Efficacy and safety of OATD-01, an oral inhibitor of chitinase-1, for treatment of active pulmonary sarcoidosis: study protocol for a randomized, double-blind, placebo-controlled, multicenter, phase 2 trial.

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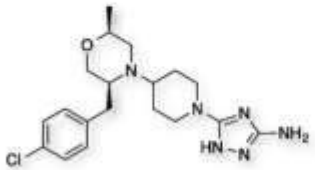
THE KITE STUDY

Introduction

Therapeutic target

Sarcoidosis is a complex, multisystem granulomatous disease of unknown etiology that affects individuals worldwide. **Chitinase-1** (CHIT1) is a macrophage-specific enzyme implicated in the pathology of the process of granuloma formation in sarcoidosis. CHIT1 expression and activity correlates with severity and progression of sarcoidosis, including its pulmonary form. Induced CHIT1 expression in pathologically activated **macrophages** drives glycolysis contributing to inflammation. This provides rationale for CHIT1 as a target for therapeutic intervention.

OATD-01 is a CHIT1 inhibitor



- OATD-01 is a *first-in-class* small-molecule CHIT1 inhibitor with *in-vivo* efficacy demonstrated in several non-clinical models, including murine model of granulomatous inflammation.
- The histological hallmark of sarcoidosis is formation of non-caseating granulomas, composed mainly of macrophages (epithelioid and multinucleated giant macrophages MNGMa) and CD4+ T cells. Inhibition of CHIT1 alters the macrophage pro-inflammatory phenotype, including reduction in chemokines needed for recruitment of CD4+ T cells.

Prior to the KITE study OATD-01 was administered to 129 healthy volunteers in four clinical pharmacology (Phase 1) studies, as single doses up to 600 mg or multiple doses up to 50 mg once daily (q.d.). At 25-50 mg/day doses, at steady state with >80% inhibition of blood chitinolytic activity was achieved.

Explanation

Still there is no specific targeted/disease modifying treatment in place for sarcoidosis, and current therapeutic approaches (corticosteroids) are often associated with side effects limiting their use.

The objective of the KITE study is provide proof of concept for treatment of pulmonary sarcoidosis i.e. evaluate the response to a 12-week treatment with OATD-01 as a reduction of granulomatous inflammation in pulmonary parenchyma evaluated by [^{18}F]FDG PET/CT imaging in patients with active pulmonary sarcoidosis.

Study population	Male and female subjects with active pulmonary sarcoidosis, treatment-naïve or currently untreated
Test treatment	OATD-01, first-in-class small-molecule inhibitor of CHIT1
Dosing scheme	25 mg q.d.
Randomization ratio	1:1 OATD-01 or placebo
Treatment duration	12 weeks
Study sites	Approx. 25 sites in 7 countries: USA, UK, Denmark, France, Germany, Greece, Norway
Sample size	Adaptive design: the total sample size may range between 80 & 120 randomized patients (expected average sample of 98 patients)

Key Inclusion criteria:

Diagnosis of currently symptomatic active pulmonary sarcoidosis
Parenchymal pulmonary involvement

Key Exclusion criteria:

Established alternative diagnosis of a non-infectious or infectious systemic disease, or suspicion thereof
Pulmonary sarcoidosis requiring immediate start of treatment
Cardiac sarcoidosis confirmed with Magnetic Resonance Imaging (MRI)
History of / active Löfgren's syndrome
Presence of lung disease other than sarcoidosis (e.g. asthma, COPD, ILD, lung cancer)

Method

Study des

- ✓ Randomized, double-blind, placebo-cont
- ✓ 0-30 days of screening, 12 weeks of treat
- ✓ Adaptive design [see the schematic belo
- ✓ Onsite study visits ⇒ randomization, We
- ✓ Telehealth visits at W1, W6, and W10; F

50 patients randomized and completed W12 or discontinued the study prematurely → Interim ana

Assessments

- Imaging: [^{18}F]FDG PET/CT imaging (at screeni
- Safety: vital signs, physical examination, 12 FDA-cleared ECG capturing device (wearable) sperm parameters and testosterone in conse testing), Adverse Event recording
- Pharmacokinetics, genotyping
- Pharmacodynamics: Sarcoidosis biomarkers interleukin-2 receptor [sIL-2R], chemokine (Necrosis Factor α (TNF-α) levels), CHIT1 activi
- Patient and clinically meaningful assessme Sarcoidosis Questionnaire Lung and General a

Primary endpoint – primary estimand

- Difference between the two treatment of subjects with success
- Will be analyzed using a logistic regres variable
- Success is defined as the achievement with PET/CT imaging at EOT

Timelines and ongoing activities

The study is fully approved in 7 countries in EU, UK and USA: CTIS May 2024, MHRA Nov 2023, FDA Jul 2023. First Patient First Visit Feb 2024. Sites activation and recruitment is ongoing.

Study registries

https://www.thekitestudy.com
https://www.isrctn.com/ISRCTN16728593
https://clinicaltrials.gov/study/NCT06205121
https://euclinicaltrials.eu/search-for-clinical-trials/?langven&EUCT=2023-508642-23-01

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