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Clinical Development of OATD-01: a Novel Chitinase Inhibitor for Treatment of Interstitial Lung Diseases

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Clinical Rationale

Chitinases are the enzymatically active chitinases hydrolases, which have been implicated in the pathology of diverse lung diseases where their activity strongly correlates with a disease stage, clinical progression and prognosis. While the exact mechanisms through which chitinases promote lung inflammation and airway remodeling have not been fully elucidated, several studies have demonstrated that chitinases mediate both the pro-inflammatory and the pro-fibrotic responses in the lungs.

OATD-01 as clinical candidate

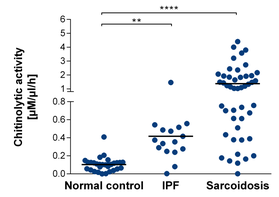
OATD-01 is a small molecular weight, potent inhibitor of both human chitinases. It has good oral bioavailability and excellent pharmacokinetic profile in several animal species.

Chitinases are strongly induced in *in vivo* mouse models of respiratory diseases in a chitin-independent fashion (e.g. bleomycin-induced pulmonary fibrosis and ovalbumin-induced airway inflammation model).

Results from preclinical studies demonstrated significant anti-inflammatory and anti-fibrotic efficacy of OATD-01 in mouse models of asthma (OVA, HDM, chronic HDM) and in the bleomycin-induced pulmonary fibrosis model.

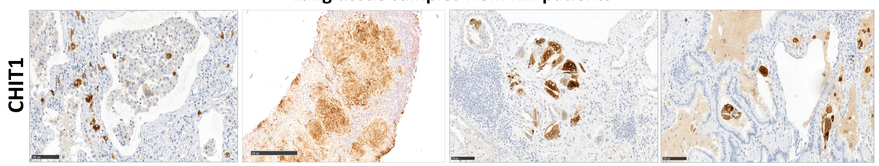
OATD-01	hAMCase	hCHIT1
IC_{50} (nM)	8.5	20.8
IC_{90} (nM)	68	188
K_i (nM)	3.8	13.3

Chitotriosidase (CHIT1) activation and localization in the lungs of ILD patients



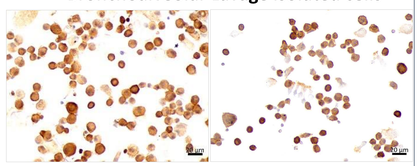
Chitinolytic activity in serum of patients with ILDs: IPF (n=16) and sarcoidosis (n=47) is significantly increased as compared **to** normal controls (n=30)

Lung tissue samples from ILD patients



CHIT1 immunolocalization in lung tissue samples obtained from patients with Interstitial Lung Diseases such as Idiopathic Pulmonary Fibrosis and sarcoidosis but also rheumatoid arthritis- and scleroderma-associated secondary lung fibrosis. Results demonstrated strong CHIT1-positive staining in disease-affacted areas of the lungs and CHIT1 was macrophage-specific

Bronchoalveolar Lavage isolated cells



Immunocytological staining of BALf cells smears (IPF and sarcoidosis) demonstrated that majority of BALf cells were CHIT1-positive with macrophages being the predominant cell type expressing CHIT1.

OATD-01 FiH clinical study (Phase I)

***Phase Ia** - Single Ascending Dose (SAD) study design*

Study objectives
Primary objective:
- To assess safety and tolerability of OATD-01 following ascending single oral doses

Secondary objective:
- To assess the pharmacokinetics (PK) of **OATD-01** following ascending single oral doses

Methodology
A randomized, double-blind, placebo-controlled dose escalation study with ascending single oral doses of **OATD-01**

Number of subjects
48 male subjects (8 subjects per cohort: 6 subjects on **OATD-01**, 2 subjects on placebo) were included

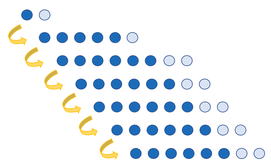
Criteria for evaluation
Safety variables:
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG (heart rate, PQ, QRS, QT, QTc)
- Urine and blood clinical safety laboratory testing
- Physical examination/adverse events

Pharmacokinetic (PK) variables:
- AUC0-inf, AUC0-tlast, Cmax, Cmax(tmax), t1/2, Vz/f, CL/f

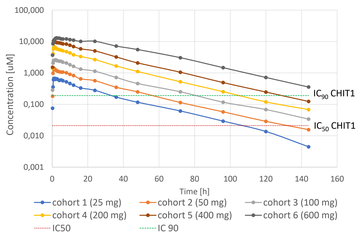
In-house evaluation
Determination of the plasma chitinolytic activity
Determination of the OATD-01 metabolites

*Dosing for SAD study: **Phase Ia***

Cohort 1a: 25 mg (1 x 25 mg tablet)
Cohort 1b: 25 mg (1 x 25 mg tablet)
Cohort 2: 50 mg (2 x 25 mg tablet)
Cohort 3: 100 mg (4 x 25 mg tablet)
Cohort 4: 200 mg (1 x 200 mg tablet)
Cohort 5: 400 mg (2 x 200 mg tablet)
Cohort 6: 600 mg (3 x 200 mg tablet)

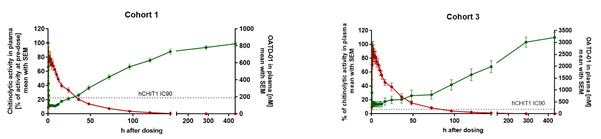


***Phase Ia PK:** Mean plasma concentration of **OATD-01** for Cohorts 1-6*

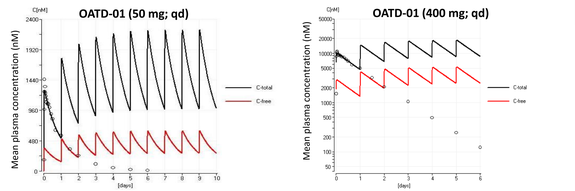


- **At 24h OATD-01 remained at the level above IC_{90}.**
- A dose-proportional increase in C_{max} was observed for **OATD-01** in the dose interval of 25 mg to 600 mg. $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ increased slightly more than dose-proportional.
- Median t_{max} ranged from 0.75 hours to 2.25 hours.
- Geometric mean clearance varied from 38.49 mL/min to 58.08 mL/min.
- Geometric mean half-life varied from about 22 hours to about 37.5 hours.

PK/PD** properties of OATD-01 and **PK prediction for MAD Phase Ib studies



Chitinolytic activity in plasma is efficiently suppressed by all doses tested with >80% of inhibition at 24h at the lowest dose of 25 mg. The inhibition of chitinolytic activity is prolonged by higher doses.



Predicted steady state PK profile (protein-free and total plasma concentration) following oral daily administration of OATD-01.

***Phase Ib** - Multiple Ascending Dose (MAD) study design*

Study objectives
Primary objective:
- To assess safety and tolerability of **OATD-01** following multiple oral doses

Secondary objective:
- To assess the pharmacokinetics (PK) of **OATD-01** following multiple oral doses

Methodology
A randomized, double-blind, placebo controlled dose escalation study with ascending multiple oral doses of **OATD-01**

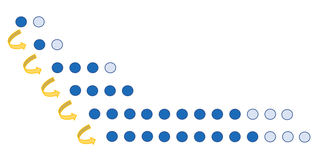
Number of subjects
27 male and 9 female subjects (12 subjects per cohort; 9 subjects on **OATD-01** and 3 subjects placebo) to be included

Criteria for evaluation
Safety variables:
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG (heart rate, PQ, QRS, QT, QTc), Holter ECG (Day -1, 10)
- Urine and blood clinical safety laboratory testing
- Physical examination/adverse events

Pharmacokinetic (PK) variables
- $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tlast}$, C_{max}, $C_{max(tmax)}$, $t_{1/2}$, Vz/f, CL/f

In-house evaluation
Determination of the chitinolytic activity
Determination of the OATD-01 metabolites

*Dosing for MAD study: **Phase Ib***



Cohort 1a: 25 mg (1 x 25 mg tablet x 10 days)
Cohort 1b: 25 mg (1 x 25 mg tablet x 10 days)
Cohort 1c: 25 mg (1 x 25 mg tablet x 10 days)
Cohort 1d: 25 mg (1 x 25 mg tablet x 10 days)
Cohort 2: 50 mg (2 x 25 mg tablet x 10 days)
Cohort 3: 100 mg (4 x 25 mg tablet x 10 days)

Summary

***Translational studies** in samples from ILDs*

- Chitinolytic activity was significantly increased in serum of patients with ILDs such as IPF and sarcoidosis
- CHIT1 localizes to remodeled areas of lungs of ILD patients (IPF, sarcoidosis, rheumatoid arthritis- and scleroderma-associated pulmonary fibrosis)
- Immunodetection of CHIT1 in human BAL cells and lung sections from ILD patients demonstrates predominantly macrophage-specific CHIT1 expression
- Very high and granulomatous structures-restricted expression of CHIT1 in sarcoidosis indicate strong association with disease pathology

***Phase Ia**: Safety Results*

- Single oral doses of 25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 600 mg OATD-01 were well tolerated
- Overall, 22 (45.8%) of 48 randomized subjects reported 39 treatment-emergent AEs (TEAEs)
- No serious treatment related adverse were recorded
- All TEAEs were of mild to moderate intensity and resolved by the end of the study.
- There were no deaths, other SAEs or other significant AEs; no subject discontinued the study due to AEs

***Phase Ia**: Conclusions*

- Single doses of **OATD-01** in the range of 25-600 mg **were well tolerated**.
- **OATD-01** was rapidly absorbed and generated dose-proportional plasma levels
- **OATD-01** exhibited excellent PK with plasma level > IC_{90} at 24h indicating once a day dosing
- **OATD-01** demonstrated strong PD activity in plasma even at the lowest dose of 25 mg with >80% target inhibition at 24h time-point.

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„Preclinical research and clinical trials of a first-in-class development candidate in therapy of asthma and inflammatory bowel disease”

European Funds Smart Growth

European Union
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