Multicenter, randomized, double-blind, phase 2 study to assess the efficacy and safety of OATD-01, an oral inhibitor of chitinase-1 for the treatment of active pulmonary sarcoidosis ("the KITE study") – Study Design

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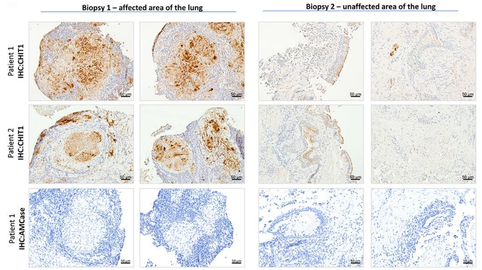
Therapeutic target

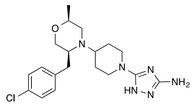
Chitinase-1 (CHIT1) is an activated macrophage-specific enzyme implicated in pathology of several interstitial lung diseases, in particular in the process of granuloma formation in sarcoidosis. CHIT1 expression and activity correlates with severity and progression of lung sarcoidosis. CHIT1 can process LacdiNAC glycans and therefore regulates protein glycosylation, which is altered in various disease states including sarcoidosis. Induced CHIT1 expression in pathologically activated macrophages drives glycolysis contributing to inflammation providing rationale for therapeutic intervention.



Pathological macrophages are a source of CHIT1 in sarcoidosis. *J Inflamm Res. 2022 Sep 29;15:5621-5634.*

OATD-01 is a first-in-class CHIT1 inhibitor

In vivo efficacy of OATD-01 was demonstrated in several models of inflammatory diseases such as chronic and acute asthma, inflammatory bowel disease, idiopathic pulmonary fibrosis, and non-alcoholic steatohepatitis. Importantly, data from *in vivo* studies showed that OATD-01, administered in the therapeutic mode, demonstrated efficacy in a mouse model of granulomatous inflammation. OATD-01 has been so far administered to 129 healthy volunteers, as single (up to 600 mg) or multiple (up to 50 mg/day) doses, in four Phase 1 clinical studies (two dose escalation and two drug-drug interaction studies). At doses of 25 to 50 mg/day, at steady-state, the total time with the inhibition of the plasma chitinolytic activity of >80% was maintained for 24h.



OATD-01 is a once-a-day, direct compression tablet for compliance and ease of use

25 mg FC tablets

Objective of the study

To 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 subjects with active pulmonary sarcoidosis.

Study population

- Male and female subjects with active pulmonary sarcoidosis, treatment-naïve or currently untreated, no recruitment cap
- Previous treatment status as a stratification factor

Primary endpoint

Response to treatment from baseline to End-of-Treatment (EOT) using the criteria determined for each subject as: Complete response, Partial response, Stable disease and Progressive disease wrt to the uptake for [^{18}F]FDG-PET/CT above the background (pulmonary parenchyma / ascending aorta) in pulmonary target lesions.

For the response classification the PET/CT imaging data will be analyzed to identify changes between baseline and posttreatment SUV.

The primary estimand has been constructed and will be used for efficacy evaluation, in line with the Addendum on estimands and sensitivity analysis in clinical trials to the Guideline on statistical principles for clinical trials (E9(R1), 2019) by International Council for Harmonisation; likewise, secondary estimands are constructed for the secondary endpoints as presented below.

Secondary endpoints

- Difference in pulmonary function in patients with active pulmonary sarcoidosis (FVC/FEV1)
- Number of patients escaping to corticosteroids
- Change in the quality of life measured by the Kings Sarcoidosis Questionnaire Lung (KSQ LUNG) and Change in the Fatigue Assessment Scale (FAS)
- Safety and PK/PD

Exploratory endpoints and biomarker evaluations

- CHIT1 activity in plasma and sputum
- CHIT1 protein level in serum
- soluble interleukin-2 receptor [sIL-2R]
- chemokine (C-C motif) ligand 18 [CCL18]
- Tumor Necrosis Factor α (TNFα)

Study criteria

Key Inclusion criteria:

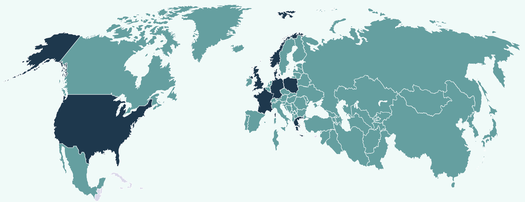
- Diagnosis of active pulmonary sarcoidosis
- Parenchymal pulmonary involvement
- Symptomatic patients who do not require immediate start of standard of care treatment

Key Exclusion criteria:

- Ambiguous Sarcoidosis Diagnosis
- Pulmonary sarcoidosis requiring immediate start of treatment
- Cardiac sarcoidosis
- History of / active Löfgren's syndrome
- Presence of other lung disease other than sarcoidosis (e.g. asthma, COPD, ILD, lung cancer)

Study plans

Planned countries	France, Germany, Denmark, Norway, Poland, Greece, UK, USA
Study treatment	• 25 mg OATD-01 administered once daily (qd) for 12 weeks • Comparator: placebo • 1:1 randomisation
Recruitment	• Ca 15 months • Drop-outs will not be replaced • Re-screening under some circumstances considered
Interim analysis	After 50 subjects randomized and completed Week 12 or discontinued.



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THE KITE STUDY