Pharmacokinetic and Pharmacodynamic Response in Individual NASH Patients Receiving Two Dose Levels of DUR-928

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INTRODUCTION

DUR-928 (5-cholesten-3β,25-diol 3-sulfate) is a highly conserved endogenous intracellular sulfated oxysterol that has been shown to play an important role in mammalian lipid metabolism, inflammatory responses and cell survival (1). DUR-928 is shown to be safe in toxicology studies and effective in reversing certain histopathological and biochemical changes associated with Non-alcoholic Steatohepatitis (NASH) in multiple *in vivo* models (2). Phase I studies in healthy subjects demonstrated that DUR-928 was well tolerated with no significant drug related adverse events. Previously, we reported that DUR-928, after a single oral dose in patients with NASH, significantly improved serum markers of liver function, and reduced markers of inflammation and cell death (3).

AIMS

- The study was to assess safety and pharmacokinetics (PK) of oral DUR-928 in hepatic function impaired (NASH) patients at two ascending doses (3)
- This presentation is to examine the reproducibility of changes of biological signals in individual NASH patients, who received both 50 mg and 200 mg doses of DUR-928 administered approximately two months apart

METHODS

- As previously described (3), DUR-928 was given orally as a single dose at two dose levels, 50 mg and 200 mg. Each dose cohort consisted of 10 NASH patients (both cirrhotic and non-cirrhotic) and 6 matched control subjects (MCS), matched by age, BMI and gender, with normal liver function
- Eight patients participated in both cohorts and received both doses of DUR-928 administered approximately 2 months apart. Their PK parameters and biological responses to DUR-928 were examined for possible dose-dependence and reproducibility
- In this poster presentation, the data are presented as observed values and percent change from baseline over 24 hours after dosing

RESULTS

Demographics	Cohort 1 - 50 mg	Cohort 2 - 200 mg
# of Patients	8	8
Age (yrs)	52.9 (11.9)*	53.0 (11.8)*
BMI (kg/m^2)	34.1 (6.8)*	35.2 (6.4)*
Gender (M/F)	4/4	
Baseline ALT (U/L)	70.3 (19.6)*	70.8 (14.0)*
Cirrhotic Patients	1	
Indeterminate	2	
Non-Cirrhotic Patients	5	

* Mean (SD)

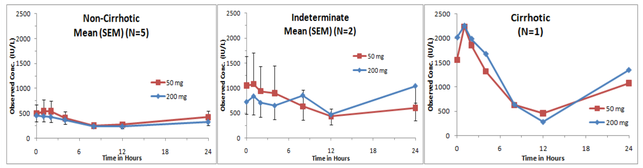
Individual Patient PK Data

Patient #	Severity	Dose (mg)	Cmax (ng/mL)	AUCinf (ng*h/mL)	Ratio Cmax	Ratio AUCinf
1	Non-cirrhotic	50	84.2	311.1		
		200	338.0	1539.1	**4.01**	**4.95**
2	Non-cirrhotic	50	123.0	574.2		
		200	495.0	2768.2	**4.02**	**4.82**
3	Non-cirrhotic	50	137.0	532.9		
		200	343.0	1885.3	**2.50**	**3.54**
4	Indeterminate	50	60.6	293.5		
		200	241.0	1198.2	**3.98**	**4.08**
5	Cirrhotic	50	138.0	612.5		
		200	368.0	1650.6	**2.67**	**2.69**
6	Indeterminate	50	111.0	501.6		
		200	450.0	2132.8	**4.05**	**4.25**
7	Non-cirrhotic	50	141.0	632.4		
		200	394.0	1969.7	**2.79**	**3.11**
8	Non-cirrhotic	50	92.6	450.6		
		200	275.0	1341.5	**2.97**	**2.98**

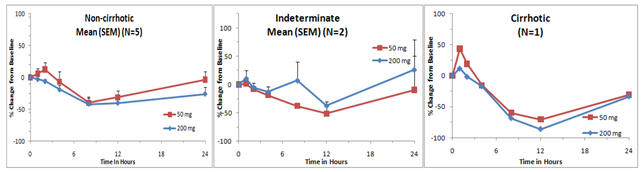
Mean (SEM) % Change from Baseline for hs-CRP and IL-18 following Two Single Ascending Oral Doses of DUR-928

Time Post Dose (h)	hs-CRP		IL-18	
	50 mg	200 mg	50 mg	200 mg
8	- 9.6 (16.4)	- 8.3 (2.0)	- 5.4 (1.8)	- 11.2 (2.4)
12	- 8.7 (14.1)	- 7.5 (2.8)	- 7.0 (2.4)	- 5.3 (3.0)
24	- 7.4 (4.5)	- 7.5 (4.5)	- 3.1 (3.9)	- 4.3 (3.2)

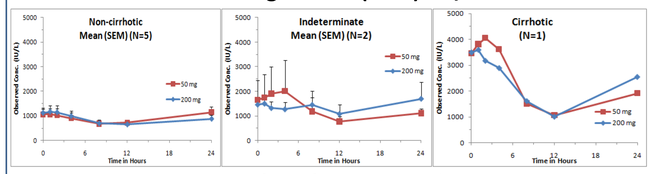
Cleaved CK18 (M30): IU/L



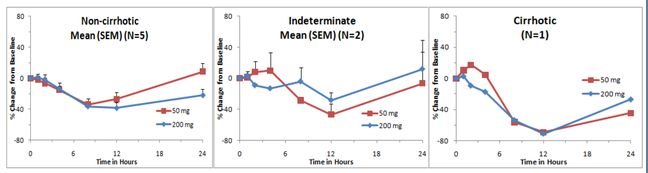
Cleaved CK18 (M30): - % Change from Baseline



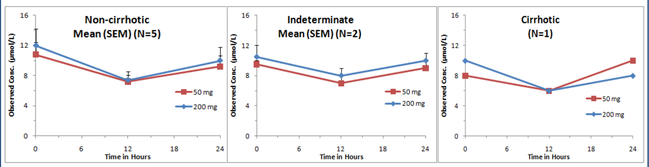
Full Length CK18 (M65): IU/L



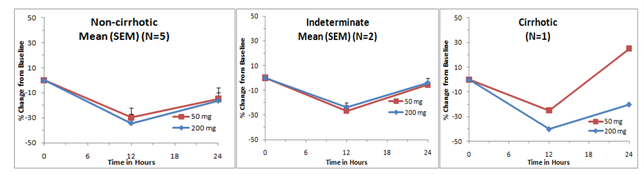
Full Length CK18 (M65): % Change from Baseline



Total Bilirubin: µmol/L



Total Bilirubin: % Change from Baseline



Mean (SEM) % Change from Baseline for hs-CRP and IL-18 following Two Single Ascending Oral Doses of DUR-928

Time Post Dose (h)	cCK18		fCK18		Total Bilirubin	
	50 mg	200 mg	50 mg	200 mg	50 mg	200 mg
8	- 41.7 (6.3)	- 32.9 (12.6)	- 35.2 (5.5)	- 30.4 (9.1)	-	-
12	- 41.1 (8.5)	- 45.2 (8.5)	- 37.1 (8.1)	- 39.9 (6.7)	- 28.4 (4.9)	- 32.4 (5.0)
24	- 8.5 (14.0)	- 13.7 (14.6)	- 1.8 (13.9)	- 14.1 (8.4)	- 7.6 (5.9)	- 13.7 (6.7)

SUMMARY

Systemic exposure of DUR-928 was dose dependent in individual NASH patients receiving both oral doses of DUR-928

Reproducible improvement of bilirubin and the reduction of markers of inflammation and cell death were observed in the same patients after receiving two single ascending oral doses of DUR-928 administered approximately 2 months apart. However, there were no dose-dependent changes of these biological responses between 50 – 200 mg dose levels

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