A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intravenous efzofitimod in patients with pulmonary sarcoidosis

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This study has been transitioned to CTIS with ID 2023-506039-13-00 check the CTIS register for the current data. OBJECTIVESPrimary Objective• To assess the efficacy of efzofitimod in patients with pulmonary sarcoidosis Secondary Objectives• To...

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

Summary

ID

NL-OMON53570

Source
ToetsingOnline

Brief title
EFZO-FIT

Condition

- Autoimmune disorders

Synonym
lung sarcoidosis, lymphogranuloma benignum

Research involving
Human

Sponsors and support

Primary sponsor: aTyr Pharma, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: efzofitimod, Phase III, pulmonary sarcoidosis, study

Outcome measures

Primary outcome

• To assess the efficacy of efzofitimod in patients with pulmonary sarcoidosis

Secondary outcome

• To assess the safety and tolerability of efzofitimod in patients with

pulmonary sarcoidosis

Study description

Background summary

Efzofitimod is being evaluated in a double-blind, randomized, placebo-controlled (3 mg/kg: 5 mg/kg: placebo in a 1:1:1 ratio) trial in patients with pulmonary sarcoidosis over a 48-week treatment period (Figure 1). The primary objective of the study is efficacy, with safety and tolerability being secondary objectives (Section 5). The primary efficacy parameter is average daily steroid dose with other key efficacy parameters being FVC and QoL parameters. These parameters are consistent with treatment goals in standard guidelines for sarcoidosis (Baughman et al, 2021b).
Figure 1: Study Schema

OCS = oral corticosteroids.
Consistent with the steroid sparing nature of the primary efficacy parameter, a mandatory steroid taper forms one of the key elements of the study design. The extent to which steroids may be tapered is a function of the steroid dose at baseline and the use of concomitant immunosuppressant therapy. Randomization is therefore stratified based on the OCS dose at baseline (< 10 mg/day versus >= 10 mg/day [prednisone or equivalent]) and the presence or absence of concomitant immunosuppressant therapy.
The study population comprises patients with pulmonary sarcoidosis who have

chronic, symptomatic disease requiring continuous steroids with or without immunosuppressive agents. This study will enroll patients on stable steroids of >= 7.5 mg/day to <= 25 mg/day of prednisone equivalent. This allows for a patient population that will benefit most from a steroid taper. Regardless of their ability to achieve the protocol-directed OCS taper, patients will continue to receive blinded study drug and be followed through to the end of the study.
Patients who are significantly symptomatic, as defined by a KSQ-Lung score <= 70 and a modified Medical Research Council (MRC) Dyspnea score of >= 1 will be included in the study. Patients with less severe symptoms, who may achieve disease remission with existing therapies are not included in the study.
The effect of efzofitimod in reversing established fibrosis is unknown. Therefore, the study population will exclude patients with significant fibrotic disease (> 20% fibrosis on computed tomography [CT]) or with significant pulmonary disease potentially suggestive of fibrosis: an FVC percent predicted of < 50% or KSQ-Lung score < 30.
Patients with comorbidities that may confound assessment of efficacy such as pulmonary complications (eg, mycetoma, significant bronchiectasis and pulmonary hypertension) and concomitant medications (recent use of biologic immunomodulators) are excluded from the study. Since protocol-mandated steroid taper is a key design element, patients who cannot undergo taper (eg, due to Addisonian symptoms on previous taper) are also excluded.
The treatment duration is 48 weeks. This is considered adequate for a chronic condition like sarcoidosis and is also consistent with the 48- to 52-week treatment period for other interstitial lung diseases (King et al, 2014; Richeldi et al, 2014).

Study objective

This study has been transitioned to CTIS with ID 2023-506039-13-00 check the CTIS register for the current data.

OBJECTIVES

Primary Objective
• To assess the efficacy of efzofitimod in patients with pulmonary sarcoidosis

Secondary Objectives
• To assess the safety and tolerability of efzofitimod in patients with pulmonary sarcoidosis

Exploratory Objectives
• To explore the utility of serum biomarkers in evaluation of interventions to treat pulmonary sarcoidosis

Study design

Methodology:
This is a multicenter, randomized, double-blind, placebo-controlled, study comparing the efficacy and safety of intravenous (IV) efzofitimod 3 mg/kg and 5 mg/kg versus placebo after 48 weeks of treatment.
This study will enroll adults with histologically confirmed pulmonary sarcoidosis receiving stable treatment with oral corticosteroids (OCS), with or without immunosuppressant therapy.
After the initial screening period (up to 4 weeks), eligible patients will be randomized 1:1:1 to efzofitimod 3 mg/kg, efzofitimod 5 mg/kg, or placebo. Randomization will be stratified by the presence or absence of concomitant immunosuppressant therapy and OCS dose at baseline (< 10 mg/day versus >= 10 mg/day [prednisone or equivalent]).
During the treatment period (48 weeks), study drug will be administered as IV infusion every 4 weeks for a total of 12 doses.
Starting on Day 15, patients will begin a protocol-directed OCS taper from a starting dose of >= 7.5 mg/day to <= 25 mg/day of prednisone (or equivalent), such that OCS are weaned off completely (0 mg/day) on or before Day 85 (Section 6.2.1.). The goal is to maintain patients without OCS after the taper until the end of study. Patients who are unable to tolerate the OCS taper may receive rescue treatment with higher OCS doses as outlined in the OCS Taper Guidelines (Section 6.2.1.). Regardless of their ability to achieve the protocol-directed OCS taper, patients will continue to receive blinded study drug and be followed through to the end of the study.
Treatment with 1 oral immunosuppressant therapy at a stable dose for >= 4 weeks prior to Day 1 is allowed, but not required. The dose should remain stable during the study. Allowed immunosuppressants include, but are not limited to methotrexate, azathioprine, and leflunomide. Treatment with an immunomodulator, e.g. hydroxychloroquine is allowed in addition to treatment with 1 oral immunosuppressant.
During the treatment period, efficacy assessments include OCS dosing information, pulmonary function tests (primarily forced vital capacity [FVC]), and patient-reported outcomes (King's Sarcoidosis Questionnaire [KSQ], Leicester Cough Questionnaire [LCQ] Fatigue Assessment Scale [FAS], and Patient Global Assessment [PGA]).
Safety will be evaluated based on adverse events (AEs), laboratory evaluations, vital signs, and electrocardiograms (ECGs). Blood samples for the analysis of serum efzofitimod concentrations and anti-drug antibodies will also be collected for the assessment of immunogenicity. Infusion-related reactions, immunogenicity, and malignancy will be evaluated as adverse events of special interest (AESI).
Ongoing review of blinded safety and tolerability data will be performed by the Medical Monitor and Sponsor personnel.
In addition, an external independent Data Safety Monitoring Board (DSMB) will perform interim reviews of unblinded safety, tolerability, and immunogenicity data and ad hoc per Sponsor request if a pattern of unexpected, clinically significant trends or changes in other safety assessments is identified through blinded safety data reviews. The DSMB will provide its recommendation to the

Sponsor, which may include stopping the study if required, or continuing the study with modifications to gain more information on the safety and tolerability of efzofitimod in patients with pulmonary sarcoidosis.
Patients will be followed after Week 48 for an additional 4 weeks.

Intervention

This is a placebo-controlled, randomized, double-blind study. These terms are explained below. Approximately 264 subjects with pulmonary sarcoidosis will participate in this global study at up to 80 clinical sites. The study includes 3 treatment groups: 2 groups with different doses of efzofitimod and 1 group with placebo. You will only be in one group during the study.

For this study, we will have 3 groups:
• Group 1. The people in this group will get the study drug, dose 3.0 mg/kg of your body weight.
• Group 2. The people in this group will get the study drug, dose 5.0 mg/kg of your body weight.
• Group 3. The people in this group will get the placebo.

You will receive intravenous (IV) infusions (delivery of medication using a catheter inserted using a needle into your vein) of the study drug or placebo over about 60 minutes, every 4 weeks, for a total of 12 doses

For the study, there is then a 48-week treatment period during which you will receive the study drug once a month. You will be monitored during each infusion of the study drug.
The clinic visits where an infusion is administered (Visit 1 through 12) may take approximately 4 hours, while Visit 13 and end of study visit may take approximately 2 hours. You may have up to a total of 15 clinic visits and telephone contacts during the treatment period. The telephone contacts may take approximately 15 minutes and will occur between clinic visits to see how you are doing.

Finally, there will be a follow-up period when you will no longer receive study drug; during this period, you will come back to the clinic for an End of Treatment (EOT) Visit (Visit 13) 4 weeks after your last dose and again for an (End of Study) EOS Visit 8 weeks after your last dose so that your study doctor can check your health.

You may be asked to come back to the clinic or contacted by phone for follow-up on any adverse events (side effects) that may have occurred or to obtain additional blood testing.

Study burden and risks

Risk Benefit (Page 25 of protocol)
From limited clinical data, there are no expected toxicities for efzofitimod. Potential toxicities were identified based on a review of the primary target (NRP2), absence of a secondary target (NRP2 was found to be the sole binding partner for efzofitimod identified from a screen of > 4500 cell surface receptors including NRP1), biological nature of drug (fusion protein), nonclinical studies (NOAEL was highest dose tested, no embryo-fetal toxicity), and the intravenous route of administration. Based on this review, the potential toxicities are infusion-related reactions (IRRs) and immunogenicity (development of ADAs, Jo-1 antibodies).
Subjects with an IRR will be closely monitored for as long as medically indicated. If symptoms constitute cardiorespiratory events, vital signs, pulse oximetry, electrocardiogram (ECG), and infusion site examination will be performed to monitor and manage the patient as medically indicated (see Section 8.4.1 on management of IRRs). The development of ADAs and Jo-1 antibodies will also be monitored during the study (Table 1 and Section 6.3.4).
In a Phase 2 study, preliminary efficacy for efzofitimod was shown for its steroid-sparing effect and improvement in FVC and sarcoidosis symptoms. These are meaningful outcomes for patients with sarcoidosis, a chronic or progressive disease fatal in 15% of patients.
The present benefit seems to outweigh the risk. Notwithstanding this, an external independent Data Safety Monitoring Board (DSMB) will perform interim reviews of unblinded safety, tolerability, and immunogenicity data. The DSMB will conduct ad hoc reviews as per Sponsor request if a pattern of unexpected, clinically significant trends or changes in other safety assessments is identified through blinded safety data reviews. The DSMB will provide its recommendation to the Sponsor, which may include stopping the study if required or continuing the study with modifications to gain more information on the safety and tolerability of efzofitimod in patients with pulmonary sarcoidosis.

Contacts

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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

1. Male or females aged 18 to 75 years, inclusive at the time of informed consent
2. Confirmed diagnosis of pulmonary sarcoidosis for at least 6 months, defined by the following criteria:
a. Documented histologically proven diagnosis of sarcoidosis by tissue biopsy (any organ)
b. Documented evidence of parenchymal lung involvement by historical radiological evidence (eg, computed tomography [CT], magnetic resonance imaging [MRI], fluorodeoxyglucose [18F-FDG] positron emission tomography [PET]/CT or chest X-ray; or on screening CT)
3. Evidence of symptomatic pulmonary sarcoidosis, as demonstrated by the following criteria:
a. Modified Medical Research Council (MRC) dyspnea scale grade of at least 1
b. KSQ-Lung score <=70
4. Patients must be receiving treatment with OCS (prednisone or equivalent) and fulfill the following criteria:
a. Treatment of >= 3 months
b. Starting dose between >= 7.5 and <= 25 mg/day
c. Stable dose for >= 4 weeks prior to Day 1
d. Willing to attempt OCS taper to 0 mg/day
5. Body weight >= 40 kg and < 160 kg
6. If female of childbearing potential, must
a. Not be pregnant or lactating, and have a negative pregnancy test at Screening (serum) and at Day 1 (urine) prior to first study drug infusion
b. Be willing to use acceptable or highly effective methods of contraception from Screening until 8 weeks after the last study drug administration (refer to Appendix 6 for acceptable and highly effective methods of contraception)
Note: To be considered of non-childbearing potential, the patient must be

either surgically sterile or postmenopausal (confirmed by amenorrhea duration of at least 12 months with no alternative medical cause
7. Provide written informed consent
8. Agree to comply with all study procedures and requirements

Exclusion criteria

1. Current disease presentation consistent with Lofgren*s syndrome (ie, presence of the triad of erythema nodosum, bilateral hilar lymphadenopathy on chest X-ray, and joint pain)
2. Treatment with > 1 oral immunosuppressant therapy (eg, methotrexate, leflunomide)
3. Treatment (within 4 months of Day 1) with biological immunomodulators, such as tumor necrosis factor-alpha (TNF-α) inhibitors (eg, infliximab, adalimumab) or antifibrotics (pirfenidone, nintedanib) or interleukin inhibitors (eg, canakinumab, ustekinumab)
4. Likelihood of significant pulmonary fibrosis as shown by any 1 or more of the following:
a. CT fibrosis > 20% within the last 12 months
b. FVC percent predicted < 50%
c. KSQ-Lung score < 30
5. Clinically significant bronchiectasis or cavitary sarcoidosis with mycetoma at Screening or during the previous 12 months
6. Clinically significant pulmonary hypertension requiring treatment with vasodilators
7. Patients with cardiac sarcoidosis (inclusive of but not limited to active inflammation with low ejection fraction, presence of arrhythmias), neurosarcoidosis, or renal sarcoidosis
8. Clinically significant cutaneous and ocular sarcoidosis
9. History of Addisonian symptoms that precluded previous OCS taper attempts
10. History of severe allergic or anaphylactic reactions to therapeutic proteins or known sensitivity to efzofitimod or its inactive components (L-histidine, sodium chloride, sucrose, L-methionine, and polysorbate-20)
11. In the opinion of the Investigator and Medical Monitor, current evidence of clinically significant cardiovascular, hepatic, neurological, renal, hematological, lymphatic, metabolic, or gastrointestinal disease, or any condition that requires other treatment or surgery, that may preclude the assessment of efficacy, confound the assessment of safety, or compromise patients' compliance with study procedures
12. Active or history of malignancy within the last 5 years, except for resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma
13. Major surgery or hospitalization within 3 months prior to Day 1 or anticipated surgery during the study
14. Participation in another clinical study of an investigational agent or

device within 3 months (small molecules and device), 6 months (biologics), or 5 half-lives (if known) of the agent, whichever is longer
15. Is an active, heavy smoker of tobacco/nicotine-containing products (defined as > 20 cigarettes/day or e-cigarette equivalent)
16. Active substance abuse (drugs, alcohol, or cannabis) or history of substance abuse within 12 months prior to Screening
17. Clinically significant abnormalities in the Screening physical examination, vital signs, ECG, or clinical laboratory test results that, in the opinion of the Investigator and Medical Monitor, preclude the patient*s participation in the clinical study
18. History of (anti-Jo-1) anti-synthetase syndrome or Jo-1 positive at baseline

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:	Pending
Start date (anticipated):	01-10-2022
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	efzofitimod

Ethics review

Approved WMO Date:	09-08-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-10-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	25-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-03-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-05-2023
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	CTIS2023-506039-13-00
EudraCT	EUCTR2022-001012-26-NL
CCMO	NL81646.100.22