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Phase 1, First-in-Human Study of OATD-01, a Dual Chitinase Inhibitor

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OncoArendi Therapeutics

Background

Acidic mammalian chitinase (AMCase) and chitotriosidase (CHIT1) are the enzymatically active chitinases, which have been implicated in the pathology of diverse lung diseases. While the 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**, a small molecule, potent inhibitor of both AMCase and CHIT1, was identified as a promising clinical candidate based on its physicochemical and pharmacological properties. Following completion of pre-clinical evaluation we progressed the compound to the FiH study with healthy male volunteers with the goal to develop **OATD-01** as a treatment for respiratory diseases *e.g.* sarcoidosis, idiopathic pulmonary fibrosis (IPF) and/or asthma.

Clinical Rational

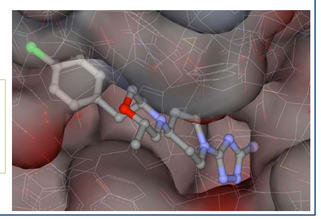
- Both active chitinases – AMCase and CHIT1 have been implicated in pathology of several respiratory diseases in humans including asthma.
- Highly elevated chitotriosidase (CHIT1) levels and activity were demonstrated in serum and BALf from patients with IPF and sarcoidosis to correlate with disease stage and progression.
- Results from preclinical and clinical studies demonstrated a role of CHIT1 in pathology of fibrosis and in formation of granulomas confirming that CHIT1 represents a novel therapeutic target for the interstitial lung diseases.
- Chitinases are strongly induced in *in vivo* mouse models of respiratory diseases in a chitin-independent fashion (e.g. bleomycin-induced pulmonary fibrosis).
- **OATD-01** demonstrated a significant, dose-dependent therapeutic efficacy in several mouse models including HDM-induced chronic model of asthma and bleomycin-induced model of lung fibrosis.

OATD-01 as a clinical candidate

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

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

X-Ray crystallography of **OATD-01** at the active site of CHIT1



OATD-01 FiH clinical study (Phase Ia)

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

Main inclusion criteria
Healthy male subjects, between 18 and 45 years of age inclusive, with a body mass index (BMI) 18 and 30 kg/m^2 inclusive and a body weight of ≥50 kg; non-smokers

IMP
Immediate release, non-coated tablets of 25 and 200 mg strength, with matching placebos

Criteria for evaluation

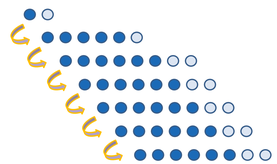
Safety variables:
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG (heart rate, PQ, QRS, QT, QTc)
- Urine and blood clinical safety laboratory testing
- Physical examination/adverse events

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

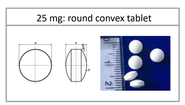
In-house evaluation
Determination of the chitinolytic activity
Determination of the OATD-01 metabolites

Dosing

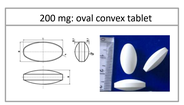
Cohort 1a: 25 mg (1 x 25 mg tablet)
Cohort 1b: 25 mg (1 x 25 mg tablet)
Cohort 2: 50 mg (2 x 25 mg tablet)
Cohort 3: 100 mg (4 x 25 mg tablet)
Cohort 4: 200 mg (1 x 200 mg tablet)
Cohort 5: 400 mg (2 x 200 mg tablet)
Cohort 6: 600 mg (3 x 200 mg tablet)



25 mg: round convex tablet



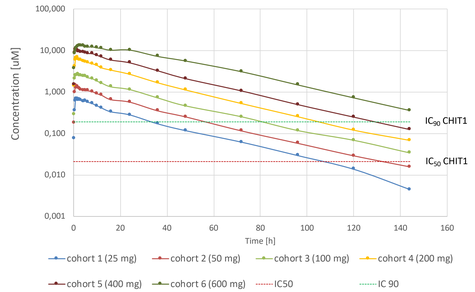
200 mg: oval convex tablet



Results – PK versus PD

Pharmacokinetics

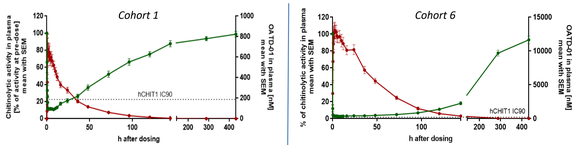
Mean plasma concentration of **OATD-01** for Cohorts 1-6



- After dosing, concentration of **OATD-01** in plasma rapidly increased. Mean plasma concentration curves of **OATD-01** reached their respective peaks at about 45 minutes to 2.5 hours post-dose. Thereafter, plasma concentrations of **OATD-01** declined, but remained above LLOQ in all subjects until 120 hours after dosing. Even at the follow-up visit, **OATD-01** plasma concentrations were still above LLOQ for 5 subjects of the 600 mg dose group.
- 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 volume of distribution ranged from 111.1 L to 155.5 L and geometric mean half-life varied from about 22 hours to about 37.5 hours.

PK/PD relationship

OATD-01 levels (red) *versus* chitinolytic activity (green) in plasma of subjects in Cohorts 1 and 6



- Chitinolytic activity in plasma is efficiently suppressed by all doses tested.
- The inhibition of chitinolytic activity is prolonged by higher doses.

Results - safety

Analysis of adverse events

- 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).
- 10 subjects reported 17 treatment-emergent adverse events (TEAE) considered as reasonably drug-related by the investigator.
- The most frequently recorded drug-related TEAE was electrocardiogram QT prolongation (QTcB formula) which was experienced by two subjects in the 400 mg group and by one subject in the 600 mg group.
- According to the Fridericia formula (QTcF) QT prolongation was experienced by only one subject in the 600 mg group.
- All electrocardiogram QT prolongation events were of mild intensity.
- 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.
- Laboratory parameters and vital signs showed no clinically relevant time- or dose-related changes and no relevant difference between active treatment and placebo. Most ECGs were judged as normal or abnormal not clinically relevant.

Conclusions

- Single doses of **OATD-01** in the range of 25-600 mg were well tolerated.
- Key adverse event was mild QT prolongation observed in the 400 and the 600 mg dose group.
- **OATD-01** was rapidly absorbed and generated proportional plasma levels depending on the dose.
- **OATD-01** was eliminated with Half-life of about 24 hours is suitable for once-a-day dosing.
- Based on the encouraging results of this FiH Phase Ia study we plan to progress **OATD-01** to a Phase Ib Multiple Ascending Dose study, followed by Phase II studies in sarcoidosis and/or IPF.

Financial Support

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

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