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

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 PiZ 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 hepatocyte 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

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.

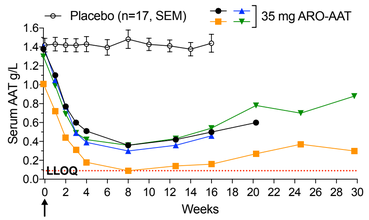
METHODS

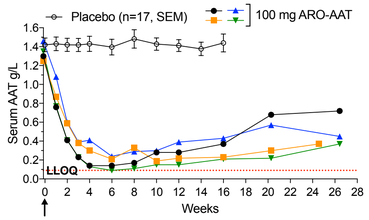
A single-center randomized, double-blind, placebo controlled single- and multiple-dose escalation study.

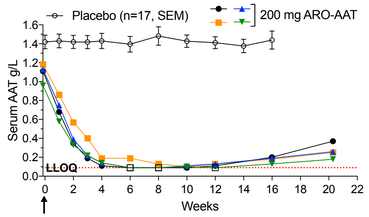
- Healthy volunteers, age 18-52.
- 4 single-dose escalating cohorts: 35 (4 active: 4 placebo), open label (n=4): 100, 200, 300 mg.
- 3 multiple-dose escalating cohorts: 100, 200, 300mg (4 placebo: 4 active).
- Multiple-dose cohorts received three doses of ARO-AAT on Days 1, 29 and 57.
- Assessments include 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.
- Data Cut offs: 24 Oct 2018, Serum AAT; 26 Oct 2018, Safety.

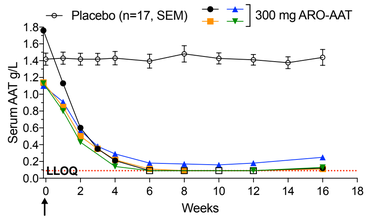
RESULTS

Individual Single-Dose Serum AAT Reduction

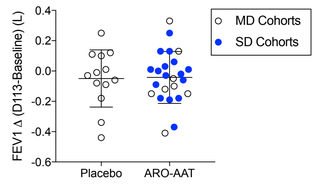




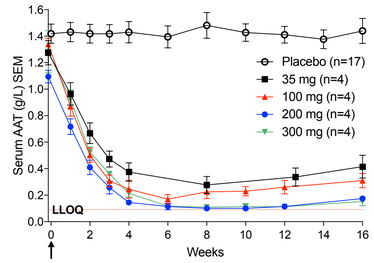




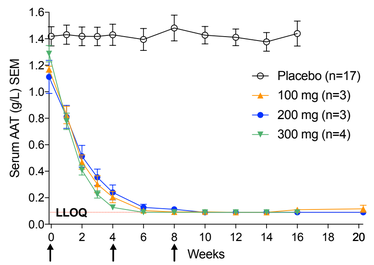
Pulmonary Function



Single-Dose Cohorts



Multiple-Dose Cohorts



- 45 healthy volunteers enrolled in the study. All have completed their End of Study visit.
- 16 received a single-dose of 35, 100, 200 or 300 mg ARO-AAT. 10 received 3 doses q28 days of 100, 200 or 300 mg ARO-AAT. 2 subjects did not receive their 3rd dose. 17 received placebo.
- Serum AAT values BLQ were set at the LLOQ of 0.09 g/L for cohort mean calculations and indicated with an open square in the individual serum AAT graphs.

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

AE Terms	SD 35 mg n = 4	MD 100 mg n = 4	SD 100 mg n = 4	MD 200 mg n = 4	SD 200 mg n = 4	MD 300 mg n = 4	SD 300 mg n = 4	Placebo n = 17 (#/%)	ARO-AAT n = 28 (#/%)
Upper respiratory tract infection		2	1	1	1	2	4	4/24%	11/39%
Headache	2	1		2	1	1	2	2/12%	9/32%
Sore throat/throat irritation/dry throat	1	1	2		1	1		5/29%	6/21%
Rhinorrhea		1	2	1			1	3/18%	5/18%
Nausea, Dyspepsia	1			2		1	2	1/6%	6/21%
Pain/phlebitis at cannula site	2		2			1		2/12%	5/18%
AE at injection site (e.g. pain, bruising, erythema)			2	1	1	1	1	0/0%	6/21%
Cough			1			1	1	3/18%	3/11%
Abdominal Pain			1	2			2	1/6%	5/18%
Back or neck pain		2				1		2/12%	3/11%
Venipuncture bruise or tenderness		1			2			2/12%	3/11%
Sinus/nasal congestion, sinusitis							1	3/18%	1/4%
Emesis		1	1	1				1/6%	3/11%
Lightheadedness, Dizziness	1			1			1	1/6%	3/11%
Insect bites	2							1/6%	2/7%
Ankle pain, injury	1		1					0/0%	2/7%
Musculosketetal chest pain			1					1/6%	1/4%
Laceration/Abrasion								2/12%	0/0%
Nose bleed, Blood stained nasal mucous		1		1				0/0%	2/7%
Cold sores, Scattered mouth blisters		1	1					0/0%	2/7%
Gastroenteritis								2/12%	0/0%
Feeling Feverish								2/12%	0/0%
Total AEs occurring in >1 subject	10	11	15	12	6	9	15	38	78

- There were no AEs that increased in frequency or severity with dose
- No AEs were rated as serious, or severe
- Most AEEs were graded as mild
- Most frequent AEs in subjects receiving ARO-AAT were upper respiratory tract infection (39%) and headache (32%)
- Fifty doses of ARO-AAT were administered with 6 (12%) resulting in an AE at the injection site

SD, Single-Dose; MD, Multiple-Dose

Serum AAT Relative Percentage Reduction Summary

	NADIR Single Dose				NADIR Multiple-Dose		
	35 mg N=4	100 mg N=4	200 mg N=4	300 mg N=4	100 mg N=3	200 mg N=3	300 mg N=4
Average Max	79.0	87.7	>91.5	>91.1	>92.2	>91.2	>93.0
SD	8.5	4.5	0.6	4.0	0.2	2.7	0.7
Max	91.1	93.3	>92.0	>94.9	>92.7	>93.3	>93.7
BLQ, n=	0	0	3	3	2	3	4

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 is 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

Clinicaltrials.gov identifier: NCT03362242

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