A phase 3, randomized, double-blind, multicenter, placebo-controlled study of Inebilizumab efficacy and safety in IgG4-related disease

Published: 29-09-2020
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This study has been transitioned to CTIS with ID 2023-508290-81-00 check the CTIS register for the current data. Primary objective: To evaluate the efficacy of inebilizumab in reducing the risk of a disease flare in patients with IgG4-RD.Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON55954

Source
ToetsingOnline

Brief title
MITIGATE

Condition

- Autoimmune disorders

Synonym
IgG4-related disease

Research involving
Human

Sponsors and support

Primary sponsor: Viela Bio, Inc. / Horizon Therapeutics Ireland DAC

Source(s) of monetary or material Support: Viela Bio

Intervention

Keyword: IgG-related disease, Inebilizumab, rare disease

Outcome measures

Primary outcome

Time to disease flare, defined as the time in days from Day 1 (dosing) to the date of the first treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week RCP. The date of disease flare is defined as the date of initiation of any flare treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.

Secondary outcome

Secondary endpoints:

• Annualized flare rate for treated and AC-determined flares during the RCP.

• The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

• The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for

flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

• Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the Investigator within the RCP, regardless of AC determination of flare.

• Annualized flare rate for AC-determined flares, whether or not treated, during the RCP.

• Glucocorticoid use, calculated as the cumulative GC dose taken for the purpose of IgG4 RD disease control during the RCP.

• Incidence of treatment emergent adverse events (TEAEs), serious TESAEs, and TEAEs of special interest (AESIs) during the 52-week RCP and during the OLP.The incidence of ADAs directed against inebilizumab during the RCP.

Exploratory endpoints:

• Serum concentration of inebilizumab and noncompartmental PK parameters.

• Changes from baseline in peripheral B cell counts, including total B cells and B cell subsets.

• The change from baseline to Week 52 in the Physician Global Assessment of Disease Activity.

• Changes in patient functioning and health-related quality of life, as measured by changes from baseline to Week 52 in the following:

o The 36-item Short Form Health Survey version 2® (acute recall) questionnaire

o Functional Assessment of Chronic Illness Therapy-Fatigue

o Patient Global Assessment of Disease Activity

• Annualized flare rate for treated and AC-determined flares during the OLP.

• The number of inpatient hospitalizations, days of hospitalization, days in an intensive care unit, emergency department visits, non-study-related physician visits, home-health visits (physician or nurse), disease-related imaging procedures, and disease-related procedures/surgeries (stenting, other).

• The change from baseline in immunoglobulin levels (IgG, IgG subclasses including IgG4, IgM, IgA, IgE, and total immunoglobulins).

• Changes from baseline in serum levels of complement components C3 and C4 and the ELF score.

• Changes from baseline in:

o Blood gene expression profiles

o Serum biomarker expression (eg, inflammation-related cytokines/chemokines)

• Analysis of genetic alterations associated with disease activity and response to treatment.

Study description

Background summary

There are currently no medicinal products approved for the treatment of immunoglobulin G4-related disease (IgG4-RD), a rare disease. The majority of cases follow a relapsing course that can lead to permanent tissue damage with attendant morbidity and potential mortality. Glucocorticoids (GCs) are widely and effectively used for acute treatment of initial disease activity and of recurrent episodes (flares), but GCs do not prevent recurrence of active

disease during their taper or after their discontinuation. Moreover, GCs are associated with substantial toxicity. Thus, there is a high unmet medical need for therapies that prevent disease recurrence and limit GC exposure. The pathogenesis of IgG4-RD suggests that B-cell depletion may be an effective avenue for therapeutic intervention. An important role for B cells, particularly plasmablasts and plasma cells, in the pathogenesis of the disease appears likely. The anti-CD19 B cell-depleting activity of inebilizumab suggests that it may provide benefit as treatment for IgG4-RD. This study aims to define the efficacy and safety of inebilizumab for the prevention of flare of IgG4-RD.

Primary Hypothesis: By depleting CD19+ B cells, including plasmablasts and plasma cells, inebilizumab will reduce IgG4-RD activity by preventing disease flares.

Secondary Hypotheses:
• Inebilizumab will reduce disease activity in patients with IgG4-RD as assessed by additional measures of efficacy.
• Inebilizumab will be well-tolerated and have an acceptable safety profile in patients with IgG4-RD.

Study objective

This study has been transitioned to CTIS with ID 2023-508290-81-00 check the CTIS register for the current data.

Primary objective: To evaluate the efficacy of inebilizumab in reducing the risk of a disease flare in patients with IgG4-RD.

Secondary objectives:
• To evaluate the safety and tolerability of inebilizumab in patients with IgG4-RD.
• To evaluate the effect of inebilizumab on other measures of disease activity.

Exploratory objectives:
• To characterize the pharmacokinetics (PK) of inebilizumab in patients with IgG4-RD.
• To characterize the primary pharmacodynamic effect of inebilizumab in patients with IgG4 RD.
• To explore the effect of inebilizumab on other measures of disease activity.
• To assess the effect of inebilizumab on health resource utilization in patients with IgG4-RD.
• To assess the effect of inebilizumab on circulating immunoglobulins.
• To assess effect of inebilizumab on complement components and the enhanced liver fibrosis (ELF) score.

• To evaluate the effects of inebilizumab on other disease-relevant measures, including other immune cell populations, biomarkers, and gene expression in patients with IgG4-RD.
• To assess the relationship between genetic variations, disease activity, and efficacy.

Study design

Randomized, double-blind, placebo-controlled, parallel-cohort study.

Intervention

Randomized-controlled period (RCP) Blinded treatment on Day 1, Day 15, and Week 26:
• Inebilizumab group: Inebilizumab 300 mg intravenous (IV)
• Placebo group: IV placebo

Both groups: Oral prednisone (or equivalent) tablets from Day 1 to the end of Week 8 (tapering dose regimen: 2 weeks each at 20, 15, 10, and 5 mg/day of prednisone or equivalent, open-label, from commercial supply).

Optional OLP: Open-label inebilizumab 300 mg IV on Day 1, blinded inebilizumab 300 mg or matching placebo on Day 15 (depending on assigned RCP treatment), and then a single inebilizumab 300 mg IV infusion every 6 months for the duration of the OLP.

Study burden and risks

Burden: During the study, the patients have to visit the hospital 15 times for part 1 and 10 times for part 2. For part 2, there are also 12 phone calls. Patients will be treated three times with inebilizumab or placebo in part 1 and 7 times in part 2 with inebilizumab (7x) or inebilizumab (6x, 1st & 3rd trough 7th IV) and placebo (1x, 2nd IV). Placebo and inebilizumab are administered via IV. Subjects will be required to take pre-medications prior to the infusion. The following measurements and procedures are conducted for the study: a review of medical history, medicine use, demographics, vaccination history; assessment of adverse events and serious adverse events; full physical exam; symptom-driven physical exam; measure vital signs, height, and weight and; ECG. Blood and urine are collected. If the subject gives consent, the blood samples are used for genetic research. Subjects are asked to complete two questionnaires about their general health and level of fatigue and the impact of fatigue of the subjects' lives in the past week. Subjects will also be asked to mark on a scale on a piece of paper to indicate how active they consider their IgG4-RD is. Subjects are tested for hepatitis B, hepatitis C, tuberculosis, HIV, pregnancy, and possible also for John Cunningham virus (JVC) Risk: Possible side effects of the study drug and study procedures. Treatment

with inebilizumab may make vaccinations less effective. Very common known side effects of inebilizumab are infusion reaction, reduced immunoglobulin levels and urinary tract infection. Common known side effects of inebilizumab are joint pain, back pain, headache, Nasopharyngitis and low white blood count. If subjects receive placebo, their disease may get worse, stay the same, or improve, just at it might have done without any treatment. Blood collections may cause pain or bruising, light-headedness, or, rarely, fainting. Answering the questions of the questionnaires might be uncomfortable. Removal of the ECG patches may lead to slight skin irritation. Because genetic information is unique for each person, it may be possible that someone may trace the coded samples back to the subject(s). Subjects might be exposed to radiation (one 1 scan) during this study if they did not have full-body imaging in the past three months. The PI may also request additional scans during the study to confirm flare response.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1. Male or female adults, who have reached the age of consent in the applicable region (eg, >= 18 years in the US).

2. Written informed consent and any locally required authorization (eg, data Privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3. Clinical diagnosis of IgG4-RD.

4. Fulfillment of the 2019 ACR/EULAR classification criteria (Appendix A) as determined by the Eligibility Committee. Specifically, subjects must meet the classification criteria entry requirements (including involvement of one of the following organs: pancreas, bile ducts/biliary tree, orbits, lungs, kidneys, lacrimal glands, major salivary glands, retroperitoneum, aorta, pachymeninges, or thyroid gland [Riedel*s thyroiditis]), must not meet any of the classification criteria exclusions, and must achieve at least 20 classification criteria inclusion points.

5. Experiencing (or recently experienced) an IgG4-RD flare that requires initiation or continuation of GC treatment at the time of informed consent. This criterion may be met in two ways:

* On GC therapy for recent IgG4-RD flare, having received a maximum of 4 weeks of treatment prior to informed consent at a dose no higher than 60 mg/day prednisone or equivalent, and at 20 mg/day prednisone or equivalent on the day prior to randomization, or

* Experiencing active disease not currently being treated at the time of informed consent, with planned initiation of treatment for flare with GC at a maximum dose of 60 mg/day prednisone (or equivalent) and with a plan to be treated at a dose of 20 mg/day of prednisone (or equivalent) on the day prior to randomization, for a total duration of GC treatment during screening period of at least 3 weeks at the time of randomization.

This GC therapy can either be newly initiated or be increased from a maintenance dose of <= 10 mg/day of prednisone or equivalent. Subjects unable to be tapered to 20 mg/day of prednisone or equivalent by Visit 2 may not be randomized.

Total duration of GC treatment must be at least 3 weeks and not exceed 8 weeks prior to randomization.

6. IgG4-RD affecting at least 2 organs/sites at any time in the course of IgG4-RD with documentation to confirm. One organ must meet the requirements for the ACR/EULAR classification criteria (inclusion 4); the second organ is as defined by the investigator.

7. Willing and able to comply with the protocol, complete study assessments, and complete the study period.

8. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide (where spermicide is available) from Day 1 through to the end of the study and must agree to continue using such precautions for at least 6 months after the final dose of IP.

Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception (Table 2 on page 36 of Protocol Amendment 3 dated 16 April 2020) from signing informed consent and must agree to continue using such precautions through the end of the follow-up of the study and at least 180 days after the last dose of IP; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. A recommendation will be made that the female partners (of childbearing potential) of male study participants should use a highly effective method of contraception other than a barrier method.

Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone within the postmenopausal range as established by the clinical laboratory).

Exclusion criteria

1. Severe cardiovascular, respiratory, endocrine, gastrointestinal, hematological, neurological, psychiatric, or systemic disorder, or any other condition that, in the opinion of the Investigator, would place the patient at unacceptable risk of complications, interfere with evaluation of the IP, or confound the interpretation of patient safety or study results. 2. History of solid organ or cell-based transplantation. 3. Known immunodeficiency disorder. 4. Active malignancy or history of malignancy that was active within the last 10 years, except as follows: * In situ carcinoma of the cervix following apparently curative therapy > 12 months prior to screening, * Cutaneous basal cell or squamous cell carcinoma following apparently curative therapy, or *

Prostate cancer treated with radical prostatectomy or radiation therapy with curative intent > 3 years prior to screening and without known recurrence or current treatment. or * Thyroid cancer for which surgery has been performed and there is no evidence of active disease. 5. Receipt of any biologic B cell-depleting therapy (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, inebilizumab) in the 6 months prior to screening. 6. Receipt of non-depleting B-cell-directed therapy (eg, belimumab), abatacept, or other biologic immunomodulatory agent within 6 months prior screening. 7. Receipt of non-biologic DMARD or immunosuppressive agent other than GCs (eg, azathioprine, mycophenolate mofetil, methotrexate, others) within 4 weeks prior to screening. 8. Receipt of any investigational agent < 12 weeks or < 5 half-lives of the drug (whichever is longer) prior to screening. 9. Inability to be tapered off of GC therapy by 8 weeks post-randomization (other than <= 2.5 mg/day prednisone or equivalent for treatment of adrenal insufficiency or intolerance of taper) in the opinion of the Investigator. 10. Receipt of live vaccine or live therapeutic infectious agent within the 2 weeks prior to screening. 11. Pregnancy, lactation, or planning to become pregnant within 6 months of the last dose of IP. 12. Positive test for, or prior treatment for, hepatitis B or HIV infection. A positive test for hepatitis B is detection of either (1) hepatitis B surface antigen (HBsAg); or (2) hepatitis B core antibody (anti-HBc); and in Japan only (3) hepatitis B surface antibody (HBsAb). 13. History of untreated hepatitis C infection, or positive antibody test for hepatitis C virus (HCV) unless patient is considered to be cured following antiviral therapy and has a HCV viral load below the limit of detection at least 24 weeks after completion of treatment at site or central lab. 14. Evidence of active tuberculosis (TB) or being at high risk for TB based on: * History of active TB or untreated/incompletely treated latent TB. Patients with a history of active or latent TB who have documentation of completion of treatment according to local guidelines may be enrolled. * History of recent (<= 12 weeks of screening) close contact with someone with active TB (close contact is defined as >= 4 hours/week OR living in the same household OR in a house where a person with active TB is a frequent visitor). * Signs or symptoms that could represent active TB by medical history or physical examination. * Positive, indeterminate, or invalid interferon-gamma release assay test result at screening, unless previously treated for TB. Patients with an indeterminate test result can repeat the test once, but if the repeat test is also indeterminate, the patient is excluded. * Chest radiograph, chest computed tomography (CT) or MRI scan that suggests a possible diagnosis of TB or suggests that a work-up for TB should be considered; all patients must have had lung imaging with an acceptable reading within 6 months prior to consent, or during screening. 15. History of > 1 episode of herpes zoster (any grade) and/or any other definite or probable opportunistic infection in the 12 months prior to screening (see Appendix D for details on opportunistic infections that require exclusion). 16. Known history of allergy or reaction to any component of inebilizumab formulation or history of anaphylaxis to any human gamma globulin therapy. 17. Allergy to or intolerance of protocol-required treatment, including medications for prophylaxis of infusion reactions (antipyretic such

as paracetamol/acetaminophen or equivalent, diphenhydramine or equivalent, and methylprednisolone or equivalent). 18. Estimated glomerular filtration rate < 30 mL/min/1.73 m2 by Modification of Diet in Renal Disease Study (MDRD) equation (NIDDK). 19. Blood tests at screening that meet any of the following criteria: * Hemoglobin < 7.5 g/dL * Neutrophils < 1200/mm3 * Platelets < 110 × 10^9/L * Eosinophil count > 3000/mm3 * Prothrombin time > 1.2 x upper limit of normal (ULN); however, subjects who are anticoagulated due to atrial fibrillation and who have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <= 2 x ULN are not excluded * Total immunoglobulins < 600 mg/dL * CD19+ B cells at screen < 40 cells/*L; an exclusionary value may be repeated. 20. Subjects with the following abnormal liver function tests in the absence of hepatobiliary IgG4-RD activity: * Aspartate aminotransferase (AST) > 2 × ULN * Alanine aminotransferase (ALT) > 2 × ULN * Total bilirubin (TBL) > 2 × ULN unless AST, ALT, and hemoglobin are within central laboratory normal range and the patient has a known history of Gilbert syndrome OR Subjects with the following abnormal liver function tests in the presence of hepatobiliary IgG4-RD activity: * AST > 10 × ULN * ALT > 10 × ULN * TBL > 5 × ULN Screening liver function tests may be repeated prior to randomization to permit abnormal values due to hepatobiliary IgG4-RD activity to respond to GC treatment. 21. Known positive anti-neutrophil cytoplasmic antibodies (ANCA) targeted against proteinase 3 or myeloperoxidase based on patient records. 22. History of alcohol or drug abuse that, in the opinion of the Investigator, might affect patient safety or compliance with visits or interfere with safety or other study assessments. 23. Active, clinically significant infection at the time of randomization (IP administration may be delayed until recovery, if within screening window, otherwise subject may be rescreened). 24. Participation in any clinical trial that includes use of any pharmacologic intervention.

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:	Recruitment stopped
Start date (anticipated):	29-08-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Inebilizumab
Generic name:	Inebilizumab
Product type:	Medicine
Brand name:	Premedication (from commercial supplies)
Generic name:	NA

Ethics review

Approved WMO Date:	29-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	29-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	16-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	20-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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
EU-CTR	CTIS2023-508290-81-00
EudraCT	EUCTR2020-000417-33-NL
ClinicalTrials.gov	NCT04540497
CCMO	NL73315.018.20