

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

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Supplement 1: Eligibility Criteria

Randomized controlled period

Inclusion Criteria

To be eligible for the RCP, the following criteria apply:

1. Males and females, ≥ 18 years of age at the time of signing the informed consent, and who have reached the age of consent in the applicable region
2. Clinical diagnosis of IgG4-RD
3. Patients must meet the 2019 ACR/EULAR Classification Criteria for IgG4-RD with a score of ≥ 20
4. Patients must have active IgG4-RD signs/symptoms (i.e., flare) that require, as assessed by the investigator, the initiation of GC therapy or the increase in background long-term GC therapy (if previously on stable dose of ≤ 10 mg/day prednisone equivalent)
5. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
 - a. Not a woman of childbearing potential (WOCBP), OR
 - b. A WOCBP who agrees to follow the contraceptive guidance until at least 8 weeks after the last administration of study drug
 - c. Agrees to refrain from egg donation until at least 8 weeks after the last dose of study drug
6. A male patient must:
 - a. Agree to (i) abstain from intercourse, or (ii) use contraception until at least 8 weeks after the last dose of study drug, or (iii) be surgically sterile for the duration of the study, AND
 - b. Agree to refrain from donating sperm until at least 8 weeks after the last dose of study drug
7. A WOCBP must have a negative serum pregnancy test at screening and a negative urine test prior to the first dose of study drug
8. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in the protocol
9. Willing to comply with all study protocol procedures and complete all study visits
10. Total duration of GC treatment prior to randomization must be ≥ 3 weeks and a maximum of 6 weeks at a dose of 20 to 60 mg/day

Exclusion Criteria

Patients are excluded from the RCP if any of the following criteria apply:

1. Any exclusion criteria listed in the ACR/EULAR Classification Criteria for IgG4-RD

2. Has disease in only one organ system whose primary manifestation is fibrosis (i.e., retroperitoneum fibrosis without aortitis, Riedel's thyroiditis, fibrosing mediastinitis, sclerosing mesenteritis involvement, etc.)
3. Has received prednisone equivalent given orally at a dose greater than 60 mg/day within the 4 weeks prior to screening or during screening
4. Has received a non-biologic, disease-modifying anti-rheumatological drug or immunosuppressive agent other than GCs within the 2 weeks prior to screening
5. Has received an investigational treatment or direct medical intervention on another clinical study within 12 weeks or <5 half-lives of the investigational treatment, whichever is shorter, prior to screening
6. Has received live vaccine or live therapeutic infectious agent within the 2 weeks prior to screening
7. Acute hepatitis B infection (hepatitis B surface antigen-positive), active hepatitis C virus, or human immunodeficiency virus (HIV) infection. Patients will be excluded from the RCP if they have a positive test for active hepatitis B through detection of (a) hepatitis B surface antigen or (b) hepatitis B core antibody. In Japan, patients will be excluded if there is detection of (a) hepatitis B surface antigen, (b) hepatitis B surface antibody, or (c) hepatitis B core antibody. Note: In China only, patients who are hepatitis B surface antigen negative and hepatitis B core antibody positive and negative for hepatitis B DNA, without history of cirrhosis and treatment as directed in protocol Section 6.1.4, are not excluded.
8. Evidence of active tuberculosis (TB) or at high risk for TB, as shown by at least one of the following:
 - a. Documented history of active TB or latent TB, unless completion of treatment according to local guidelines
 - b. Positive, indeterminate, or invalid interferon-gamma release assay results at screening, unless treatment is documented. Patients with an indeterminate test result can repeat the test once either centrally or locally, but if the repeat test is also indeterminate, the patient is excluded
 - c. Signs of symptoms that could represent active TB
 - d. Chest radiograph, computed tomography (CT), or magnetic resonance imaging (MRI) that suggests possible diagnosis of TB
9. History or evidence of a clinically unstable/uncontrolled disorder, condition, or disease (including, but not limited to, cardiopulmonary, oncologic, renal, hepatic, metabolic, hematologic, psychiatric, active infection) other than IgG4-RD that, in the opinion of the investigator, would pose a risk to patient safety or interfere with study evaluation, procedures, or completion
10. Malignancy within 5 years (except successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin, breast cancer with no recurrence ≥ 5 years following therapy, or prostate cancer with no recurrence ≥ 3 years following prostatectomy)
11. Any known allergy to monoclonal antibody therapy
12. Hematology or clinical chemistry parameters that meet any of the following criteria at screening:

- a. White blood cell count $<2.5 \times 10^3/\mu\text{L}$
 - b. Absolute neutrophil count $<1.0 \times 10^3/\mu\text{L}$
 - c. Elevated serum creatinine $>2.5 \times$ upper limit of normal (ULN) OR estimated creatinine clearance <40 mL/min calculated by the Cockcroft-Gault formula at screening
 - d. Hemoglobin <10 g/dL
 - e. Platelet count $<75 \times 10^3/\mu\text{L}$
13. Abnormal liver function tests meeting any of the following criteria:
- a. In the absence of known IgG4-RD hepatobiliary activity:
 - i. Alanine aminotransferase (ALT) $>2 \times$ ULN
 - ii. Aspartate aminotransferase (AST) $>2 \times$ ULN
 - iii. Total bilirubin $>2 \times$ ULN
 - b. In the presence of known IgG4-RD hepatobiliary activity:
 - i. ALT $>10 \times$ ULN
 - ii. AST $>10 \times$ ULN
 - iii. Total bilirubin $>5 \times$ ULN
14. Has been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
15. Hypersensitivity to dextran or components of dextran or any component of the study drug and placebo, including excipients
16. Use of B-cell depleting, B-cell targeted, or other biologic immunomodulatory agents ≤ 6 months prior to randomization. Patients who received B-cell targeted therapy >6 and ≤ 12 months prior to randomization must have a B-cell count that is within the laboratory reference range at screening, as measured by the central laboratory
17. Continued active disease on the day of randomization, per the investigator

Eligibility Criteria: Open-Label Extension

Patients are eligible to be included in the OLE period only if all the following criteria apply:

1. Have remained on study and completed the Week 52 RCP visit
2. Have not had the investigational product discontinued due to the following safety reasons:
 - a. Grade ≥ 3 treatment-emergent AE that is considered related to obexelimab
 - b. Pregnancy
 - c. Malignancy
 - d. Hypersensitivity to IMP
 - e. Determination that the patient was ineligible for the RCP
 - f. For any reason deemed necessary by the investigator for patient safety
3. Have not discontinued from IMP due to unblinding of a patient

4. Have not received B-cell-depleting, B-cell targeted, or other biologic immunomodulatory agents (apart from obexelimab) within the 6 months prior to enrollment in the OLE period. Patients who received B-cell-targeted therapy prior to enrollment in the OLE must have a B-cell count that is within the laboratory reference range, as measured by the central laboratory
5. Must receive first dose of obexelimab in the OLE period within 14 days of the Week 52 RCP visit
6. Be willing to comply with all study protocol procedures and complete all study visits
7. WOCBP must have a negative urine pregnancy test pre-dose on OLE Day 1

Supplement 2: INDIGO IgG4-RD Flare Criteria

Definition of IgG4-RD Flare

An IgG4-RD flare is defined as the reappearance of previous signs/symptoms or appearance of new signs/symptoms of IgG4-RD that, in the opinion of the investigator and the adjudication committee, fulfill the organ-specific IgG4-RD flare criteria detailed below. An increase in serum IgG4 levels alone is not sufficient to fulfill flare criteria.

Organ-Specific Flare Criteria

For each organ system, the investigator assesses the presence of new or worsening symptoms, physical examination findings, laboratory abnormalities, imaging findings, and when applicable, biopsy results. A clear alternative diagnosis must be ruled out for all flares.

1. Pachymeninges

Required criteria (both must be present):

- New or worsening symptoms or physical examination findings consistent with pachymeningitis (e.g., headache, cranial nerve palsy, motor weakness, sensory deficit, vision problems, hearing loss, seizure, cognitive decline, constitutional symptoms)
- EITHER:
 - Cerebrospinal fluid (CSF) findings consistent with pachymeningitis (pleocytosis, increased protein), OR
 - Imaging showing meningeal enhancement or thickening

2. Pituitary Gland

Required criteria:

- New or worsening imaging findings showing pituitary mass or stalk thickening

Note: For new manifestations, biopsy may be considered based on accessibility and risk/benefit analysis

3. Orbits

Required criteria (at least one):

- New or worsening symptoms or physical examination findings consistent with orbital involvement (e.g., proptosis, diplopia, retrobulbar pain, blurred vision, visual field defects, extraocular movement abnormality)
- New or worsening orbital abnormality on imaging (enlargement of extraocular muscles, optic nerve, or trigeminal nerve; orbital mass)

4. Lacrimal Glands

Required criteria (at least one):

- New or worsening symptoms of lacrimal gland swelling or discomfort with physical examination findings of gland enlargement
- New or worsening lacrimal gland enlargement on imaging

5. Salivary Glands (Parotid, Submandibular, Sublingual)

Required criteria (at least one):

- New or worsening salivary gland swelling or tenderness on physical examination
- New or worsening salivary gland enlargement on imaging

6. Lymph Nodes

Required criteria:

- New or worsening lymphadenopathy (primarily non-tender) on physical examination or imaging

Note: If lymph nodes are the only site of suspected flare, biopsy is required to rule out alternative diagnoses

7. Lungs (Pleura and Parenchyma)

Required criteria:

- New or worsening imaging findings confirming pleuropulmonary involvement (e.g., pulmonary nodules/mass, infiltrates, ground glass opacities, pleural effusion/thickening, peribronchovascular thickening, paravertebral mass, fibrotic changes)

8. Aorta and Large Blood Vessels

Required criteria (at least one):

- New or worsening vessel wall thickening or evidence of aortitis (dissection, aneurysm) on imaging
- Incidental finding during surgery that confirms new or worsening aortic involvement

9. Retroperitoneum

Required criteria (at least one):

- New or worsening imaging evidence of soft tissue surrounding the aorta or iliac vessels, with or without ureteral involvement
- Incidental finding during surgery that confirms new or worsening retroperitoneal involvement

Note: For new manifestations, biopsy may be considered based on feasibility

10. Pancreas

Required criteria:

- New or worsening imaging findings indicating pancreatic involvement (diffuse enlargement with loss of lobulations, pseudocapsule, focal mass after malignancy exclusion, pancreatic duct irregularities/strictures)

Note: For new manifestations, biopsy may be considered to rule out alternative causes

11. Bile Ducts (IgG4-Related Sclerosing Cholangitis)

Required criteria (both must be present):

- New or worsening laboratory findings consistent with cholangitis (elevated bilirubin, alkaline phosphatase, gamma-glutamyl transferase, alanine aminotransferase, and/or aspartate aminotransferase)
- New or worsening imaging or endoscopic evidence of bile duct involvement (common bile duct/hilum strictures, wall thickening, intrahepatic duct irregularities)

12. Kidney

Required criteria (at least one):

- New or worsening laboratory findings consistent with kidney involvement (elevated creatinine, decreased eGFR, proteinuria, hematuria, or low complement C3/C4)
- New or worsening imaging findings (renal cortical lesions, pelvis thickening, atrophy, hydronephrosis)

13. Skin

Required criteria:

- New or worsening IgG4-RD skin lesions (papular, plaque, or macular rash)

Note: Biopsy is required for new manifestations or if skin is the only organ with suspected flare

14. Other Organs (Breast, Prostate, Pericardium, Thyroid, etc.)

Required criteria (at least one):

- New or worsening organ-specific symptoms or physical examination findings
- New or worsening imaging findings confirming organ involvement

Note: Imaging or biopsy is required for new manifestations