Safety and Pharmacokinetics of DUR-928 in Hepatic Function Impaired Subjects

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BACKGROUND

- *DUR-928, 5-cholesten-3β, diol 3-sulfate (25HC3S), is a*n endogenous sulfated oxysterol and an epigenetic regulatory molecule.
- Modulates hepatic lipid metabolism
  - Decreases fatty acid, cholesterol and triglyceride biosynthesis
  - Regulates lipid absorption and transportation
  - Improves insulin sensitivity and glucose tolerance
- Regulates inflammatory response
  - Reduces inflammatory cell infiltration in organs, including liver, kidney and lungs
  - Reduces 'cytokine storm' induced by LPS
- Improves cell survival
  - Reduces markers of cell death
- Improves liver function
  - Lowers serum bilirubin
- Under development for multiple indications, including treatment of acute organ injury, such as alcohol-associated hepatitis, and treatment of chronic liver/metabolic disease, such as NASH.

STUDY OBJECTIVES AND DESIGN

Phase 1 Study: Safety and PK of DUR-928 in Subjects with Hepatic Function Impairment (HI)

- Open label, multi-center
- Objectives:
  1. Evaluate the safety and tolerability of DUR-928
  2. Determine the PK of a single oral dose of DUR-928
  3. Assess pharmacodynamic signals (biomarkers) of DUR-928
- Key eligibility criteria:
  - Age 18 or older
  - Moderate HI had CP Score of 7 – 9, and Severe, CP score of 10 -15 on the CP classification at screening, and had a diagnosis of chronic (> 6 months) and stable HI
  - Matched Control Subjects (MCS) with normal hepatic function were matched by gender, BMI (± 20%) and age (± 10 years)

STUDY OBJECTIVES AND DESIGN

Exclusion Criteria for HI Subjects

- eGFR < 50 mL/min/1.73 m^2
- Presence of > 8x ULN of AST, ALT or bilirubin
- Require frequent paracentesis
- Presence of cholestatic liver disease
- History of liver transplantation
- Active infection
- Uncontrolled diabetes

Study Design

Part	Cohort	Hepatic Function Classification	CP Score	Cohort Size
A	1	Moderate HI	B (7 - 9 points)	10
		Normal (MCS[1])	N/A (Normal)	10
B	2	Severe HI[2]	C (10 - 15 points)	7

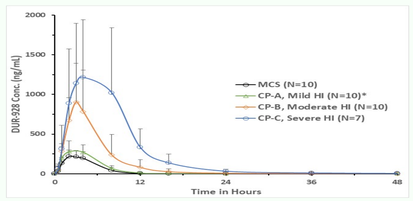
[1] Only one demographically matched MCS cohort was needed across both the HI groups

[2] The dose for this cohort was determined by the Dose Escalation Committee (Investigator, Medical Monitor, and the Sponsor) based on the review of safety and PK results from Cohort 1

- Subjects were housed at the CRU until 48 hour after dosing. The time points for sample collection were: Time 0 (pre-dose), 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 36 and 48 hr. post-dose.
- Biomarker samples were collected at pre-dose, 12, 24 and 48 hr. post-dose.

RESULTS

Mean (SD) Concentration vs. Time Profile of 200 mg oral DUR-928



* Data of CP-A, Mild HI were from an earlier study

RESULTS

Demographics

Characteristic	MCS (N=10)	Moderate HI (N=10)	Severe HI (N=7)
Age (years)			
Median	59.0	60.5	58.0
Min - Max	50 - 72	53 - 69	51 - 60
Gender			
Male	3	3	2
Female	7	7	5
Body Mass Index (kg/m^2)	29.6	32.1	28.4
Median	23.4 – 34.0	25.4 – 38.8	22.3 – 39.4
Min - Max			
Race, N (%)			
White	8 (80%)	9 (90%)	6 (85.7%)
Non-white	2 (20%)	1 (10%)	1 (14.3%)
Hepatic comorbidities			
ascites	---	10 (100%)	7 (100%)
peripheral edema	---	8 (80%)	5 (71.4%)
encephalopathy	---	7 (70%)	5 (71.4%)

PK Parameters of DUR-928 Following 200 mg PO Dose

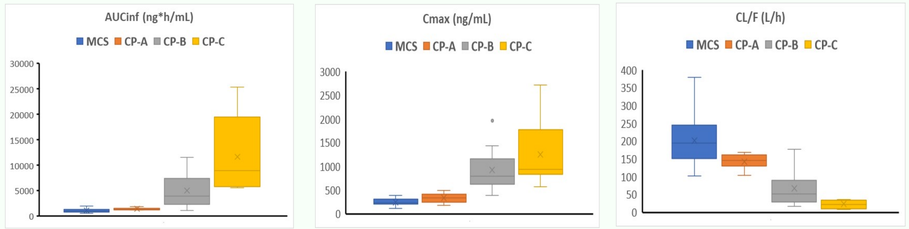
PK Parameter Mean ± SD	MCS	Mild HI (CP-A)* (N=10)	Moderate HI (CP-B) (N=10)	Severe HI (CP-C) (N=7)
T½ (h)	2.1 ± 0.7	2.51 ± 1.75	4.3 ± 2.8	6.2 ± 1.8
T_{max} (h)	2.8 ± 0.9	2.91 ± 1.2	2.8 ± 0.4	4.3 ± 1.7
C_{max} (ng/mL)	248.7 ± 75.5	332.7 ± 99.5	927.3 ± 466.5	1253 ± 750
@Fold change in C_{max}	**1**	**↑1.3x**	**↑3.7x**	**↑5.0x**
CL/F (L/h)	192.1 ± 69.4	143.2 ± 21.7	66.7 ± 51.8	23.1 ± 11.1
@Fold change in CL/F	**1**	**↓1.3x**	**↓2.9x**	**↓8.3x**
AUCinf (ng*h/mL)	1158 ± 411	1429 ± 247	4995 ± 3666	11645 ± 7702
@Fold change in AUCinf	**1**	**↑1.2x**	**↑4.3x**	**↑10x**

@ Compared to MCS

*,2 Data of Mild HI (CP-A) were from an earlier study

PK Parameters of DUR-928 in MCS and HI Subjects

Data are shown as Median (IQR)

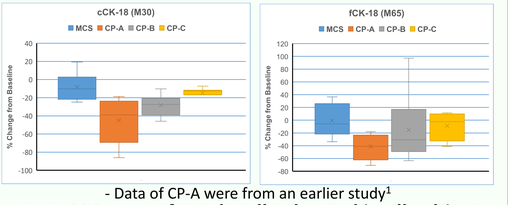


- Data of CP-A were from an earlier study[2]

Cell Death Markers

Data are shown as Median (IQR)

12 hour post-dose



- Data of CP-A were from an earlier study[1]

DUR-928 was safe and well-tolerated in all subjects

- No AEs or SAEs were reported throughout the study
- No discontinuations, early withdrawal or termination of study drug or study participation due to AEs

SUMMARY

- DUR-928 was safe and well-tolerated by moderate and severe hepatic impairment (HI) subjects
- Exposure (Cmax and AUC) of DUR-928 increased by 4 – 10 fold, depending on the severity of HI, as compared to MCS with normal hepatic function
- As expected, apparent systemic clearance of DUR-928 in moderate and severe HI was decreased as much as 70 – 90% as compared to the subjects with normal hepatic function
- No dose-limiting toxicity was observed in this study in spite of increased drug exposure (Cmax and AUC) in subjects with moderate or severe HI
- A single oral dose of 200 mg DUR-928 resulted in statistically significant mean reductions from baseline of (cCK-18, M30), an apoptosis biomarker, at 12 hr. post-dose in all subjects with HI

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References

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