A Randomized, Double-blind, Placebo-controlled Phase 2 Study with Open-label Extension to Assess the Efficacy and Safety of Namilumab in Subjects with Chronic Pulmonary Sarcoidosis

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This study has been transitioned to CTIS with ID 2024-511115-25-00 check the CTIS register for the current data. Primary Objective:The primary objective of this study is:• To evaluate the efficacy of namilumab in subjects with chronic pulmonary...

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

Summary

ID

NL-OMON51528

Source
ToetsingOnline

Brief title
Resolve-Lung

Condition

- Autoimmune disorders

Synonym
Besnier-Boeck-Schaumann disease / inflamatory disease

Research involving
Human

Sponsors and support

Primary sponsor: Kinevant Sciences Inc.
Source(s) of monetary or material Support: Kinevant Sciences GmbH

Intervention

Keyword: Chronic Pulmonary Sarcoidosis, Phase II, Placebo-controlled, Randomized

Outcome measures

Primary outcome

• Mean change from baseline in percent predicted forced vital capacity (ppFVC)

at 26 weeks;

Secondary outcome

Primary Endpoint:

• Mean change from baseline in percent predicted forced vital capacity (ppFVC)

at 26 weeks;

Key Secondary Endpoint:

• Proportion of subjects successfully achieving OCS taper without rescue;

Other Secondary Endpoints:

Other secondary endpoints of the study include the following:

• Safety and tolerability, including assessment of physical examinations (PEs),

vital signs, electrocardiograms (ECGs), clinical laboratory measurements, serum

surfactant protein D (SP-D) measurements, local injection site tolerability,

concomitant medications, and adverse events (AEs);

• Pulmonary function tests (PFTs):

• Mean change from baseline in FVC (mL);

• Percent of subjects in each category: > +10%, +10%

to -10%, < -10% change in ppFVC with sensitivity analyses using 5%, 15% and 20%

thresholds;

• Mean change from baseline and categorical assessment in other lung function

measurements (% predicted): FEV1, FEV1/FVC, DLCO, TLC, RV.

• Mean change from baseline in PROs:

• SGRQ;

• mKSQ (General health status and organ specific modules);

• FAS;

• SGA;

• LCQ;

• Pain VAS;

• GSDS;

• BSGIC;

• Baseline/Transition Dyspnea Index (BDI/TDI);

• Cumulative OCS use and toxicity index (modified Glucocorticoid Toxicity Index

(mGTI);

• Clinical Benefit Rate: defined as an improvement of >=10% from baseline in

ppFVC or DLCO, or mKSQ Lung Score improvement of >=4 points, or improvement in

Fatigue FAS of >=4 points, without clinically relevant decline in these

parameters or need for rescue with OCS and/or ISTs;

• Time-to-clinical worsening (TTCW) is defined by the time to the first

occurrence of the following: Decline of >=10% from baseline in ppFVC or

diffusing capacity of lung for carbon monoxide (DLCO), or mKSQ Lung score decline of >=4 points, or decline in Fatigue FAS of >=4 points, or need for rescue with OCS and/or ISTs.

• Mean change from baseline in sarcoid associated skin lesions (when present at baseline) and/or development of new skin lesions as assessed by the Sarcoidosis Activity and Severity Index (SASI);

• Mean change from baseline in extrapulmonary Physician Organ Severity Tool (ePOST);

• Proportion of subjects requiring use of rescue therapy;

• PPK and E-R relationship assessments for efficacy and safety, where data permit:

• area under the concentration-time curve (AUC), maximum observed concentration (Cmax), minimum plasma concentration (Cmin), average plasma concentration over the dosing interval (Cavg), and time of Cmax (Tmax);

• Exposure-change from baseline in ppFVC and change from baseline of mKSQ General and Lung Score;

• Exposure-Treatment-Emergent Adverse Events (TEAE)

with an overall incidence rate >=10%.

• Safety laboratory assessments, biomarkers, cytokine and chemokine analyses, and anti-drug antibody (ADA) assays;

• Mean change from baseline in high-resolution computed tomography (HRCT) on Likert scale (centrally assessed);

• Mean change from baseline in [18-F] fluorodeoxyglucose-positron emission tomography (18-F FDG PET) score (maximum and mean standardized uptake value)

(centrally assessed);

• Mean change from baseline in 6MWD.

• Note: For endpoints defined as change from baseline the primary assessment

will be at Week 26.

Study description

Background summary

Sarcoidosis is a multi-organ autoimmune disease characterized by non-necrotizing granulomas believed to be formed from an exaggerated immune response to unidentified antigens. Granulomas are tight clusters of monocytes/macrophages and multinucleated giant cells (MGCs) interspersed with CD4+ T cells. Nearly all (~90%) subjects exhibit pulmonary involvement. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a proinflammatory cytokine and myeloid cell growth factor, is thought to play a key role in the granulomatous response by stimulating the fusion of macrophages into MGCs, activating the mobilization of macrophage precursors into tissues, and supporting the crosstalk between CD4+ T cells and myeloid cells. Successful late-phase clinical trials of anti-GM-CSF monoclonal antibodies in rheumatoid arthritis, giant cell arteritis, and severe coronavirus disease 2019 (COVID-19) have provided strong evidence for the pathogenic role of GM-CSF in aberrant immune responses. Over the past 30 years, a multitude of human tissue and mouse model studies have shown that GM-CSF plays a key role in the formation of granulomas, including sarcoid granulomas. Namilumab, a monoclonal antibody that neutralizes GM-CSF, has the potential to improve outcomes in CPS by downregulating the granulomatous response that drives the disease.

Study objective

This study has been transitioned to CTIS with ID 2024-511115-25-00 check the CTIS register for the current data.

Primary Objective:
The primary objective of this study is:
• To evaluate the efficacy of namilumab in subjects with chronic pulmonary sarcoidosis (CPS).

Key Secondary Objective:
• To evaluate the effect of namilumab on proportion of subjects on OCS taper without rescue.

Other Secondary Objectives:
The other secondary objectives of this study are:
• To assess the safety and tolerability of namilumab;
• To assess the effect of namilumab on measures of pulmonary function;
• To assess the effect of namilumab on Patient Reported Outcomes (PROs):
o St. George*s Respiratory Questionnaire (SGRQ);
o Modified King*s Sarcoidosis Questionnaire (mKSQ);
o Fatigue Assessment Scale (FAS);
o Subject Global Assessment (SGA);
o Leicester Cough Questionnaire (LCQ);
o Pain Visual Analog Scale (VAS);
o General Sleep Disturbance Scale (GSDS);
o Bothersomeness and Subject Global Impression of Change (BSGIC).
• To assess the effect of namilumab on dyspnea;
• To assess the effect of namilumab on cumulative OCS use and toxicity;
• To assess the effect of namilumab on the rate of clinical benefit;
• To evaluate the effect of namilumab on clinical worsening.
• To assess the effect of namilumab on sarcoid associated skin lesions (when present);
• To assess the effect of namilumab on the severity of extrapulmonary organ involvement;
• To assess the effect of namilumab on use of rescue therapy;
• To assess the population pharmacokinetics (PPK) and exposure-response (E-R) relationships for efficacy and safety of namilumab;
• To assess the effect of namilumab on laboratory parameters;
• To assess the efficacy of namilumab on the radiologic features of CPS;
• To assess the effect of namilumab on 6-Minute Walking Distance (6MWD).

Study design

Randomized, double-blind and placebo-controlled with an optional open-label extension (OLE).

Intervention

Screening Assessments:
- Physical examination / Vital signs
- ECG
- CT and FDG-PET scan
- Breathing tests
- Blood and urine collection

Treatment period
- Physical examination / Vital signs
- ECG
- CT and FDG-PET scan

- Breathing tests
- Blood and urine collection
- Questionnaires
- Daily record of corticosteroid
- 6-minute walk test

Study burden and risks

If patient gets a placebo in the study, he/she will not get a potential treatment for his/her health problem, which may stay the same or might get worse.

As the study drug is experimental, even if patient gets active drug, it may not help his/her health problem(s), which may stay the same or might get worse.

Namilumab has never been given to people with sarcoidosis but it has been given to a group of healthy people and another group of people with other diseases where their immune system is believed to be *overworking*.

Namilumab was generally well tolerated in studies so far. Some more common side effects observed with namilumab include influenza-like illness, rhinitis (runny nose), headache, temporary increases in liver function tests, and decreases in white blood cell count. One healthy participant had a potentially serious change in heart rhythm that lasted a few seconds and caused no apparent harm.

Because of the way namilumab works in the body (through the immune system), other possible side effects that could occur include:
• Infection of any kind (from a virus, bacteria, or fungus).
• Allergic reactions. These could range from a mild rash to severe allergic or anaphylactic type reactions- ie a severe life threatening reaction. To date no such allergic reactions have been seen with namilumab.
• A rare lung condition caused by a build-up of a type of protein in the lungs (also called pulmonary alveolar proteinosis or PAP). While this can potentially happen with namilumab treatment it has not been seen in any patient or volunteer to date.

Study medication is given by sub-cutaneous injection into the fat under the skin. Patient may have pain at the injection site, bruising, occasional light-headedness, fainting and, very rarely, infection at the injection site.

Side effects may go away after the treatment is stopped. It is also possible that the side effects may last a long time or may never go away. They may range from mild to life threatening and/or fatal. If a severe side effect or reaction occurs, study doctor may need to stop the patient receiving the study medication. Study doctor will discuss with the patient the best way of managing any side effects.

There may be other side effects to namilumab that are not yet known. It is important patient tells the study doctor right away about any changes in health during participation in this study.

Contacts

Public
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Scientific
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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 subjects age >=18 years.
2. Able and willing to provide written informed consent, which includes compliance with study requirements and restrictions listed in the consent form.
3. >=6-month history of documented sarcoidosis including histological confirmation in the subject*s medical records.
4. Have HRCT and [18F]-FDG PET/CT scans at Screening consistent with active pulmonary sarcoidosis of the lung parenchyma by central read.

5. ppFVC >=50% to <=90% and DLCO >=50% at Screening.
6. If receiving prednisone (or equivalent), dose must have been <=25 mg, and dose must have been stable for at least 4 weeks prior to Screening. In addition, subject must agree to taper their steroids beginning at the time of randomization.
7. If receiving methotrexate and/or other IST, dose must have been stable for >=3 months prior to Screening and subject must agree to cessation of their IST therapy at randomization.
8. Symptomatic as indicated by modified Medical Research Council Dyspnea scale >1 (i.e., Grade 2 or more) in the prior 6 months.
9. Female subjects must agree to use an approved highly effective birth control (BC) method (<1% failure rate per year) for at least 28 days prior to randomization, throughout the study and for 8 weeks (56 days) post last dose of study drug, unless documented to have a reproductive status of non-childbearing potential or is postmenopausal as defined below:
• Non-childbearing potential defined as pre-menopausal female with medical history of total hysterectomy, bilateral oophorectomy
(removal of ovaries), bilateral salpingectomy, bilateral tubal ligation, or bilateral hysteroscopic sterilization at least 3 months prior to Screening;
• Postmenopausal defined as12 months of spontaneous amenorrhea; otherwise, a follicle stimulating hormone (FSH) confirmation will be required. For females with questionable menopausal history (e.g., irregular menstrual periods and age >40 years) a documented serum FSH level must be >=30 mIU/mL;
• Woman of childbearing potential (WCBP) who is already using an established method of highly effective contraception or agrees to use one of the allowed BC methods, for at least 28 days prior to randomization and throughout the study, and for 8 weeks (56 days) following the last dose of study drug.
10. Male subjects must agree to, and attest that, female partners of childbearing potential are using one of the allowed highly effective methods of contraception as described above and for consistent duration.
11. Body Mass Index (BMI) <=40 kg/m2 at Screening.
12. Vaccination for COVID-19 with completion of the primary series at least 2 weeks prior to randomization.

Exclusion criteria

1. Hospitalized for any respiratory illness <=30 days prior to Screening.
2. >=20% fibrosis as indicated on HRCT-scan assessed by central read prior to randomization.
3. Estimated glomerular filtration rate (eGFR) <=30 mL/min/1.73 m2 (Modification of Diet in Renal Disease [MDRD] equation) or requiring chronic renal replacement therapy.
4. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or alkaline phosphatase (ALP) >2 × upper limit of normal range (ULN).
5. Platelet count <100,000 per mm3.

6. Hemoglobin <=9.5 g/dL.
7. Absolute neutrophil count <1,000 per mm3.
8. Corrected serum calcium >3.5 mmol/L (14 mg/dL).
9. Positive for anti-GM-CSF autoantibody, or history of pulmonary alveolar proteinosis (PAP).
10. Use of any biologic immunomodulator agent (approved or investigational) within the 6 months prior to Screening. Allergens for hypersensitivity desensitization or vaccines are not excluded per this criterion. Treatment with immunoglobulin within 6 months prior to Screening. Treatment with any investigational immunomodulator (e.g., Neuropilin 2 (NRP2) modulator) within 6 months prior to Screening.
11. Treatment with any Janus kinase (JAK) inhibitor within 3 months prior to Screening.
12. Participation in another interventional clinical trial within 6 months prior to Screening.
13. History of left ventricular ejection fraction (LVEF) <=30% or New York Heart Association (NYHA) class III or IV heart failure.
14. ECG abnormalities that warrant further clinical investigation or management at Screening or Fridericia corrected QT interval (QTcF)
> 480 msec on the 12-lead ECG at Screening; if QTcF exceeds 480 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF measures should be used to determine eligibility.
15. Pulmonary hypertension requiring therapy.
16. Systolic blood pressure (SBP) <90 or >180 mm Hg; Diastolic blood pressure (DBP) <60 or >110 mm Hg at screening.
17. Has documented laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other approved clinical testing <=3 months prior to randomization.
18. Administration of any fully live virus or bacterial vaccinations within 3 months prior to Screening or administration of non-live or live-attenuated vaccine within 2 weeks of randomization. Note: COVID-19 booster and influenza vaccinations are allowed to be completed during the study.
19. Systemic (oral or parenteral) antibiotic or pulse OCS treatment for any indication within 42 days prior to randomization.
20. Three or more lower, respiratory tract infections requiring antimicrobial therapy within 12 months prior to Screening.
21. History of mycetoma or fungal respiratory infection.
22. Requirement for supplemental oxygen at rest.
23. History of or planned solid organ or hematopoietic cell transplantation.
24. Prior or planned pneumonectomy and/or planned lobectomy.
Note: Lobectomy performed >=12 months prior to randomization is allowed.
25. Prior use within 12 months of Screening of, or inability to refrain from throughout the study period and 8 weeks (56 days) after last dose of study drug, smoking or using any form of inhaled tobacco, inhaled nicotine (including vaping) or inhaled cannabis preparations.
26. A diagnosis of, or presentation consistent with, Lofgren*s syndrome.
27. Other significant pulmonary disease likely to interfere with the primary

endpoint; the Principal Investigator must discuss any such concerns with the Sponsor or designee prior to randomization.
28. Autoimmune disease other than sarcoidosis likely to require treatment during the subject*s participation in this study.
29. Symptoms and/or signs of extra-pulmonary sarcoidosis that are likely to warrant treatment in addition to that required for the subject*s pulmonary disease.
30. Significant ischemic heart disease, including myocardial infarction within 6 months, unstable angina, or percutaneous transluminal coronary angioplasty (PTCA)/stent within 1 month prior to Screening; or, planned coronary intervention (e.g., coronary artery bypass graft
[CABG] or PTCA/stent) during the subject*s participation in this study.
31. Known or suspected active and untreated/inadequately treated tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection. Subjects with latent TB may be enrolled if anti-TB therapy is commenced prior to randomization. Subjects with positive serology for HIV, hepatitis B or C must have an undetectable viral load by real-time polymerase chain reaction (RT-PCR) prior to randomization.
32. Females who are pregnant or breastfeeding or intend to be during the course of the study.
33. Prior history of any malignancy (not including fully resected squamous and basal cell carcinoma of the skin, fully resected intra-epithelial neoplasia or carcinoma in situ of the cervix) or lymphoproliferative disorder within the past 5 years.
34. History of severe allergic or anaphylactic reactions to therapeutic proteins or known sensitivity to namilumab or to its inactive components.
35. History of alcohol or drug abuse, in the Investigator*s opinion, unless in full remission for greater than 12 months prior to Screening.
36. Any other acute or chronic medical condition, psychiatric condition, or laboratory abnormality, that in the judgment of the Investigator or Sponsor, may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results, and would make the participant inappropriate for entry into this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-01-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Namilumab
Generic name:	/
Product type:	Medicine
Brand name:	Placebo
Generic name:	/

Ethics review

Approved WMO Date:	10-05-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2022
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	16-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	CTIS2024-511115-25-00
EudraCT	EUCTR2021-004794-31-NL
ClinicalTrials.gov	NCT05314517
CCMO	NL80316.100.22