A Phase 1 Single and Multiple Dose-Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Effect of ARO-AAT on Serum Alpha-1 Antitrypsin Levels in Normal Adult Volunteers

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INTRODUCTION

Serum AAT levels were measured using turbidometry having a linear range of 0.0 to 20% below baseline. The primary endpoint was the change in serum AAT levels. Assessments include safety (including pulmonary function tests), PK, and change in serum AAT levels. Subjects were evaluated through at least Day 29 (35 mg single dose cohort) or Day 113 or until serum AAT returned to normal (>90 mg/dL) or to 20% below baseline. Serum AAT levels were measured using turbidometry having a LLOQ of 0.09 g/L.

METHODS

A single-center randomized, double-blind, placebo controlled single- and multiple-dose escalation study.
- Healthy volunteers, age 18-52
- A single-dose escalating cohorts: 35 (4 active: 4 placebo), open label (n=4): 100, 200, 300 mg.
- 3 multiple-dose escalating cohorts: 130, 200, 300mg (4 placebo: 4 active)
- Multiple-dose cohorts received three doses of ARO-AAT on Days 1, 29 and 57.
- Assessments include safety (including pulmonary function tests), PK, and change in serum AAT levels.
- Subjects were evaluated through at least Day 29 (35 mg single dose cohort) or Day 113 or until serum AAT returned to normal (>90 mg/dL) or to 20% below baseline. Serum AAT levels were measured using turbidometry having a LLOQ of 0.09 g/L.
- Pharmacokinetic data set, currently in progress.
- Serum AAT follow up return to baseline is ongoing.

AIM

To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics (change in serum alpha-1 antitrypsin levels) of single- and multiple-ascending doses of ARO-AAT in normal adult volunteers.

AIM

Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant genetic disorder causing liver disease in children and adults. Alpha-1 antitrypsin (AAT) is a glycoprotein produced primarily in hepatocytes. The PI2 mutation causes improper AAT folding and impaired secretion by hepatocytes leading to accumulation in the liver of AAT aggregates known as globules. Accumulated misfolded AAT (Z-AAT) can lead to a recurrent cycle of hepatic injury, fibrosis, cirrhosis and hepatocellular carcinoma. In a mouse model, reduced liver Z-AAT synthesis correlated to reduced serum AAT, and reduced Z-AAT globules and prevented progression and development of AATD-associated liver disease.

ARO-AAT is a hepatoctye targeted RNAi therapeutic designed to silence production of Z-AAT protein with the intent to:
- Prevent accumulation of disease-causing protein in liver
- Allow clearance of accumulated protein
- Prevent repeated cycles of cellular damage
- Reverse fibrosis associated with prior damage

RESULTS

Tolerability: Treatment emergent adverse events occurring in 1% subject at least possibly related to treatment

Serum AAT Relative Percentage Reduction Summary

<table>
<thead>
<tr>
<th>ARO-AAT Dose</th>
<th>Single Dose</th>
<th>Multiple-Dose</th>
<th>Average</th>
<th>SD</th>
<th>Max</th>
<th>SD</th>
<th>100 mg</th>
<th>200 mg</th>
<th>300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>NADIR Single Dose</td>
<td>NADIR Multiple-Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg ARO-AAT</td>
<td>0.0</td>
<td>-2</td>
<td>91.1</td>
<td>N=4</td>
<td>2/12%</td>
<td>6/29%</td>
<td>5/29%</td>
<td></td>
<td></td>
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<tr>
<td>160 mg ARO-AAT</td>
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<td>-2</td>
<td>91.1</td>
<td>N=4</td>
<td>2/12%</td>
<td>6/29%</td>
<td>5/29%</td>
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<td></td>
</tr>
<tr>
<td>200 mg ARO-AAT</td>
<td>0.0</td>
<td>-2</td>
<td>91.1</td>
<td>N=4</td>
<td>2/12%</td>
<td>6/29%</td>
<td>5/29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg ARO-AAT</td>
<td>0.0</td>
<td>-2</td>
<td>91.1</td>
<td>N=4</td>
<td>2/12%</td>
<td>6/29%</td>
<td>5/29%</td>
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</table>

CONCLUSIONS

- ARO-AAT has been well tolerated at all doses tested (up to 300 mg) given three times every 28 days.
- No deaths, SAEs or severe AEs have been reported.
- Most AEs in subjects receiving ARO-AAT were considered mild.
- The most common AEs were upper respiratory tract infection (39%) and headache (32%).
- There was no difference in FEV1 changes between placebo and active subjects.
- ARO-AAT at single- and multiple-doses produced robust reductions in serum AAT levels.
- Single-doses of 200 and 300 mg resulted in greater than 91% serum AAT reduction with 3 of 4 subjects having concentrations below the level of quantitation.
- An average serum AAT reduction of greater than 90% was sustained for 6-weeks in 200 and 300 mg single-dose cohorts.
- An average of greater than 90% reduction in serum AAT was sustained for greater than 14 weeks in the multiple-dose cohorts of 200 and 300 mg for subjects receiving all 3 doses.
- The maximum nadir reduction was 94%.
- Monthly serum AAT follow up is ongoing with 9 of 10 subjects levels at BLQ in the multiple-dose cohorts.
- Duration of response indicates that quarterly or less frequent dosing appears feasible.

REFERENCES

Christiantrials.gov identifier: NCT03362242