A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of XmAb®5871 in Patients with IgG4-Related Disease (INDIGO)

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Primary Objective:* To evaluate the effect of every-other-week subcutaneous (SC) administration of XmAb5871 on the time to IgG4-related disease (IgG4-RD) disease flare following an initial course of corticosteroid therapy in subjects with active...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON48598

Source
ToetsingOnline

Brief title
2281/0051, XmAb5871-06 (Xencor)

Condition

- Autoimmune disorders

Synonym
IgG4 related disease, IgG4 related systemic disease

Research involving
Human

Sponsors and support

Primary sponsor: Xencor, Inc.
Source(s) of monetary or material Support: industry

Intervention

Keyword: IgG4-Related Disease, Phase 3, XmAb®5871

Outcome measures

Primary outcome

Primary Efficacy:

Time to IgG4-RD disease flare (TDF), defined as the reappearance of signs/symptoms of IgG4-RD or the appearance of new signs/symptoms of IgG4-RD that requires IgG4-RD rescue therapy. Subjects will have met the following criteria for IgG4-RD disease flare if at any time point during the study, after randomization, up to and including Study Day 701 (Week 101):

1. There has been a worsening of IgG4-RD RI of at least 1, AND

2. There is evidence of worsening of disease by change in physical exam, change in imaging, or change in biochemical parameters, AND

3. The Investigator assesses that there is a need for the institution of rescue therapy (ie, any IgG4-RD directed therapy, including but not limited to, additional corticosteroid dose or duration other than protocol-specified amounts, methotrexate, azathioprine, mycophenylate mofetil, B-cell depleting therapy, or other investigational therapy)

Secondary outcome

Secondary Efficacy:

- The proportion of subjects that remain free of IgG4-RD disease flares from

randomization to Study Day 701 (Week 101)

- Type and cumulative amount of IgG4-RD rescue therapy usage from randomization

to Study Day 701 (Week 101)

- Number and frequency of IgG4-RD disease flares from randomization to Study

Day 701 (Week 101) or study withdrawal

Study description

Background summary

IgG4-RD is currently incurable. Current treatments for the symptoms have side effects, and/or can lead to relapses when treatment is discontinued or tapered.

XmAb5871 is being developed for the treatment of autoimmune disease including IgG4-RD. Given the established role of B cells in the pathogenesis of IgG4-RD and the effects of XmAb5871 on B-cell function, XmAb5871 may provide an attractive therapeutic option for this condition.

Study objective

Primary Objective:
* To evaluate the effect of every-other-week subcutaneous (SC) administration of XmAb5871 on the time to IgG4-related disease (IgG4-RD) disease flare following an initial course of corticosteroid therapy in subjects with active IgG4-RD

Secondary Objectives:
* Evaluate the effect of every-other-week SC administration of XmAb5871 on the proportion of subjects that remain free of IgG4-RD disease flares from randomization to Study Day 701 (Week 101
* To evaluate the effect of every-other-week SC administration of XmAb5871 on the type and cumulative amount of IgG4-RD rescue therapy administered from randomization to Study Day 701 (Week 101)
* To evaluate the effect of every-other-week SC administration of XmAb5871 on the number and frequency of IgG4-RD disease flares from randomization to Study Day 701 (Week 101)
* To evaluate differences between treatment arms in corticosteroid-associated toxicity as measured by the Glucocorticoid Toxicity Index (GTI)
* To evaluate the safety and tolerability of every-other-week SC administration of XmAb5871 in subjects with active IgG4-RD

Exploratory Objectives:
* To evaluate IgG4-RD disease activity, as measured by the IgG4-RD Responder Index (RI) at baseline and over time, and its associations with time to IgG4-RD disease flare, frequency of IgG4-RD disease flares, and the cumulative amount and type of rescue therapy
* To evaluate the effect of every-other-week SC administration of XmAb5871 on selected quality of life (QoL) and health outcomes assessments
* To evaluate XmAb5871 trough serum concentrations and the immunogenicity of every-other-week SC administration of XmAb5871 in subjects with active IgG4-RD
* To characterize the pharmacodynamics (PD) of every-other-week SC administration of XmAb5871 in subjects with active IgG4-RD as follows:
o To evaluate the effect of XmAb5871 on changes in the absolute B-cell count (ABC) and B-cell cluster of differentiation 19 (CD19) receptor occupancy (RO)
o To evaluate the effect of XmAb5871 on changes in serum IgG4 concentrations
o To evaluate the effect of XmAb5871 on changes in the ratio of IgG4/IgG B-cell receptor (BCR) ribonucleic acid (RNA) in circulating B cells (exploratory studies may be done on this sample to elucidate B- and T-cell receptor repertoires and major histocompatibility complex alleles; if done, these may be reported in a separate report)
o To evaluate the effect of XmAb5871 on pancreatic exocrine and endocrine function
o To evaluate the effect of XmAb5871 on changes in the circulating plasmablast count and CD4+ cytotoxic T lymphocytes (CTLs); (may be performed at selected sites)
o To evaluate the effect of different Fc gamma receptor (Fc*R) IIa and Fc*RIIb genotypes on serum trough concentrations, PD, and efficacy of XmAb5871

Study design

Study Procedures:
After obtaining informed consent (study entry), all screening procedures and tests establishing eligibility will be performed within a period of 28 days prior to randomization. Corticosteroid therapy is the standard-of-care (SOC) treatment for IgG4-RD. Investigators therefore are not restricted from initiating corticosteroid therapy as SOC therapy prior to study entry by the subject. Subjects that have been on long-term corticosteroid therapy of * 10 mg prednisone equivalent per day and that have had worsening of signs/symptoms of IgG4-RD may also have their corticosteroid dose increased prior to study entry. Subjects will be eligible to enter screening, after informed consent is obtained, as long as the following criteria are met:
1. The prestudy corticosteroid therapy has not been initiated (or increased from previous long-term dose of * 10 mg prednisone equivalent per day) for more than 14 days prior to the start of screening,
2. The protocol-defined corticosteroid starting dose range has not been exceeded (60 mg/day prednisone equivalent given orally),
3. Corticosteroids have not been given by the intravenous (IV) or intramuscular (IM) route within 14 days prior to screening and will not be given by these

routes of administration during screening, and
4. All screening procedures required for study eligibility can be completed within 28 days before randomization.

Likewise, Investigators may begin corticosteroids as SOC therapy at any time point during the screening period; ie, Investigators need not wait to establish study eligibility before starting SOC corticosteroid therapy. All other IgG4-RD directed therapy, except as noted in allowed concomitant medications, must be discontinued during screening. A completed adjudication form (see Appendix 1) must be submitted to the Sponsor for review and approval prior to randomization. An IgG4-RD RI score and reports of any imaging done within 2 weeks prior to the start of SOC corticosteroid therapy, even if performed before informed consent is signed, should be included as baseline values for the screening visit (subjects agree to allow this by signing the informed consent).

After subjects receive an initial course of corticosteroid therapy to stabilize or improve IgG4-RD disease activity, subjects will then be randomized and start a protocol-defined corticosteroid tapering period. Subjects entering the study on no IgG4-RD directed therapy, or those who need an increase in their corticosteroid dose, will receive a dose of 20 to 60 mg/day prednisone equivalent by the oral route. Oral corticosteroids must be maintained at a stable dose for 14 to 28 days during the 28-day screening period. Both the corticosteroid dose and the duration of the dose period prior to randomization will be at the Investigator*s discretion; however, duration must be at least 14 days and not greater than 28 days at the stable corticosteroid dose. Following this initial period of stable corticosteroid therapy, Investigators will determine when the subject is ready to begin the protocol-defined taper period, and the subject will be randomized 1:1 to SC 250 mg XmAb5871 or placebo. On Day 1 (Visit 2) of the study, the subject will be administered the first SC dose (XmAb5871 or placebo) and begin a protocol-specified corticosteroid taper of 8 to 12 weeks, dependent on the stable corticosteroid dose.

All subjects will be observed for at least 2 hours after the completion of the first SC administration, during which time safety assessments will be performed.

The full treatment period is 51 doses given every other week for 101 weeks. Subjects will return to the Investigator*s site every 2 weeks on study Days 15, 29, 43, 57, 71, and 85 (Visits 3 through 8) for their injections, corticosteroid taper instructions, and scheduled safety, pharmacokinetic (PK), PD, and IgG4-RD disease response assessments. Subjects will be required to remain at the study site for observation for at least 30 minutes after the completion of injections during Visits 3 through 8. Subsequent dosing will not require a post-administration observation period. Starting with Visit 9 on Day 99, subjects may opt to have home healthcare personnel administer the injections on the odd-numbered visits. On even-numbered visits (Visits 10, 12,

14, etc.), the subjects will be seen at the Investigator*s site for their injections and scheduled assessments.

Subjects will be counted as treatment failures for the primary endpoint of time to IgG4-RD disease flare and first secondary endpoint of proportion of subjects that remain free of IgG4-RD disease flares from randomization to Study Day 701 (Week 101), if the following occur at any time point during the study after randomization:
1. There has been a worsening of IgG4-RD RI of at least 1, AND
2. There is evidence of worsening of disease by change in physical exam, change in imaging or change in biochemical parameters, AND
3. The Investigator assesses that there is a need for the institution of rescue therapy (ie, any IgG4-RD-directed therapy, including but not limited to, additional corticosteroid dose or duration other than protocol-specified amounts, methotrexate, azathioprine, mycophenylate mofetil, B-cell depleting therapy, or other investigational therapy).

When a subject demonstrates an IgG4-RD disease flare, a physical exam, imaging, and biochemical parameters specific to the area of flare (eg, creatinine, C3, C4 for kidney flare) should be obtained together with the prespecified assessments for that particular visit to correlate symptoms and to document the disease worsening.
Subjects that receive any rescue therapy other than B-cell depleting agents will continue to receive allocated study drug on study to collect data on the remaining secondary and exploratory endpoints, such as the number and frequency of IgG4-RD disease flares and cumulative amount and types of IgG4-RD rescue therapy. An important component of the study is to collect natural history data on the use of corticosteroids and any associated toxicity in IgG4-RD over the 2-year treatment period.

IgG4-RD rescue therapy should consist of reintroduction of corticosteroid therapy. In subjects with documented corticosteroid toxicity or intolerance, other immunosuppressant agents may be used. If B-cell depleting therapy (eg, rituximab) is chosen, the subject will be counted as a treatment failure and will terminate the study early. Investigators are free to determine the type of rescue therapy administered during the study.

All subjects completing the treatment period will have follow-up safety visits 4 weeks and 8 weeks after the last injection at which time safety, PK, PD, and disease response assessments will be collected. Subject participation will be considered complete once the follow-up visits have been performed, or when the subject terminates the study, whichever comes first. All adverse events (AEs; including serious AEs [SAEs] and deaths) and concomitant medication use information will be collected throughout the study from screening through study termination. Subjects developing treatment-emergent AEs (TEAEs) or clinically significant safety laboratory abnormalities, including anti-drug antibodies (ADAs), will be followed until resolution or until stabilization of the

AEs/abnormalities.

Intervention

Test Product, Dose and Mode of Administration:
The SC formulation of XmAb5871 drug product is a sterile liquid product supplied in single-use glass vials.
Each 2-mL glass vial is filled with 1.0 mL of drug product that contains 125.0 mg/mL (± 10%) of XmAb5871, 20mM sodium acetate, 3% (weight-to-volume; w/v) proline and 0.01% (w/v) polysorbate 80 at pH 5.5.
Dose and route of administration: XmAb5871 (250 mg) will be given as SC injections every other week for up to 51 doses. All subjects will receive 2 SC injections of 1 mL volume with each dose. The single-use glass vial is masked to make it indistinguishable from the placebo. Dosing is completed with a similarly masked syringe.

Placebo, Dose and Mode of Administration:
The SC formulation of the placebo is a sterile liquid product supplied in single-use glass vials.
Each 2-mL glass vial is filled with 1.0 mL of placebo that contains 20mM sodium acetate, 3% (w/v) proline, 0.01% (w/v) polysorbate 80, and 11.5% (w/v) dextran-40 at pH 5.5.
Dose and route of administration: Placebo will be given as SC injections every other week for up to 51 doses. All subjects will receive 2 SC injections of 1 mL volume with each dose. The single-use glass vial is masked to make it indistinguishable from the XmAb5871 drug product. Dosing is completed with a similarly masked syringe.

After a screening period of up to 28 days, eligible subjects will be randomized to XmAb5871 or placebo (1:1). They will receive SC doses every other week for a total of up to 51 doses (101 weeks). Subjects will be followed on study for 8 weeks following the last dose for a total study period of up to 113 weeks.

Study burden and risks

Please refer to patient information sheet section 7 and appendix D.

Contacts

Public
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Monrovia CA 91016

US
Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects will be considered eligible to participate in the clinical study if they meet the following criteria:
1. Are male or female 12 years of age or older. In the NL, both sites have confirmed that only adults 18 and older will be included.
2. Are able to provide written informed consent. For subjects 12 to 18 years of age, the adolescent signs a patient assent form and the parent or the legal guardian must sign the ICF. In the NL, both sites have confirmed that only adults 18 and older will be included. So, informed consent for minors in NL is not applicable.
3. Meet the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-RD with a score of * 20 (see Appendix 1).
4. Must have active IgG4-RD signs/symptoms that require, as assessed by the Investigator, the initiation of corticosteroid therapy or the increase in background long-term corticosteroid therapy (if previously on a stable dose of * 10 mg/day prednisone equivalent).
5. An oral corticosteroid dose must be maintained at a stable dose for 14 to 28 days during the 28-day screening period prior to randomization.
6. Must be able and willing to receive corticosteroid therapy during the induction phase of the trial and be able to taper off any systemic corticosteroid therapy per protocol.
7. Must be willing to stop other IgG4-RD directed medications during screening (eg, methotrexate, mycophenolate mofetil, 6-mercaptopurine, or azathioprine).
8. Must have a negative serum pregnancy test within 14 days before randomization.

9. Female subjects of childbearing potential must agree to use a highly effective method of birth control from screening until 8 weeks after the last dose of XmAb5871/placebo is given. Women are considered to be of childbearing potential unless it is documented that they are premenarche OR postmenopausal by history with no menses for 1 year and confirmed by follicle stimulating hormone (FSH) OR have a history of bilateral salpingectomy. Highly effective methods of birth control include combined hormonal birth control (oral, intravaginal, transdermal) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, intrauterine), intrauterine devices (IUDs), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided partner is the sole sexual partner and there has been a medical assessment of surgical success), or sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject).
10. No history of severe allergic reactions to monoclonal antibodies.
11. Are able and willing to complete the entire study according to the study schedule.
12. Are willing to forego other forms of experimental treatment during the study.

Exclusion criteria

Subjects will not be considered eligible to participate in the clinical study if they meet 1 or more of the following criteria:
1. Any Exclusion Criteria as listed in the ACR/EULAR IgG4-RD Classification Criteria (see Appendix 1).
2. Initiation of corticosteroid therapy (or increase in long-term corticosteroid therapy) for new or exacerbated signs/symptoms of IgG4-RD > 14 days before enrolment.
3. Corticosteroid dose has exceeded 60 mg/day prednisone equivalent given orally within 14 days prior to screening or will exceed 60 mg/day during the screening period.
4. Corticosteroids have been given by the IV or IM route within 14 days prior to screening or will be given by these routes of administration during the screening period.
5. IgG4-RD requiring long-standing corticosteroid therapy at a dose of > 10 mg/day prednisone equivalent.
6. Subjects with disease in only 1 organ system whose primary manifestation is fibrosis (for example, neuro-meningeal involvement, retroperitoneal fibrosis, fibrosing or sclerosing mesenteritis) will be excluded. History or evidence of a clinically unstable/uncontrolled disorder, condition or disease (including, but not limited to, cardiopulmonary, oncologic, renal, hepatic, metabolic, hematologic, or psychiatric) other than IgG4-RD that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
7. History or evidence of a clinically unstable/uncontrolled disorder, condition or disease (including, but not limited to, cardiopulmonary, oncologic, renal, hepatic, metabolic, hematologic, or psychiatric) other than IgG4-RD that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
8. 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).
9. Presence of recurrent or chronic infections, defined as * 3 infections requiring

antimicrobials over the past 6 months prior to screening.
10. Active infection requiring hospitalization or treatment with parenteral antimicrobials within the 30 days prior to randomization or oral antimicrobials within the 14 days prior to randomization.
11. Prior use of rituximab (or other B-cell depleting agents) within 5 months of randomization.
12. Use of any investigational agent within 5 half-lives of the agent (or 3 months if the half-life [t*] is unknown) prior to randomization.
13. White blood cell count < 2.5 × 103/µL.
14. Absolute neutrophil count (ANC) < 1.0 × 103/µL.
15. Elevated serum creatinine > 2.5 × upper limit of normal (ULN) OR estimated creatinine clearance (CL) < 40 mL/minutes calculated by the Cockroft-Gault formula at screening.
16. Hemoglobin < 10 g/dL.
17. Platelet count < 75 × 109/L.
18. Positive test result for human immunodeficiency virus (HIV) I and II antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus antibody (HCV Ab).
19. Has received live vaccines within 4 weeks before randomization.
20. Inability to communicate reliably with the Investigator.
21. Subject is pregnant or breast feeding or planning to become pregnant while enrolled in the study.
22. Positive pregnancy test at screening or at any time during the study.
23. Subjects who do not agree to use medically acceptable methods of contraception.
24. Known or suspected sensitivity to mammalian cell-derived products or any components of the study drug.
25. Unable or unwilling to partake in follow-up assessments or required protocol procedures.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	XmAb5871
Generic name:	XmAb5871

Ethics review

Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002214-31-NL

Register	ID
CCMO	NL66482.091.18