Safety and pharmacokinetics of DUR-928 in patients with non-alcoholic steatohepatitis– A Phase 1b study

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INTRODUCTION

DUR-928 is an endogenous, small molecule, epigenetic regulator with a role in lipid metabolism, inflammation and cell survival. Pre-clinical data have demonstrated that DUR-928 is well tolerated and can reverse certain histopathological changes associated with Non-alcoholic Steatohepatitis (NASH).[1] Previous studies in healthy subjects indicated that DUR-928 was well-tolerated with no significant drug-related adverse events.

AIMS

To assess the safety and pharmacokinetics (PK) of DUR-928 in liver function impaired (NASH) patients using single oral administration at two dose levels.

To explore the biological effects of DUR-928 through biomarker analysis.

METHODS

- We performed a Phase 1b single dose ranging (50 mg and 200 mg) safety/PK study of orally-administered DUR-928 in biopsy-confirmed NASH patients and matched control subjects (MCS) (matched by age, BMI, and gender) with normal liver function (**Table 1**).
- NASH was defined as:
  - NAS ≥ 4 on biopsy, or
  - Radiological evidence of steatosis in conjunction with elevated ALT and exclusion of other liver diseases.
- Safety and PK were recorded and examined pre-dosing and post-dosing.
- PK parameters, biochemical, haematological and exploratory biomarkers were monitored pre-dosing and post-dosing.

Table 1. Patient Demographics (mean ±SD)

	Cohort 1 (50 mg)		Cohort 2 (200 mg)	
Demographics	NASH	MCS	NASH	MCS
# of Patients	10	6	10	6
Age (yrs)	53.4 (10.7)	56.8 (6.5)	53.2 (12.9)	54.7 (6.0)
BMI (kg/m2)	34.7 (6.2)	31.2 (2.4)	36.6 (6.4)	33.2 (4.4)
Gender (M/F)	5/5	5/1	5/5	3/3
Baseline ALT (U/L)	66.7 (18.9)	19.3 (6.5)	78.9 (45.5)	20.8 (4.8)
Cirrhotic Patients	2	--	3	--
Non-Cirrhotic Patients	6	--	5	--
Undetermined	2	--	2	--

Table 2. Pharmacokinetic Parameters (mean ±SEM)

	Cohort 1		Cohort 2	
PK Parameters	**NASH**	**MCS**	**NASH**	**MCS**
Cmax (ng/mL)	113.2 (36.3)	94.0 (27.4)	332.7 (99.5)	260.5 (54.8)
Tmax (hr)	2.4 (0.8)	3.0 (1.1)	2.9 (1.2)	2.7 (1.0)
T½ (hr)	1.6 (0.2)	1.7 (0.3)	1.9 (0.4)	1.7 (0.4)
AUClast (ng*hr/mL)	512.7 (219.1)	476.5 (187.6)	1723.7 (470.9)	1316.9 (203.4)
AUCinf (ng*hr/mL)	528.1 (216.4)	487.9 (190.2)	1732.6 (470.5)	1325.5 (202.9)

BIOMARKERS

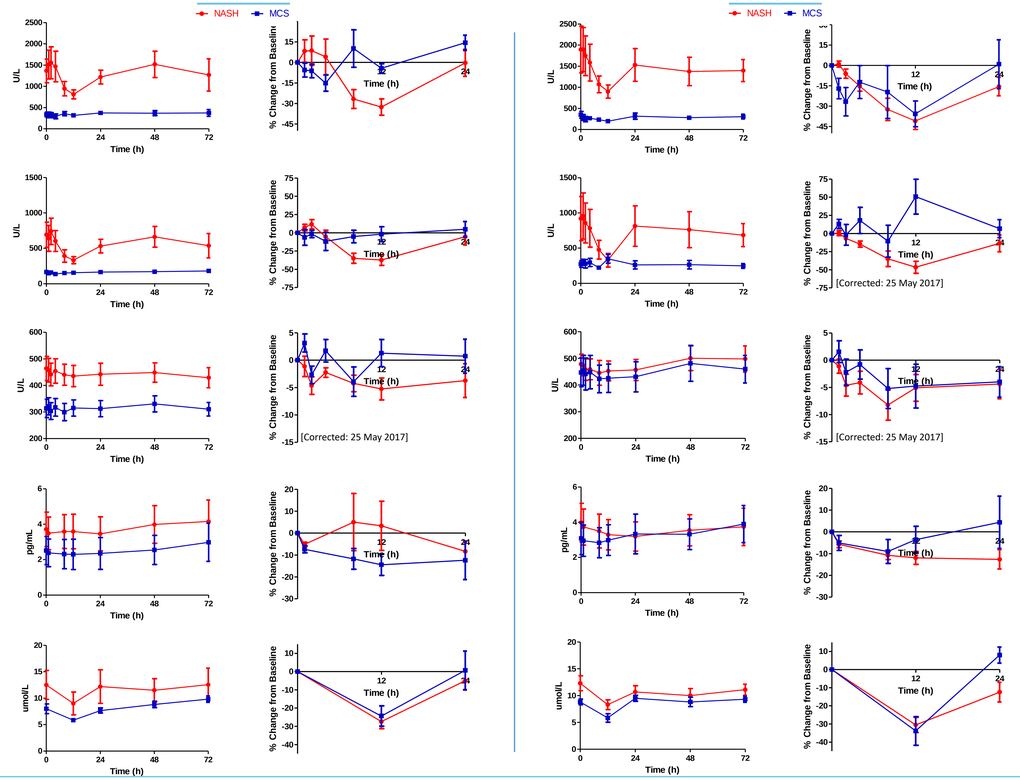
Figure 1. fCK-18

Figure 2. cCK-18

Figure 3. IL-18

Figure 4. hsCRP

Figure 5. Total Bilirubin



RESULTS

In both cohorts, DUR-928 was well tolerated overall. There was approximately a 10-30% increase in DUR-928 exposure in NASH patients compared to MCS. (**Table 2**). A single SAE (shortness of breath), designated as possibly related to study drug, was reported in Cohort 2 in a NASH patient with prior history of arrhythmia and an ongoing viral infection. No unusual abnormal biochemistry was observed and the symptom spontaneously resolved. **Table 4** summarizes all adverse events reported during the study.

Exploratory biomarker analysis indicated a single oral dose of DUR-928 resulted in reduction from baseline of both full-length and cleaved cytokeratin-18 (CK-18), IL-18, hsCRP and bilirubin (**Figures 1-5**) in both cohorts. Other cytokine levels are shown in **Table 3**. There was also a reduction of creatine kinase observed, following DUR-928 dosing in both cohorts (data not shown). Overall, there were small or no changes in serum liver enzymes, including ALT, AST, GGT, and ALP, as well as in other biochemical markers, including HOMA-IR, creatinine, and BUN (data not shown).

Table 3. Cytokines (mean ±SEM)

Cytokine (pg/mL)	Dose	Group	Time (hr) 0	12	24	48	72
TNFα	Cohort 1	NASH (N=6)	48.2 (24.3)	62.4 (28.0)	52.2 (26.3)	59.2 (27.2)	48.6 (26.5)
		MCS (N=3)	1.9 (0.8)	2.2 (0.8)	2.3 (0.9)	2.6 (1.0)	2.0 (0.8)
	Cohort 2	NASH (n=8)	20.9 (12.2)	21.3 (12.9)	20.3 (11.9)	18.2 (13.2)	21.0 (12.4)
		MCS (n=4)	43.5 (23.6)	42.3 (23.0)	41.8 (22.6)	44.8 (24.4)	43.6 (23.6)
IL-1β	Cohort 1	NASH (N=6)	11.6 (5.3)	12.3 (5.2)	10.5 (4.8)	11.3 (5.2)	9.0 (4.9)
		MCS (N=3)	1.4 (0.4)	1.1 (0.3)	1.1 (0.3)	1.3 (0.3)	1.5 (0.2)
	Cohort 2	NASH (n=8)	6.7 (3.6)	6.1 (3.3)	6.2 (3.1)	4.7 (3.1)	6.6 (3.5)
		MCS (n=4)	8.3 (4.7)	7.7 (4.4)	7.6 (4.1)	7.9 (4.4)	8.0 (4.4)
IL-6	Cohort 1	NASH (N=6)	7.6 (1.7)	12.7 (2.0)	9.8 (1.9)	7.8 (2.1)	7.4 (2.0)
		MCS (N=3)	5.0 (0.7)	18.8 (8.6)	7.1 (1.0)	4.8 (0.8)	4.9 (0.9)
	Cohort 2	NASH (n=8)	10.4 (3.6)	10.3 (1.9)	15.8 (5.3)	7.9 (1.3)	7.4 (1.5)
		MCS (n=4)	8.6 (1.7)	14.9 (3.0)	11.7 (2.0)	7.7 (2.4)	7.8 (2.0)
IL-12	Cohort 1	NASH (N=6)	202.3 (87.3)	259.0 (95.1)	205.6 (88.0)	209.5 (92.7)	170.6 (89.6)
		MCS (N=3)	12.3 (7.4)	11.8 (6.7)	13.5 (8.4)	12.9 (7.7)	16.3 (10.0)
	Cohort 2	NASH (n=8)	91.5 (47.8)	91.6 (48.8)	89.9 (47.2)	58.8 (38.7)	93.0 (49.2)
		MCS (n=4)	166.2 (84.4)	163.1 (82.3)	170.1 (84.0)	172.9 (88.7)	166.0 (84.8)

Table 4.

Adverse Event	Cohort 1		Cohort 2	
	NASH	MCS	NASH	MCS
Headache	3	2	3	1
Diarrhea	2	0	1	2
Vessel puncture site bruise	2	0	0	0
Fatigue	0	0	1	1
Dry Mouth	1	0	0	0
Palpitations	1	0	0	0
Polydipsia	1	0	0	0
Motion sickness	1	0	0	0
Edema peripheral	1	0	0	0
Dizziness	1	0	0	0
Epistaxis	1	0	0	0
Hot flush	0	0	1	0
Dyspnea	0	0	1	0
Dysgeusia	0	0	1	0
Epigastric discomfort	0	0	1	0

CONCLUSIONS

This study confirms the safety and tolerability of orally-administered DUR-928 across a spectrum of cirrhotic and non-cirrhotic NASH patients. DUR-928 plasma exposure is not significantly increased in NASH patients compared to MCS.

Biomarker analysis provides biological plausibility for a potential therapeutic effect of DUR-928 in NASH. In particular, a single oral dose of DUR-928, at both low and high doses, resulted in a reduction of CK-18 and bilirubin, especially in NASH patients.

These findings, together with the preclinical data, support the ongoing development of DUR-928 as a potential therapy for NASH.

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REFERENCE

1. **Kim M-J et al**. DUR-928, an endogenous regulatory molecule, exhibits anti-inflammatory and antifibrotic activity in a mouse model of NASH. *AASLD: Emerging Trends in NAFLD* Meeting*, 2017*

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