ARO-HSD reduces hepatic HSD17B13 mRNA expression and protein levels in patients with suspected NASH

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INTRODUCTION

HSD17B13 is a member of the hydroxysteroid dehydrogenase family involved in the metabolism of hormones, fatty acids, and bile acids. HSD17B13 expression is markedly upregulated in hepatocytes of mice and humans with NAFLD (Su et al., 2014). Human genetic data indicate that a loss-of-function mutation in HSD17B13 provides strong protection against alcoholic and non-alcoholic steatohepatitis (Abul-Husn et al. 2018). Additionally, no phenotypic adverse findings has been described in individuals harboring HSD17B13 LOF mutations. This protective effect has inspired therapeutic interest in HSD17B13 gene silencing as a potential therapy for liver disease.

ARO-HSD is an RNAi based therapeutic composed of a synthetic double-stranded RNAi trigger designed to selectively target HSD17B13 mRNA in hepatocytes, thereby reducing the expression of HSD17B13 protein.

AIM

The aim of the ongoing study AROHSD1001 (NCT04202354) 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

NHVs were eligible to receive ARO-HSD by subcutaneous injection in a double blind, placebo-controlled manner and patients with NASH or suspected NASH in an open label fashion.

- Male and female adult NHVs received a single-dose of 25, 50, 100 and 200 mg (4 active, 4 placebo per dose level) and were followed through Day 113.
- In the first NASH patient cohort (cohort 3b) five patients with suspected NASH based on MRI-PDFF liver fat > 8% and ALT > ULN received two doses of 100 mg on days 1 and 29 and were followed through day 85 (n=1) or day 113 (n=4).
- Safety was assessed in all subjects including laboratory measures of liver function.
- A liver biopsy was collected at baseline and Day 71 in patients.
- Change from baseline in hepatic HSD17B13 mRNA expression (qRT-PCR) and protein levels (Western blot) were measured by validated methods.

RESULTS

Baseline Demographics

Normal healthy volunteers

Median (min, max)	25 mg (n=4)	50 mg (n=4)	100 mg (n=4)	200 mg (n=4)	Placebo (n=16)
Age (years)	22 (19, 31)	25 (24, 50)	32 (20, 45)	35 (22, 41)	35 (19,52)
Male (%)	3 (75%)	2 (50%)	3 (75%))	1 (25%)	6 (38%)
Weight (kg)	65.5 (53.2, 68.8)	72.1 (58.3, 88.6)	75.6 (64.0, 89.1)	82.2 (56.5, 93.0)	74.3 (51.5, 96.6)
BMI (kg/cm^2)	22.1 (21.9, 24,1)	23.8 (20.2, 27.3)	25.6 (20.6, 28.1)	30.6 (21.0, 31.5)	25.3 (21.8, 31.0)

Patients with suspected NASH

Median (min, max)	Patients with suspected NASH (n=5)
Age (years)	43 (40,50)
Male (%)	4 (80%)
Weight (kg)	81.6 (65.80, 115.65)
BMI (kg/cm^2)	29.0 (25.7, 36.5)
MRI-PDFF (%)	17.7 (10.6, 25.2)
ALT (U/L)	68 (31, 144)
Genotype	
HSD17B13, n (%) T/T T/TA	 3 (60%) 2 (40%)
PNPLA3, n (%) C/C G/G	 4 (80%) 1 (20%)
Relevant Medical History	
NASH	1 (20%)
Hepatic steatosis	3 (60%)
Hyperlipidaemia	3 (60%)
Type 2 diabetes mellitus	1 (20%)

Safety

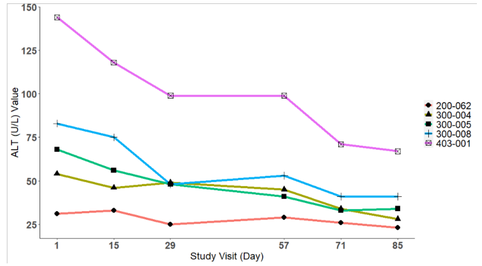
Treatment emergent adverse events observed in >1 subject						
	NHV (%)					Patients with suspected NASH (%)
Preferred Term	25 mg (n=4)	50 mg (n=4)	100 mg (n=4)	200 mg (n=4)	Placebo (n=16)	100 mg (n=5)
Headache	0	0	1 (25.0)	0	2 (12.5)	1 (20)
Abdominal pain	0	0	1 (25.0)	0	1 (6.3)	0
Dermatitis	0	0	0	0	2 (12.5)	0
Injection site bruising	1 (25.0)	0	1 (25.0)	0	0	0
Injection site erythema	0	0	0	2(50.0)	0	0
Upper respiratory tract infection	1 (25.0)	0	0	0	1 (6.3)	0

- All adverse events were mild. There were no ARO-HSD associated grade 3 or 4 laboratory abnormalities (NCI-CTCAE v5.0).
- No drug related serious or severe adverse events were reported and there were no drug discontinuations.
- Adverse events were similar between subjects receiving ARO-HSD or placebo. Two instances of mild injections site bruising and mild injection site erythema were observed in ARO-HSD treated subjects only.

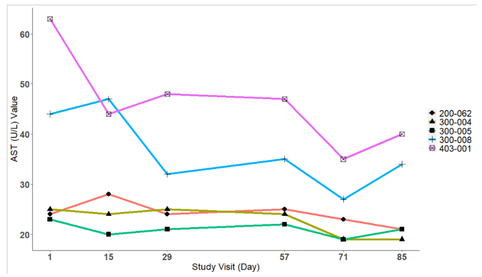
Pharmacodynamic Responses

Pharmacodynamic Response (Percent Change from Baseline)						
	100 mg ARO-HSD					
Patient Number	200-062	300-004	300-005	300-008	403-001	Cohort Mean N=5
Hepatic HSD17B13 mRNA at Day 71	-61.6%	-86.7%	-94.6%	-96.1%	-79.8%	-83.8%
Hepatic HSD17B13 Protein at Day 71	-91.9%	-96.7%	<-63.0%* (<LLOQ)	<-82.6%* (<LLOQ)	<-83.7%* (<LLOQ)	<-83.6%*
Serum ALT at Day 85 Baseline (U/L) Day 85 (%)	 31 -25.8%	 54 -48.1%	 68 -50.0%	 83 -50.6%	 144 -53.5%	 76 -45.6%
MRI-PDFF at Day 71	23.6%	19.2%	-40.7%	5.4%	-27.2%	-3.9%
*D71 value < lower limit of quantitation (LLOQ), LLOQ used for calculation						

ALT reductions in patients with suspected NASH



AST reductions in patients with suspected NASH



- There were no significant changes in weight or lipid parameters (total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, VLDL-C)
- PD effect was not affected by HSD17B13 (rs72613567, T>TA) or PNPLA3 (rs738409, C>G) mutations.

CONCLUSIONS

ARO-HSD was well tolerated without any identified safety signal in healthy volunteers given a single dose of ARO-HSD at 25, 50, 100 or 200 mg and in 5 patients with suspected NASH given 100 mg ARO-HSD on Days 1 and 29.

All suspected NASH patients showed a strong PD effect measured by liver biopsy at Day 71.

- HSD17B13 mRNA reductions were a mean of 84% with a range of 62-96%.
- HSD17B13 protein reductions were greater than 83%. Two patients had a protein decrease of 92% and 97%, while the other 3 patients Day 71 measurements were below the assay's level of quantitation.

Mean ALT reduction from baseline was 46% with all patients showing reductions ranging 26-53%.

ARO-HSD is the first investigational RNAi therapeutic to demonstrate robust inhibition of hepatic HSD17B13 mRNA and protein expression with associated reductions in ALT.

These data support continued development of ARO-HSD in patients with alcoholic and non-alcoholic steatohepatitis.

Additional multi-dose patient cohorts receiving 25 mg or 200 mg ARO-HSD will be analyzed pending availability of day 71 liver biopsies.

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