Safety and Single Ascending Dose Pharmacokinetic Study of DUR-928 in Patients with Chronic Kidney Disease versus Matched Control Subjects

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ABSTRACT

BACKGROUND

DUR-928 ((5-cholesten-3β,25-diol 3-sulfate (25HC3S)) is an endogenous intracellular sulfated oxysterol that has been shown to regulate lipid metabolism, inflammatory response, and cell survival. This first-in-class investigational product is being developed for the treatment of various liver and kidney diseases. Animal ADME studies have shown that ≈ 17% of DUR-928 is eliminated through the urine. This study was to evaluate the impact of renal impairment in chronic kidney disease (CKD), on the safety and pharmacokinetics (PK) of DUR-928.

METHODS

The study was a Phase 1b, open label, single ascending dose study to evaluate the safety and PK of IM injected DUR-928 in patients with moderate and severe kidney function impairment (Stage 3 and Stage 4 CKD) and matched control subjects (MCS), matched by age, BMI, and gender, with normal kidney function. The two doses of DUR-928 in the study were 30 mg and 120 mg. Biomarkers were also examined. All study subjects were followed through 7 days post dosing.

RESULTS

Eleven CKD patients (Stage 3 (N=8), Stage 4 (N=3)) and six MCS completed the study. A total of 13 TEAEs were reported by 8 participants, mostly mild and none were severe. A clinically non-significant decrease (≈ 10%) in exposure was observed in CKD patients as compared to MCS at both dose levels of DUR-928. The AUC values for 30 and 120 mg doses in CKD patients were 1061 and 4304 ng*hr/mL vs.1138 and 4766 ng*hr/mL in MCS. Similarly, the C_{max} values for 30 and 120 mg doses in CKD patients were 281 and 890 ng/mL vs. 345 and 997 ng/mL in MCS. The plasma half-life (T½) was in the range of 1.5 to 2 hours. Participants with elevated levels of CK-18 (markers of cell death) or bilirubin at baseline showed considerable reduction of these markers at 12 or 24 - 48 hours after a single IM injection of DUR-928.

CONCLUSIONS

Single IM doses of DUR-928 in CKD patients were found to be well tolerated. Kidney function impairment did not impact the PK of DUR-928. These data support further evaluation of DUR-928 in patients with kidney disease.

INTRODUCTION

DUR-928 ((5-cholesten-3β,25-diol 3-sulfate (25HC3S)) is a highly conserved endogenous intracellular sulfated oxysterol that has been demonstrated to play a key role in mammalian lipid metabolism, inflammatory responses and cell survival [(1)]. Studies have shown that this molecule protected against acute organ injury, such as acute kidney injury (AKI), in an ischemic-reperfusion injury (IR/I) rat model (Poster # SA-PO650), and improved survival, such as in LPS-induced endotoxin shock [(2)] and acetaminophen toxicity [(3)] mouse models.

Radiolabel ADME studies in rats and dogs have shown that > 80% drug is excreted in bile and 10 – 15% in urine [(4)]. DUR-928 is being developed for the potential treatment of various acute or chronic diseases, including kidney disease. Therefore, this study was to evaluate safety and pharmacokinetics (PK) of injected DUR-928 in patients with impaired kidney function, i.e., chronic kidney disease (CKD), and in matched control subjects (MCS).

METHODS

- This was an open-label, single dose escalating study, conducted in two successive cohorts (30 mg and 120 mg), evaluating safety and PK of intramuscular (IM) injected DUR-928.
- Each cohort consisted of 5 or 6 patients with either Stage 3 (eGFR 30 to 59 mL/min/1.73 m^2) or Stage 4 (eGFR 15 to 29 mL/min/1.73 m^2) CKD, and 3 MCS, matched by age (±10 years), gender, and BMI (±25%), with normal kidney function.
- All subjects were confined to the clinic until Day 3 of the study.
- DUR-928 was administered as a single IM dose to the gluteal muscle.
- Blood samples for PK and biochemical/biomarker analysis were taken from all subjects before dosing (baseline) and after dosing at various time points for up to 72 hours.
- Plasma samples were processed by solid phase extraction. DUR-928 was analyzed using a validated LC-MS/MS method. PK parameters, C_{max}, T_{max}, T½, $AUC_{0\text{-}last}$, AUC_{inf}, and CL/F, were determined.

RESULTS

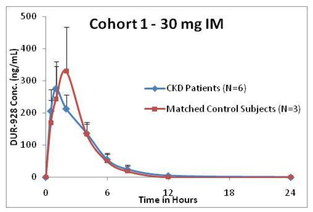
SUMMARY OF SUBJECT DISPOSITION

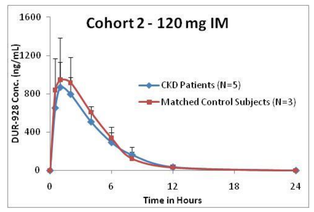
	CKD Stage 3 (N=8)	CKD Stage 4 (N=3)	MCS* (N=6)
Randomized	8	3	6
Dosed	8 (100%)	3 (100%)	6 (100%)
Completed	8 (100%)	3 (100%)	6 (100%)
Discontinued	0	0	0
30 mg	4	2	3
120 mg	4	1	3

*Matched Control Subjects

SUMMARY OF SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Stage 3, N=8	Stage 4, N=3	MCS, N=6
Age (years)			
Mean (SD)	54.0 (14.2)	41.3 (23.3)	46.5 (12.1)
Min, Max	33, 69	25, 68	36, 61
Gender, n(%)			
Male	8 (100)	3 (100)	5 (83.3)
Female	0 (0.0)	0 (0.0)	1 (16.7)
Race, n (%)			
White	7 (87.5)	3 (100)	5 (83.3)
Asian	0 (0.0)	0 (0.0)	1 (16.7)
Other	1 (12.5)	0 (0.0)	0 (0.0)
Height (cm)			
Mean (SD)	176.3 (6.73)	174.3 (3.8)	177.0 (9.7)
Min, Max	171, 191	170, 177	164, 186
Weight (kg)			
Mean (SD)	93.0 (17.6)	78.2 (15.9)	94.8 (14.9)
Min, Max	71.4, 125.5	67.7, 96.5	75.2, 117
BMI (kg/m^2)			
Mean (SD)	29.7 (3.6)	25.7 (4.8)	30.3 (4.5)
Min, Max	24.4, 34.4	22.5, 31.2	24.5, 34.9





RESULTS

MEAN (SD) PLASMA PK PARAMETERS OF DUR-928

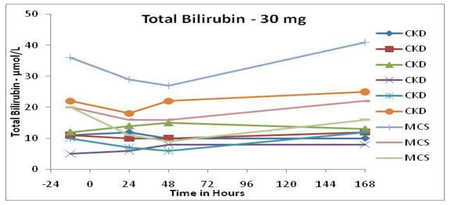
PK Parameter	CKD Patients		MCS	
	Cohort 1 – 30 mg (N=6)	Cohort 2 – 120 mg (N=5)	Cohort 1 – 30 mg (N=3)	Cohort 2 – 120 mg (N=3)
C_{max} (ng/mL)	281.3 (59.8)	890.4 (214.2)	345.0 (139.4)	997.0 (388.5)
T_{max} (h)	1.0 [1.0 – 2.0]	1.0 [1.0 – 2.0]	1.7 [1.0 – 2.0]	1.7 [1.0 – 2.0]
T½ (h)	1.6 (0.5)	2.0 (0.4)	1.5 (0.6)	1.7 (0.2)
AUC_{inf} (ng*h/mL)	1061.2 (140.9)	4303.9 (1029.4)	1137.9 (246.0)	4766.3 (484.9)
CL/F (L/h)	28.7 (4.0)	29.2 (7.3)	27.2 (5.9)	25.3 (2.5)

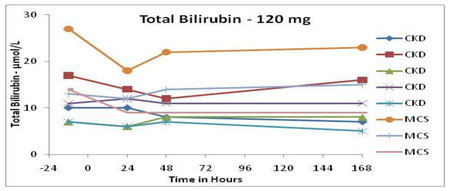
For T_{max}, the median (min, max) values are presented.
L/h = Liter/hour

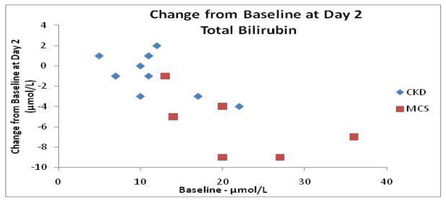
TREATMENT EMERGENT ADVERSE EVENTS

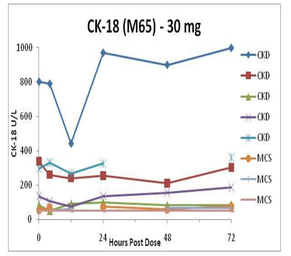
System Organ Class Preferred Term	CKD Patients (N=11)	MCS (N=6)
Dose Level: Overall		
Total Number of TEAEs	9	4
Subjects with at least 1 TEAE	6 (54.5%)	2 (33.3%)
Gastrointestinal disorders		
Abdominal discomfort	2 (18.2%)	0 (0.0%)
General disorders and administration site conditions		
Fatigue	1 (9.1%)	0 (0.0%)
Injection site discomfort	1 (9.1%)	0 (0.0%)
Injection site pain	2 (18.2%)	0 (0.0%)
Investigations		
Blood glucose fluctuation	1 (9.1%)	0 (0.0%)
Muscular skeletal and connective tissue disorders		
Flank pain	1 (9.1%)	1 (16.7%)
Muscular skeletal stiffness	0 (0.0%)	1 (16.7%)
Nervous system disorders		
Headache	1 (9.1%)	1 (16.7%)

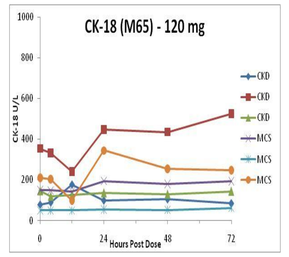
Note: A Treatment Emergent Adverse Event (TEAE) is defined as an adverse event that started or worsened in severity after start of study drug treatment.
Note: Percentages are based on the number of dosed subjects.

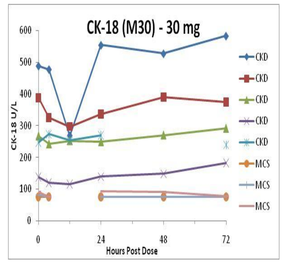


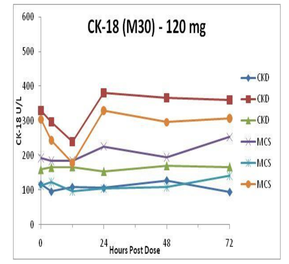












SUMMARY

- **Pharmacokinetics**
  - There were no clinically relevant differences in drug exposure between CKD patients and MCS following a single IM injection of DUR-928.
  - Dose proportional exposure was observed at the two dose levels of DUR-928 in both CKD patients and MCS.
  - No clear relationship was observed between eGFR values and DUR-928 exposure.
  - Reduction in CK-18 (markers of cell death) at 12 hours post-dose was observed in subjects with elevated baseline values.
  - While the number of subjects was small, reductions in bilirubin were observed at 24 and 48 h post-dose in subjects with elevated baseline levels.
- **Safety**
  - All subjects tolerated the treatments generally well throughout the study.
  - All reported adverse events were mild to moderate in severity with no SAEs or TEAEs leading to study discontinuation.

REFERENCES

1. Ren S and Ning Y. *Am J Physiol Endocrinol Metab* 2014; 306:E123–E130, 2014.
2. Ning Y, Kim JK, Min HK, Ren S. *Metabolism* 2017; 71:83-90.
3. Ren S, Ning Y, Kim J, Min HK, Brown JE, Lin WQ. *HEPATOLOGY* 2017; 666:S430A.
4. DePass LR, Shah J, Miksztal A, and Lin WQ (2018). Society of Toxicology, 57th Annual Meeting.