ARO-HSD, an investigational RNAi therapeutic, demonstrates reduction in ALT and hepatic *HSD17B13* mRNA and protein in patients with NASH or suspected NASH

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INTRODUCTION

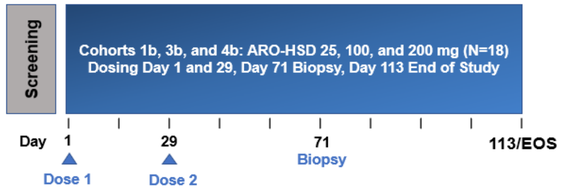
- Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Non-alcoholic steatohepatitis (NASH) describes a subgroup of NAFLD in which hepatic cell injury and inflammation has developed over background steatosis. Patients with NASH are at higher risk of adverse outcomes such as cirrhosis and liver-related mortality. There is a high unmet medical need for therapies that will slow the progress of, halt, or reverse NASH and NAFLD.
- Human genetic data indicate that a loss-of-function (LOF) mutation in *HSD17B13* provides protection against alcoholic hepatitis, cirrhosis, and NASH, with approximately 30-50% risk reduction compared to non-carriers (Abul-Husn 2018).
- ARO-HSD is a RNAi-based therapy designed to mimic the naturally occurring LOF genetic variation in *HSD17B13* by reducing its expression in hepatocytes.

AIM

The aim of the ongoing Ph.1/2a study AROHSD1001 is to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamic effects of ARO-HSD in normal healthy volunteers (NHV) as well as in patients with NASH or suspected NASH.

METHODS

Figure 1: AROHSD1001 Study Design–NASH/Suspected NASH patient cohorts



- 25, 100, or 200 mg ARO-HSD administered subcutaneously on Day 1 and Day 29
- NASH or Suspected NASH patients, based on MRI-PDFF >8% and ALT>ULN
- Liver biopsy performed at screening and at Day 71 (week 10)
- Patients were followed until Day 113 (week 16)

- **Assessments**: Safety, changes in hepatic HSD17B13 mRNA and protein, ALT and AST, liver stiffness by FibroScan®, liver fat fraction by MRI-PDFF, lipids, and other biomarkers of NAFLD/NASH
- **Data Cut**: 12 August 2021

RESULTS

Table 1: Baseline Characteristics

Mean (min, max)	ARO-HSD 25 mg (N=6)	ARO-HSD 100 mg (N=6)	ARO-HSD 200 mg (N=6)
Age (years)	46 (32,56)	45 (40,50)	43 (22,61)
Male (%)	5 (83%)	5 (83%)	4 (67%)
Weight (kg)	96 (68, 120)	87 (66,116)	97 (74,117)
BMI (kg/cm2)	32 (26,41)	29 (25,36)	34 (28,39)
Genotype			
HSD17B13 rs72613567, n (%)			
T/T	5 (83%)	4 (67%)	3 (50%)
T/TA	1 (17%)	2 (33%)	3 (50%)
PNPLA3 rs738409, n (%)			
C/C	3 (50%)	5 (83%)	3 (50%)
C/G	2 (33%)	0	2 (33%)
G/G	1 (17%)	1 (17%)	1 (17%)
Relevant Medical History			
NASH	1 (17%)	1 (17%)	2 (33%)
Hepatic Steatosis	3 (50%)	3 (60%)	2 (40%)
Hyperlipidemia	3 (50%)	3 (50%)	1 (17%)
Type 2 diabetes mellitus	2 (33%)	1 (20%)	3 (50%)

Figure 2: ARO-HSD Treatment reduces ALT, AST, and GGT levels

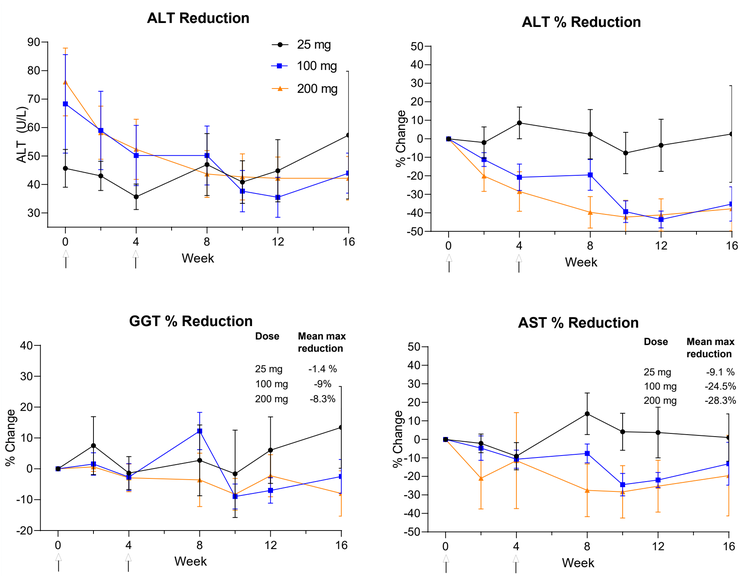


Table 2: Summary of Pharmacodynamic Response Relative to Baseline

Mean (min, max)	ARO-HSD 25 mg (N=6)	ARO-HSD 100 mg (N=6)	ARO-HSD 200 mg (N=6)
Hepatic HSD17B13 mRNA at Day 71	-56.9% (-60.5%, -50.7%)	-85.5% (-96.1%, -61.6%)	-93.4% (-98.6%, -90.8%)
Hepatic HSD17B13 Protein at Day 71[a]	<-34.2% (<-92.4%, 53.5%)	<-86% (-98.0%, <-63.0%)	-82.7% (-85.2, -80.2%)[b]
Serum ALT at Day 113			
Baseline (U/L)	45.7	68.3	76
Day 71 (%)	-7.7%	-39.3%	-42.2%
Day 85 (%)	-3.5%	-43.6%	-41.1%
Day 113 (%)[c]	2.62%	-35.2%	-37.8%
MRI-PDFF at Day 71	14.4% (-36.0%, 87.9%)	-7.6% (-40.7%, 23.6%)	-7.3% (-24.1%, 5.9%)
FibroScan (kPa) at Day 71	16.7% (-5.3%, 37.5%)	2.2% (-16.5%, 33.9%)	4.2% (-36.8%, 54.4%)

[a] Several patients had HSD17B13 protein levels at D71 below lower limit of quantitation (LLOQ), in which case LLOQ was used for calculation of means
[b] n=2 (3 samples with baseline HSD17B13 below LLOQ, 1 sample failed assay acceptance criteria)
[c] Cohort 1b (25mg): 3/6 patients have completed study. Remaining patients completed up to Day 85. Cohort 3b (100mg): 5/6 patients have completed study. Remaining patients completed up to Day 85. Cohort 4b (200mg): 5/6 patients have completed study. Remaining patients completed up to Day 85

Figure 3: Change in liver stiffness (kPa) and liver fat fraction from baseline

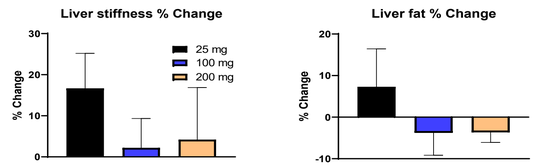


Table 3: Summary of Safety and Adverse Events

Subject Incidence, n (%)	ARO-HSD 25 mg (N=6)	ARO-HSD 100 mg (N=6)	ARO-HSD 200 mg (N=6)	All (N=18)
Treatment-emergent AEs (TEAEs)	3 (50%)	2 (33.3%)	3 (50%)	8 (44.4%)
TEAEs in 3 or more subjects[a]	--	--	--	N/A
Treatment-related TEAEs	1 (16.7%)	1 (16.7%)	2 (33.3%)	4 (22.2%)
Treatment-emergent SAE	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[a] All reported TEAEs were single event terms across various system organ classes

RESULTS

Safety

- ARO-HSD was well-tolerated in patients, with no ARO-HSD-related serious adverse events reported, no AE leading to drug discontinuations, and no ARO-HSD-related clinically significant adverse laboratory trends observed.
- One treatment emergent SAE of soft tissue injury that required hospitalization was reported in cohort 4b. This event was considered not related to study drug.

Pharmacodynamic Response of ARO-HSD:

- Dose-dependent pharmacodynamic effect on hepatic HSD17B13 mRNA was observed in all patients. At 200 mg, all patients showed >90% mRNA reductions.
- Hepatic HSD17B13 protein levels were reduced at all dose levels, with multiple measurements below the assay's LLOQ.
- Decreases in ALT and AST were observed at doses ≥ 100 mg
- 9 of 18 patients had liver fat reductions on MRI-PDFF of 4-41%.
- 6 of 18 patients had reduction in liver stiffness (kPa) on FibroScan of 4-37%.
- PD effect was not affected by HSD17B13 (rs72613567, T>TA) or PNPLA3 (rs738409, C>G) mutations

CONCLUSIONS

ARO-HSD has been well tolerated at doses up to 200 mg given on Day 1 and Day 29. Significant dose dependent reductions in liver HSD17B13 mRNA and protein were observed and corresponded with ALT and AST reductions of up to 44% and 28%, respectively, which may be a clinically meaningful signal of reduced liver inflammation. Based on duration of ALT reduction, quarterly or less frequent dosing appears feasible.

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REFERENCES

Clinicaltrials.gov identifier: NCT04202354

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