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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

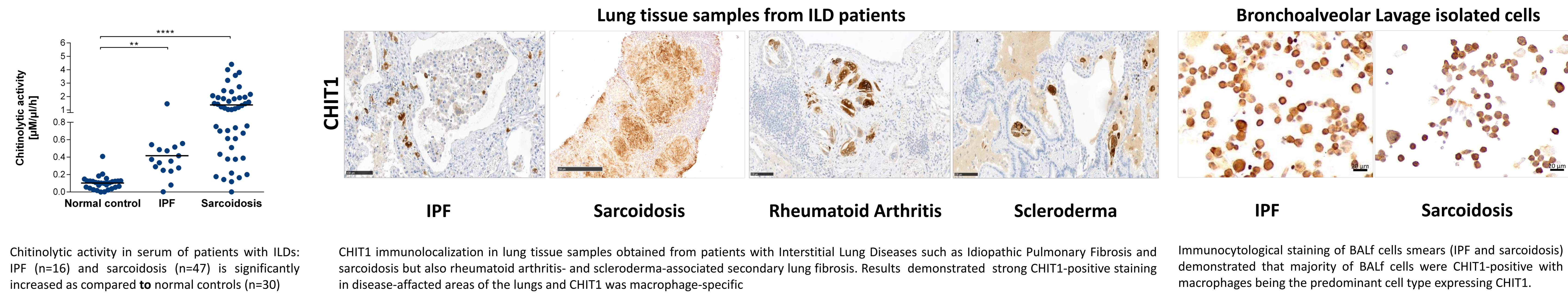
OATD-01 is a small molecular weight, potent inhibitor of both human chitinases. It has good oral bioavailability and excellent pharmacokinetic profile in several animal species.

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 <sub>50</sub> (nM)	8.5	20.8
IC <sub>90</sub> (nM)	68	188
K <sub>i</sub> (nM)	3.8	13.3

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



## 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

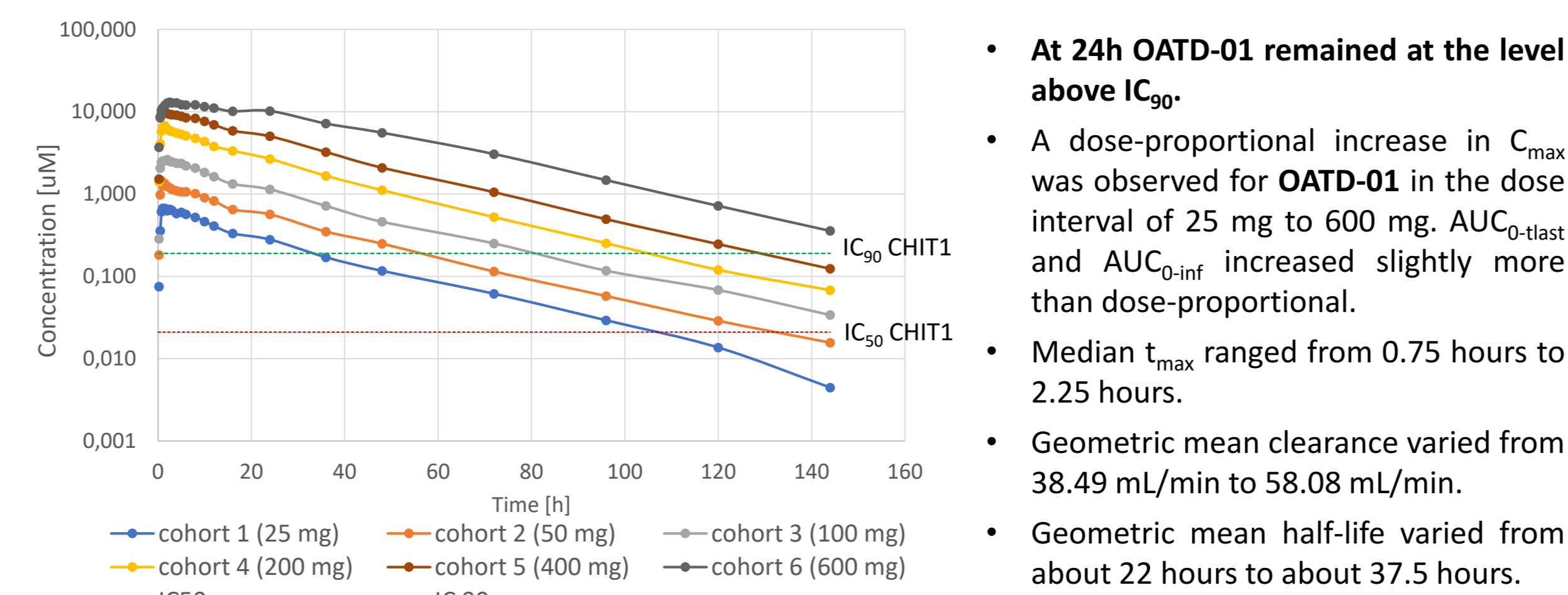
**Methodology**  
 A randomized, double-blind, placebo-controlled dose escalation study with ascending single oral doses of OATD-01

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

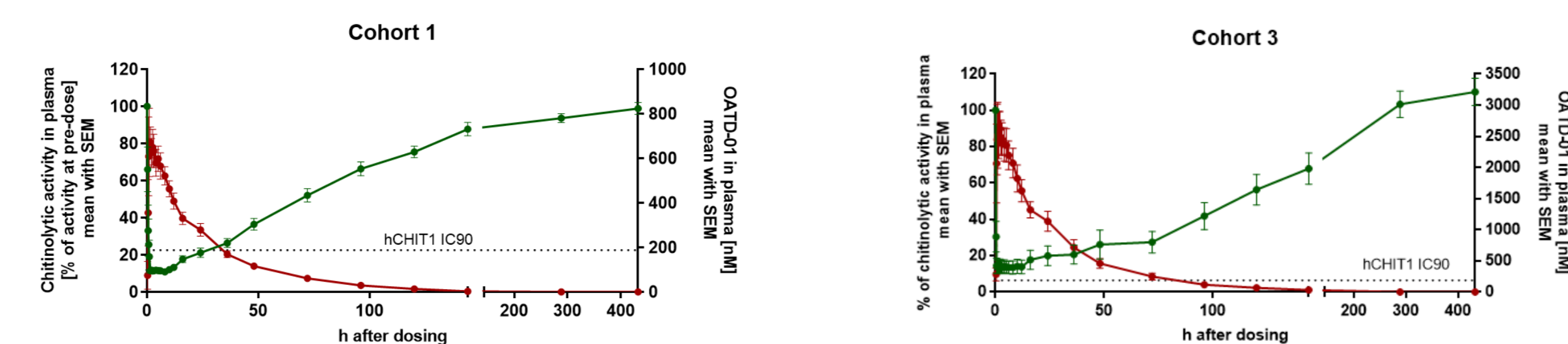
**Criteria for evaluation**  
 Safety variables:  
 • Vital signs (blood pressure, pulse rate, body temperature)  
 • 12-lead ECG (heart rate, PQ, QRS, QT, QTc)  
 • Urine and blood clinical safety laboratory testing  
 • Physical examination/adverse events  
 Pharmacokinetic (PK) variables:  
 • AUC<sub>0-inf</sub>, AUC<sub>0-tlast</sub>, C<sub>max</sub>, C<sub>max(tmax)</sub>, t<sub>1/2</sub>, Vz/f, CL/f

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

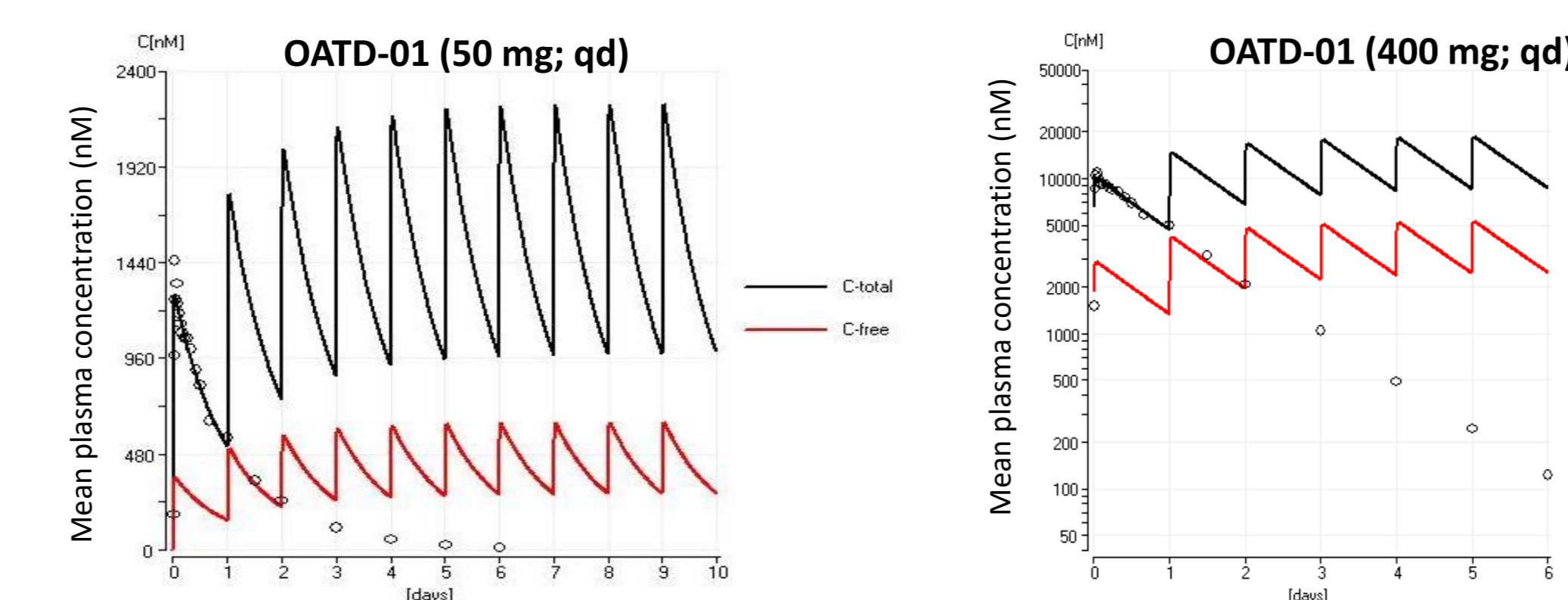
### Phase Ia PK: Mean plasma concentration of OATD-01 for Cohorts 1-6



### 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<sub>0-inf</sub>, AUC<sub>0-tlast</sub>, C<sub>max</sub>, C<sub>max(tmax)</sub>, t<sub>1/2</sub>, 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<sub>90</sub> 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.

### Financial support

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

