]. The global epidemiology of IgG4-RD remains under investigation, with estimates likely to increase with growing awareness, especially since the disease was assigned an International Classification of Diseases (ICD) code in 2023 (ICD-10 code: D89.84).

IgG4-RD pathogenesis is driven by dysregulated B-cell activation and aberrant interactions with CD4+ and CD8+ cytotoxic T lymphocytes and T follicular helper cells, leading to tissue infiltration, class switching to IgG4, and progressive fibrosis [6, 10–12]. Expanded and activated B-cell populations (particularly circulating plasmablasts) correlate with disease activity and treatment response [13, 14]. Pathogenic interactions between B cells and T cells within lesions promote inflammation and fibrosis through interferon-γ, granzymes B and K, perforin, and other mediators [6, 10]. T follicular helper cells, particularly Tfh2, drive IgG4 class switching via IL-4 and IL-21 [11, 12]. Despite these advances, key questions remain, including the identification of disease-associated autoantigens and the precise role of IgG4 antibodies [6].

IgG4-RD is associated with significant morbidity and healthcare burden. Common comorbidities include hypertension (63% of patients), diabetes mellitus (33%), and coronary artery disease (16%), along with higher risks of malignancy (particularly lymphoma) and exocrine pancreatic dysfunction [2, 9, 15]. IgG4-RD also has a strong association with a history of allergy and/or atopy [16]. Mortality among those with the condition is approximately 2.5-fold higher than in the general population [9]. In a recent US claims analysis, over a 3-year period, patients with IgG4-RD were hospitalized twice as often and incurred substantially higher healthcare costs across all categories, including hospitalizations, emergency, outpatient, and pharmacy, compared with matched controls without IgG4-RD [17]. Moreover, nearly 90% of patients with IgG4-RD report symptom-related distress and impaired quality of life (QoL) [9].

Glucocorticoids (GCs) are the standard first-line therapy for IgG4-RD, producing rapid improvement in > 90% of patients [2, 18]. However, the use of GCs in IgG4-RD is highly problematic given the typical age and comorbidity profile of patients, as well as disease- and treatment-related morbidities. Such events may include hyperglycemia, infections, insomnia, and mood disturbance and, in the longer term, osteoporosis and cardiovascular disease [19]. Unfortunately, GCs are not curative in IgG4-RD, and dose reduction or discontinuation to alleviate side effects typically leads to relapse [2, 20–22]. Conventional disease-modifying antirheumatic drugs may help reduce relapses when combined with GCs, although high-quality evidence supporting their use as monotherapy in this disease is lacking [2, 8]. Rituximab, an anti-CD20 B-cell depleting antibody, achieves disease control in > 90% of patients, but relapse following a single course is common, and sustained B-cell depletion caused by maintenance dosing increases the risk of side effects such as infections, a heightened risk of poor COVID-19 outcomes, impaired vaccine responses, and hypogammaglobulinemia [21–27].

In April 2025, inebilizumab, a CD19-directed monoclonal antibody inducing depletion of B cells (including plasmablasts) became the first US Food and Drug Administration-approved therapy for patients with IgG4-RD. In the pivotal phase 3 trial known as MITIGATE, patients receiving inebilizumab had an 87% lower risk of flares and were more than twice as likely to achieve complete, GC-free remission at 1 year compared with placebo [28]. However, inebilizumab shares the safety profile of B-cell-depleting therapies, including a higher rate of infections, such as serious or opportunistic infections, lymphopenia, and neutropenia compared to placebo [28–31].

Obexelimab is a humanized, bifunctional monoclonal antibody designed to inhibit B cells through co-engagement of CD19 and FcγRIIb (also known as CD32b) [32–34]. These receptors are expressed across the B-cell lineage, including in pro-B cells, pre-B cells, naïve B cells, memory B cells, plasmablasts, and some plasma cells [35–37]. By co-engaging CD19 and FcγRIIb, the action of obexelimab mimics the natural inhibitory signaling triggered by immune complexes. Co-engagement of these targets leads to phosphorylation of

the immunoreceptor tyrosine-based inhibitory motif domain in FcγRIIb and initiates a downstream inhibitory signaling cascade [34]. This results in broad inhibition of both B-cell receptor-dependent and receptor-independent activity, including cell proliferation and differentiation, cytokine secretion, antibody production, and antigen presentation [32, 34, 38, 39]. In contrast to anti-CD20 and anti-CD19 B-cell-depleting therapies, data suggest that obexelimab does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Clinical evidence suggests obexelimab treatment reduces circulating B cells by about 50% within 2 days, followed by rapid recovery after treatment is stopped [36, 37]. Given the central role of CD19+ B cells in IgG4-RD and the clonal expansion of plasmablasts observed in active disease, the unique mechanism of action of obexelimab makes it a rational therapeutic approach [13, 14]. Moreover, considering the role of B cells in vaccine response, characterizing vaccine-induced immunity in patients receiving obexelimab is an important clinical research objective.

Obexelimab was investigated in a phase 2, open-label pilot study in which 15 patients with IgG4-RD received 5 mg/kg intravenous (IV) obexelimab every 2 weeks for 24 weeks. All but one responded, with 12 patients achieving the primary endpoint of a ≥ 2 point reduction in the IgG4-RD responder index (RI) at Day 169. Eight patients also achieved complete remission, defined as an RI score of 0 on Day 169 with no GCs after Day 57 and no flares [36]. Treatment reduced circulating B cells with no evidence of apoptosis, and most patients showed about 75% recovery of B cells within 42 days of the final dose. Results of this study and others in healthy volunteers and patients with systemic lupus erythematosus and rheumatoid arthritis suggest the obexelimab IV formulation was well tolerated with the most common adverse reaction being mild gastrointestinal infusion-related reactions [33, 40]. A subcutaneous (SC) formulation is now available that has demonstrated sustained therapeutic exposure through favorable pharmacokinetics (PK) and bioavailability [37], allowing self-administration.

Objectives

To address the significant unmet need for effective, steroid-sparing therapies in IgG4-RD, we initiated INDIGO (NCT05662241), a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of obexelimab in a large, global IgG4-RD patient population. The primary objective of the randomized controlled period (RCP) is to evaluate the effect of weekly SC obexelimab on the rate of flares in patients with active IgG4-RD after an initial course of GC therapy. A total of 194 patients from 15 countries have been enrolled in the RCP, making this the largest clinical trial in IgG4-RD to date. The open-label extension (OLE) will evaluate the safety and tolerability of weekly, open-label SC obexelimab, as well as its effects on IgG4-RD flare and other measures of disease activity. The OLE will also characterize the immune response to vaccines in a subset of patients treated with obexelimab. Here, we present the study design and methods, including procedures and endpoints intended to maximize objectivity and generalizability to the global IgG4-RD patient population.

METHODS

Study Design

The overall design of the INDIGO study consists of a 28-day screening period followed by a 52-week RCP, an optional 3-year OLE, and a 12-week follow-up (Fig. 1). The OLE includes a vaccine substudy that will be conducted in a subset of eligible patients. The maximum duration of the trial for any individual patient is 224 weeks (approximately 4 years and 3 months).

Following the screening period, eligible patients are stratified by the number of affected organs (1 vs >1) and disease status (newly diagnosed vs relapsing). They are then randomized 1:1 to receive weekly SC obexelimab 250 mg or a matching placebo, administered as two injections of 1.0 ml each, for 52 weeks. Obexelimab

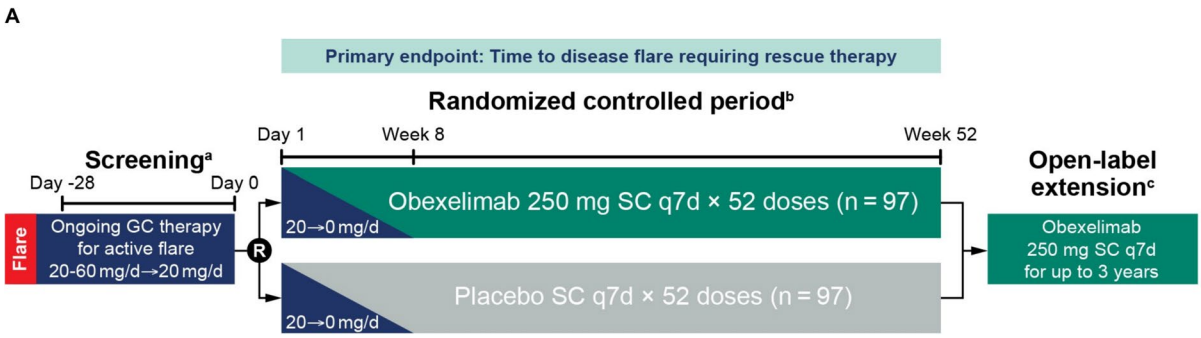

Fig. 1 INDIGO study design. The overall study design includes a screening period of at least 28 days, a 52-week randomized controlled period, and an open-label extension of up to 3 years. *GC* glucocorticoids, *q7d* every 7 days, *R* randomization, *SC* subcutaneous. [a]All patients receive 3–6 weeks of GC treatment (20–60 mg/day prednisone equivalent) initiated up to 2 weeks before the beginning of the 28-day screening period. GCs are then tapered (if needed) during screening to 20 mg/day by Day 1, followed by a standardized taper to discontinuation by Week 8. [b]During the randomized controlled period, patients attend monthly clinic visits for assessments and study treatment administration. Remaining weekly doses are self-administered or given by designated caregivers/home healthcare providers, unless patients opt for clinic administration. Patient numbers are estimates based on a total enrollment of 194 with allocation remaining blinded until completion of the controlled period. [c]Patients who complete the randomized controlled period but do not join the open-label extension are to attend a follow-up visit at Week 60 (8 weeks after Week 52). Patients who complete the extension are to attend a follow-up visit at Week 168 (12 weeks after Week 156)

dose was based on PK modeling, bioavailability of the SC formulation determined in healthy volunteers, and exposure achieved with the 5 mg/kg IV dose in phase 2 [36, 37]. On Day 1, the first dose is administered at the clinic, followed by an observation period of at least 1 h before discharge. Patients have the choice to return on Day 8 or 15 for early assessments; then, they are required to return monthly for the remainder of the RCP through Week 52. In-clinic doses are administered under supervision, while interim doses are self-administered or given by a caregiver or home health provider; however, patients can opt for in-clinic administration. Day 1 also marks the initiation of a standardized GC taper from 20 mg/day to discontinuation at Week 8, using 5-mg reductions every 2 weeks per consensus guidelines [18].

Patients completing the 52-week RCP are eligible to enter the OLE. Patients who discontinued study treatment early during the RCP are eligible, provided discontinuation was not safety-related and they are able to receive the first dose within 14 days of the last RCP visit. The first OLE dose is administered at the clinic followed by an observation period of at least 1 h, with subsequent treatments between clinic visits administered at home. During the OLE, clinic visits occur monthly in Year 1 and then every 4–5 months in Years 2 and 3. This phase of the trial includes a vaccine substudy to be performed on a subset of study patients. Patients will receive one or two selected non-live vaccines, and serial blood samples will be collected before and after vaccinations at predefined intervals to assess the immune response to vaccines in patients receiving obexelimab.

Sample Selection

A sample size of approximately 200 patients randomized 1:1 was calculated to provide 90% power (one-sided alpha of 0.025) to detect a clinically meaningful reduction in flare risk with obexelimab compared to placebo. A total of 194 patients were ultimately enrolled.

Eligibility for INDIGO was assessed based on comprehensive inclusion and exclusion criteria provided in Supplement 1. Briefly, eligible

patients must be at least 18 years of age, have a clinical diagnosis of IgG4-RD with one or more involved organ, and meet the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for IgG4-RD [4] with a score of ≥ 20. These criteria, developed for standardizing patient selection in IgG4-RD clinical trials, were validated by a panel of 86 international IgG4-RD experts and demonstrated excellent specificity (≥ 97.8%) and sensitivity (≥ 82.0%) [4, 7]. An independent, blinded adjudication committee (AC) of international IgG4-RD experts determines whether ACR/EULAR criteria are fulfilled. Eligible patients are also required to have active signs and symptoms of IgG4-RD (i.e., flare) at screening that require initiation of GC treatment or a dosage increase if already on a stable regimen of ≤ 10 mg/day prednisone equivalent. To maintain eligibility, patients must initiate and continue the new/increased GC regimen at a dose of 20–60 mg/day prednisone equivalent for 3–6 weeks, then taper (if needed) to 20 mg/day with no disease activity at the time of randomization. Exclusion criteria include active infection, GC treatment of > 60 mg/day prednisone equivalent within 4 weeks of screening, B-cell-depleting therapy, or other immunomodulatory biologic agents within 6 months of randomization, and any conditions considered exclusionary in the ACR/EULAR classification criteria.

Measurements and Planned Outcomes

Endpoints

Efficacy endpoints in INDIGO are primarily based on IgG4-RD flares. Flares are defined as the reappearance of previous symptoms or signs of IgG4-RD or the appearance of new symptoms or signs attributed to IgG4-RD. Comprehensive flare criteria developed specifically for this trial are described below and summarized in Supplement 2. The primary efficacy endpoint is the time from randomization to the first IgG4-RD flare requiring initiation of rescue therapy, as determined by both the investigator and the AC, up to Week 52. Importantly, untreated flares meeting these criteria may still meet the endpoint if there is agreement between the investigator and AC that rescue therapy is required (e.g., if a patient declines treatment for the flare). Key secondary endpoints are time to first investigator-determined IgG4-RD flare requiring initiation of rescue therapy, the number of investigator- and AC-determined flares requiring initiation of rescue therapy, the proportion of patients achieving complete remission (no AC-determined flare, no treatment for flare, and an IgG4-RD RI score of 0 or no clinical evidence of active disease based on a Physician's Global Assessment visual analog scale score of 0 mm), and cumulative dose of GC rescue therapy for IgG4-RD through Week 52.

Additional secondary and exploratory endpoints include the number of investigator- and AC-determined IgG4-RD flares (regardless of need for rescue therapy), IgG4-RD RI score, and global disease and QoL assessments (detailed below), all at Week 52. The clinical impact of GC utilization is also evaluated using changes in score of the GC toxicity index (GTI), a physician-reported measure of GC-related toxicity based on body mass index, glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection [41].

In the OLE, efficacy endpoints consist of time to first investigator- and AC-determined IgG4-RD flare requiring initiation of rescue therapy, time to first investigator-determined flare requiring initiation of rescue therapy, number of investigator- and AC-determined flares, cumulative dose of GC rescue therapy, and change in GC-related toxicity per GTI. Outcomes in the vaccine substudy conducted during the OLE will include measures of vaccine-specific antibody responses over time, along with assessments of the safety of vaccination.

Safety assessments in both the RCP and OLE encompass adverse events (AEs), serious AEs, and AEs of special interest (AESI) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. AESIs consist of malignancies, Grade ≥ 2 injection site reactions, Grade ≥ 2 hypersensitivity, and Grade ≥ 3 infections, including opportunistic infections. Vital signs, electrocardiograms,

and laboratory testing are also performed at scheduled intervals.

Data Collection

Flare Assessment and Adjudication

To ensure consistency and objectivity in efficacy assessments, comprehensive criteria for determining IgG4-RD flares, including subclinical/asymptomatic activity, were developed for the trial by an international panel of experts and are summarized in Supplement 2. Organ-specific criteria for commonly affected organs were based on patient-reported symptoms, physical examinations, and laboratory and/or imaging assessments, as appropriate, to detect flares. The evidence required to define a flare varies by organ and by whether there was previous involvement of that organ at baseline in the disease. For example, physical examination alone can be used to assess salivary glands, laboratory changes, and/or imaging are required for kidney flares, and imaging is required for flares in the aorta or lung. General criteria applicable to other organs are also included. Investigators are blinded to the serum IgG4 level, which is not included among any organ-specific flare criteria.

Investigators assess patients for a possible flare at each in-clinic visit. When a flare is suspected (Fig. 2), organ-specific assessments are performed as needed to confirm flare activity and exclude alternative diagnoses. All investigator flare assessments are periodically reviewed by the AC for independent, blinded determination of whether the protocol-specific flare criteria were met (based on majority vote). If confirmed, the AC then determines whether rescue therapy was warranted. Periodic (not real-time) AC flare adjudication ensures standardized, objective assessment while maintaining the investigator's autonomy in clinical decision making, including initiation of rescue therapy.

Imaging

In addition to investigating suspected flares, imaging is performed at prespecified time points to radiographically assess and objectively document disease activity. This includes chest, abdomen, and pelvic imaging at screening, at the end of the RCP (Week 52 or early termination visit), and at OLE Weeks 52, 104, and 156 (or early termination). Additional imaging may be performed at the investigator's discretion. Computed tomography or magnetic resonance imaging may be used, but the chosen modality should be maintained for each patient throughout the study.

Disease Activity and Patient-Reported Outcomes

INDIGO incorporates both patient- and physician-reported outcomes to capture the range of patient experience when living with IgG4-RD and receiving treatment with obexelimab. The main disease activity assessment is the IgG4-RD RI, a validated index developed to quantify disease activity and damage in IgG4-RD that uses a scoring system (0–3) rated by the physician for each organ, providing standardized measurements over time [42, 43]. Disease activity is assessed by the physician and the patient using Global Assessment of Disease Activity 100-mm visual analog scales, where the left-hand extreme of the line is considered "very good" (i.e., symptom-free and no IgG4-RD symptoms) and the right-hand extreme "very bad" (i.e., maximum IgG4-RD activity). QoL is measured with the generic scales (Short Form Health Survey – 36 Item [SF-36] and EuroQol, 5-dimension, 5-level [EQ-5D-5L]) and the recently validated, disease-specific IgG4-RD Symptom Severity Index (SSI). The SSI captures the frequency and distress associated with 24 common symptoms across eight organ systems over the preceding 30 days and also includes an open-ended component where patients can identify their three most bothersome, severe, or important symptoms [44]. The symptom frequency and distress scores from these components are calculated to generate a total burden score.

Pharmacokinetics, Pharmacodynamics, and Biomarker Assessments

INDIGO includes pharmacokinetic (PK), pharmacodynamic (PD), and biomarker assessments

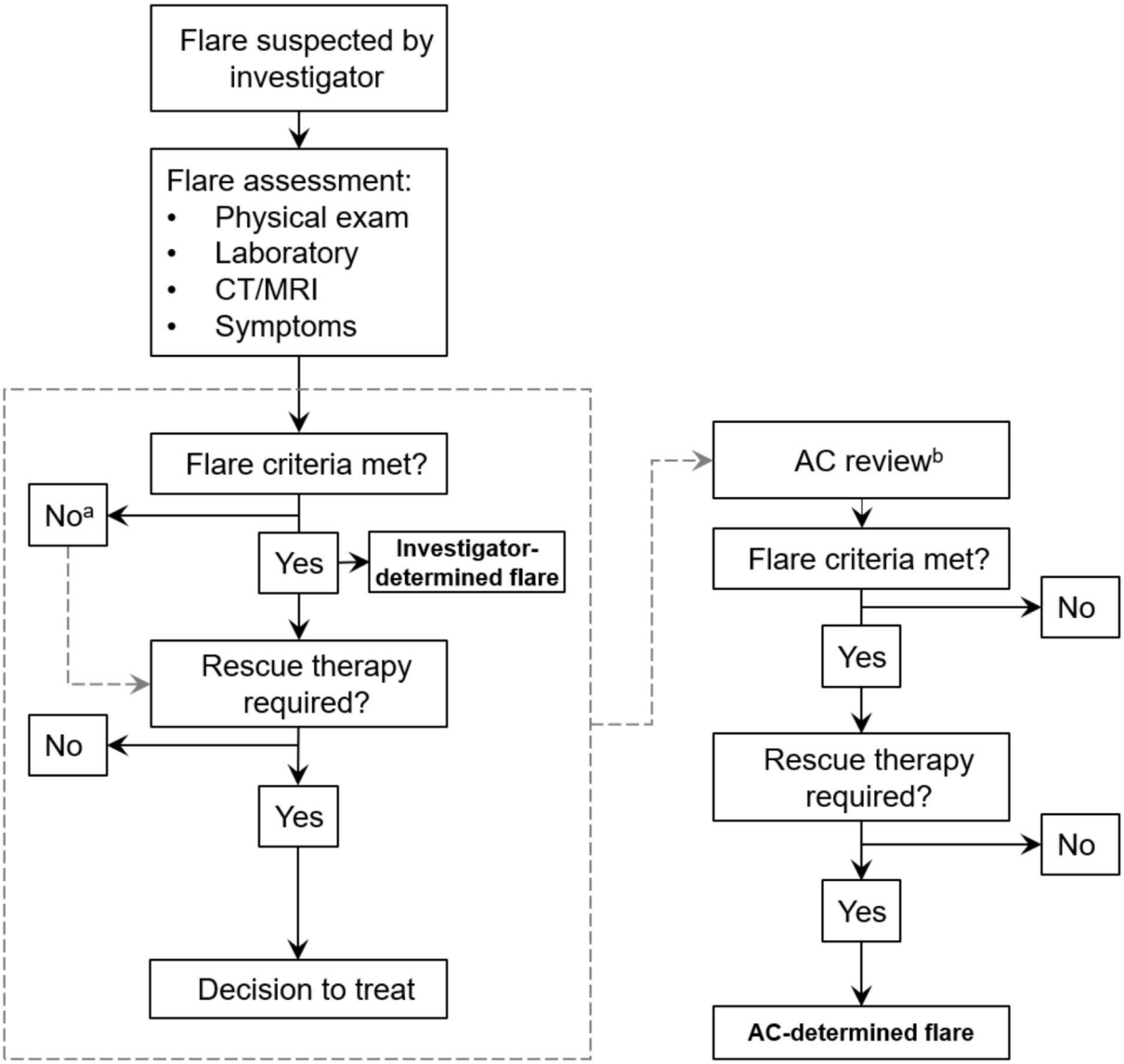

Fig. 2 Flow diagram of the flare determination and adjudication process by the investigator and blinded adjudication committee. *AC* adjudication committee, *CT* computed tomography, *MRI* magnetic resonance imaging. [a]The investigator may make the clinical decision to initiate rescue therapy even if flare criteria are not met. [b]AC review occurs retrospectively and includes all assessment data, treatment decision, and patient response to therapy when applicable but excludes the investigator's decision on whether a flare has occurred

to further characterize the mechanism of action and biological activity of weekly SC obexelimab. Serum samples collected throughout the RCP are used to generate the obexelimab PK profile and evaluate immunogenicity by detecting anti-obexelimab antibodies. PD effects are assessed by changes in circulating absolute T-, B-, and natural killer (NK)-cell counts; CD19 receptor occupancy; immunoglobulin levels and ratios; and enhanced liver fibrosis score through RCP Week 52. Biomarkers of pancreatic exocrine and endocrine function are also evaluated, including stool elastase and hemoglobin A1c. At European sites, the enhanced liver fibrosis score is used as a marker of systemic fibrosis.

DATA ANALYSIS

The primary endpoint, time to first investigator- and AC-determined IgG4-RD flare requiring rescue therapy, will be tested across treatments using a stratified log-rank test. Hazard ratios with 95% confidence intervals will be estimated using Cox proportional hazards models stratified by randomization factors. A hierarchical testing strategy is used to control Type I error across the primary efficacy analysis and four key secondary endpoints.

STRENGTHS AND LIMITATIONS

The INDIGO trial is the largest clinical trial in IgG4-RD conducted to date, designed to generate pivotal data supporting both regulatory approval for obexelimab and clinical practice guidance for this rare, chronic, and highly complex disease. Because IgG4-RD has a low prevalence and highly variable manifestations, careful trial design was essential to ensure enrollment of a representative study population and to achieve clinically meaningful outcomes. As a recently defined clinicopathological entity, validated disease-specific endpoints and prior benchmarks for phase 3 trial design are limited. To date, only one phase 3 trial in IgG4-RD (MITIGATE) has been published, which led to the recent approval of inebilizumab [28], and its open-label period remains ongoing. Despite recent advances, safe and effective treatment options remain an urgent unmet need for patients with IgG4-RD. Current therapeutic options, particularly GCs and rituximab, are limited by their safety and accessibility, underscoring the need for better long-term treatment options.

INDIGO was designed to produce rigorous, clinically meaningful results while prioritizing generalizability to reflect the real-world clinical needs of patients with IgG4-RD. The trial successfully enrolled 194 patients, providing sufficient statistical power for efficacy assessments. Global enrollment was required to achieve this sample size, which introduces additional complexities, such as local clinical practice norms and diagnostic approaches. To ensure diagnostic consistency across study sites, enrollment required meeting standardized criteria, including fulfillment of the 2019 ACR/EULAR classification criteria confirmed by an independent, blinded adjudication committee of global clinical experts on IgG4-RD.

Efficacy endpoints in INDIGO are anchored in rigorously defined flare criteria developed specifically for this trial by a panel of IgG4-RD experts. These criteria integrate clinical, laboratory, imaging, and pathology data as appropriate to detect both symptomatic and subclinical disease activity across commonly and less commonly affected organs. Organ-specific thresholds were optimized to maximize efficiency and/or sensitivity as appropriate. For instance, imaging alone is sufficient to identify pancreatic, lung, and pituitary flares, allowing detection even if a patient is asymptomatic.

The primary endpoint, time to the first flare requiring initiation of rescue therapy, was selected for its real-world clinical relevance. Measuring the need for rescue therapy, rather than its actual administration, avoids confounding by real-world factors such as patient preference or hesitation, logistical barriers, or physician discretion that could delay or prevent treatment initiation despite the need, thereby leading to underreporting of flares. Objectivity is further enhanced by adjudication, which requires both the investigator and AC to independently confirm that protocol-defined flare criteria were met and that rescue therapy was warranted.

The INDIGO trial incorporates a hybrid treatment administration model that combines clinic-supervised and at-home self-administration of study treatment. This approach leverages the favorable PK and safety profiles of the obexelimab SC formulation, allowing at-home dosing with potentially fewer adverse reactions than the IV formulation [33, 37]. At home self-administration generally offers patients greater flexibility and comfort, enhances treatment adherence, and expands treatment access while reducing dependence on infusion centers and likely saving costs of healthcare resource utilization [45–47].

Several other noteworthy aspects of the INDIGO study design have been included to maximize objectivity and real-world applicability of the findings. First, patients with a single affected organ were eligible for enrollment, as this cohort represents an estimated 25–40% of patients with IgG4-RD [2] and is thus a common presentation in routine clinical practice. However, including this cohort raises the theoretical concern that overall flare rates may be lower than in trials restricted to patients with multiorgan disease. To address this concern, randomization was stratified by number of affected organs (1 vs>1) to ensure balanced distribution across treatment arms and allow accurate comparison of treatment effects regardless of baseline flare risk. INDIGO also incorporated routine, protocol-mandated imaging to assess disease activity. In addition to imaging performed for suspected flares, all patients undergo imaging at screening, Week 52 of the RCP, and annually during the OLE. This approach enhances sensitivity and objectivity for efficacy endpoints and supports accurate scoring of the IgG4-RD RI for patients with internal organ involvement. The study also systematically evaluates GC utilization and toxicity, providing valuable insight into the steroid-sparing potential of obexelimab and helping address a critical unmet need in IgG4-RD management. The standardized 8-week steroid taper enables assessment of whether obexelimab monotherapy can maintain disease control while reducing GC exposure. The GTI will provide key information on GC-related toxicities over time. If the comorbidity risk from GCs can be mitigated, it could improve prognosis, positively influence disease management strategies, and enhance the overall health and QoL of patients with IgG4-RD [1, 2]. INDIGO is also the first IgG4-RD clinical trial investigating an SC formulation, which provides benefits for patients, including self-administration at the patient's convenience that does not require outpatient utilization.

Finally, this trial will expand understanding of B-cell-directed therapy in IgG4-RD by evaluating obexelimab, a novel B-cell inhibitor, as an alternative to B-cell depletion. Unlike B-cell-depleting therapies, obexelimab engages both CD19 and FcγRIIb to inhibit B-cell activation and function without inducing cytotoxicity [36, 48, 49]. Investigating obexelimab in a large, globally representative IgG4-RD patient population will provide comprehensive data on its efficacy, safety, and tolerability and on the overall benefit-risk profile of obexelimab, extending the previous findings obtained in early phase studies [33, 37, 40].

Overall, the INDIGO study is designed to generate pivotal data on the efficacy and safety of obexelimab in IgG4-RD, providing a comprehensive assessment of its overall benefit-risk profile. The study advances clinical research in this rare disease through global enrollment, expanded patient eligibility, and integration of systematic imaging and standardized, validated endpoint assessment tools. By incorporating patient-reported outcomes, INDIGO will deliver multidimensional insight into disease control and treatment impact. The hybrid treatment administration model in the study reflects the evolving standards of patient-centered care, emphasizing convenience and real-world applicability. Collectively, these features position INDIGO to define the therapeutic role of SC-administered obexelimab and establish a new treatment paradigm in the management of IgG4-RD.

ETHICS AND DISSEMINATION

The INDIGO study protocol has been approved by relevant health authorities and institutional review boards and was activated at 114 sites in Argentina, Canada, China, France, Germany, Hong Kong, Hungary, Italy, Japan, Mexico, The Netherlands, Poland, South Korea, Spain, Sweden, Taiwan, Turkey, the UK, and the US. The trial is conducted in accordance with consensus ethical principles derived from the Declaration of Helsinki and applicable International Council for Harmonisation-Good Clinical Practice (ICH GCP) guidelines. All patients provide written informed consent prior to any study procedures. An Independent Data Monitoring Committee provides oversight via periodic reviews of unblinded safety data during the RCP, and a Safety Review Committee monitors accumulating safety data throughout the OLE. Appropriate

permissions and licenses were obtained for all validated assessment instruments. Trial results will be disseminated as peer-reviewed publications and congress abstracts and presentations.

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Data Availability. Data sharing is not applicable to this article as no datasets have yet to be generated or analyzed at the time the manuscript was prepared.

Declarations

Conflict of Interest. Emma L. Culver has participated in advisory boards and consulting for Amgen, Zenas BioPharma, Sanofi, Acepodia, Ipsen, Mirum, GSK, Dr Falk Pharma, and Gilead, and receives research support from the NIHR Oxford Biomedical Research Centre. Matthew C. Baker has received fees from Amgen, Sanofi, Zenas BioPharma, argenx, Eli Lilly, Gilead, and Neurocrine. Emanuel Della-Torre has participated in advisory boards and consulting for Amgen, Zenas BioPharma, Sanofi, and Acepodia. Wen Zhang has participated in advisory boards and consulting for Amgen, Zenas BioPharma, Sanofi, and Acepodia. Cory A. Perugino has received consulting fees from Amgen, Sanofi, and Acepodia. Audrey Wells, Admasu Mamuye, Shauna M. Quinn, Allen Poma, and Thomas J. Greene are employees of Zenas BioPharma, Inc. and may hold stock or stock options in the company. John H. Stone has received grants from the National Institutes of Health (UM1 AI144295) and Q32Bio, serves as Chair of a Data and Safety Monitoring Board for Merck, and has received consulting fees from Amgen, Zenas, Sanofi, AcepodiaBio, Novartis, HingeBio, ZipBio, and Argenx.

Ethical Approval. The INDIGO study protocol has been approved by relevant health authorities and institutional review boards and was activated at 114 sites in Argentina, Canada, China, France, Germany, Hong Kong, Hungary, Italy, Japan, Mexico, Netherlands, Poland, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom, and United States. The trial is conducted in accordance with consensus ethical principles derived from the Declaration of Helsinki and applicable International Council for Harmonisation–Good Clinical Practice (ICH GCP) guidelines. All patients provide written informed consent prior to any study procedures.

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