# Pharmacokinetics of DUR-928 in Alcoholic Hepatitis Patients – A Phase 2a Study


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## ABSTRACT


**Background and Aims:** DUR-928 epigenetically modulates the expression of multiple clusters of master genes that are involved in many important cell signaling pathways, through which it stabilizes mitochondria, reduces lipotoxicity, regulates inflammatory or stress responses, and promotes cell survival. The potential use of DUR-928 as a treatment for acute organ injury, including alcoholic hepatitis (AH), has been demonstrated in multiple pharmacology studies in animal disease models. The primary objective of this Phase 2a study is to assess the safety and pharmacokinetics (PK) of DUR-928 in moderate and severe AH patients.

**Methods:** The study is an open-label, multi-center, dose escalation safety/PK Phase 2a trial. All patients received DUR-928, at doses of 30, 90, or 150 mg, by intravenous infusion for 2 hrs on Day 1 and Day 4 (if still hospitalized), and were followed for 28 days. Part A of the study consisted of patients with moderate AH (as defined by MELD 11-20) and Part B included patients with severe AH (as defined by MELD 21-30).

**Results:** A total of 19 patients (12 severe AH, and 7 moderate AH) participated in the study. DUR-928 was well tolerated. The drug exposure (both AUC and $C_{max}$) in AH patients was dose proportional. Time to maximum drug concentrations ($T_{max}$) was at the end of the 2 hour infusion. The half-life ($t_{1/2}$) of DUR-928 ranged from 4 – 6 hours. Mean clearance of DUR-928 was about 5 - 7 L/hr. PK parameters of DUR-928 were similar between the moderate and severe AH groups. Compared to PK parameters of DUR-928 in healthy subjects, there was a 2-fold increase in $C_{max}$ and a 6-fold increase in AUC in AH patients at the same dose level. The clearance of DUR-928 was decreased by 80% in AH patients as compared to that in healthy subjects from an earlier study. In addition, encouraging efficacy signals, including early reduction from baseline of serum bilirubin levels and reduction of MELD on Day 28, and high treatment response rate (based on Lille score) were observed in the study (1, 2).

**Conclusions:** DUR-928 was well tolerated at doses tested in AH patients, including severe AH patients. Compared to healthy subjects, AH patients had a much slower clearance, resulting in a 2-fold higher $C_{max}$ and 6-fold higher AUC. However, the drug exposure was not affected by the severity of the disease.



References:

1. C. McClain et. al., J. Hepatology, 2019; 70(1), S834A
2. T. Hassanein et. al., AASLD -2019 – Late Breaker A09


## BACKGROUND

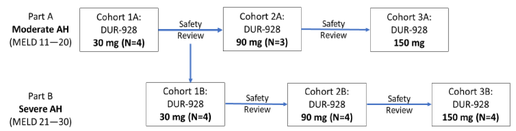
- *DUR-928, 5-cholesten-3β, diol 3-sulfate (25HC3S), is a*n endogenous sulfated oxysterol and an epigenetic regulatory molecule.
- Modulates hepatic lipid metabolism
  - Decreases fatty acid, cholesterol and triglyceride biosynthesis
  - Regulates lipid absorption and transportation
  - Improves insulin 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 AH and COVID-19 patients with acute liver or kidney injury, and treatment of chronic liver/metabolic disease, such as NASH.

## AIMS

**Phase 2a Study: DUR-928 for Alcoholic Hepatitis (AH)**

- Open label, multi-center dose escalation clinical trial (NCT 03432260)
- Objectives and endpoints:
  1. Assess the safety and tolerability of DUR-928 in patients with AH
  2. Determine pharmacokinetics of IV infused DUR-928
  3. Assess the pharmacodynamic signals (biochemical and biomarkers) of DUR-928
- Key eligibility criteria:
  - Age 21 or older
  - Clinical diagnosis of Alcoholic Hepatitis consistent with AASLD Practice Guidelines definition for probable AH
  - Serum bilirubin > 3 mg/dL AND AST > ALT, but less than 300 U/L
  - MELD 11-30
  - Excluded other or concomitant causes of liver disease

### Study Design




- Each dose cohort enrolled up to 4 subjects. Cohort 3A did not recruit.
- Study subjects received up to 2 doses of DUR-928.
- The 1st dose on Day 1 and, if still hospitalized, the 2nd dose on Day 4
- The time points for PK sample collection were as follows: Time 0 (pre-dose), 1 hr. post-dose initiation, 2 hr (end of infusion), 3, 4, 8, 12, 24 hr post-dose initiation and 50 hr post-dose initiation (only if biomarker sample was collected)

## RESULTS

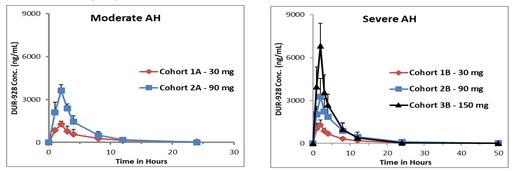
### Demographics

| Study Part | | All Patients | Part A: Moderate AH (MELD 11-20) | | | Part B: Severe AH (MELD 21-30) | | |
|---|---|---|---|---|---|---|---|---|
| Study Cohort (Dosage) | | | 1A (30 mg) | 2A (90 mg) | 3A (150 mg) | 1B (30 mg) | 2B (90 mg) | 3B (150 mg) |
| N | | 19 | 4 | 3 | Cohort 3B was completed, therefore Cohort 3A did not enroll | 4 | 4 | 4 |
| Male, N (%) | | 11 (57.9%) | 1 (25%) | 2 (66.7%) | | 3 (75%) | 3 (75%) | 2 (50%) |
| Age (Mean ± SD) | | 41 ± 20 | 36.3 ± 0.9 | 39.3 ± 5.5 | | 45.0 ± 9.6 | 42.5 ± 3.3 | 40.8 ± 6.1 |
| Race, N (%) | White | 17 (89.5%) | 3 (66.7%) | 3 (100%) | | 4 (100%) | 4 (100%) | 3 (75%) |
| | Non-White | 2 (10.5%) | 1 (Pacific Islander) | 0 | | 0 | 0 | 1 (African American) |

### Baseline laboratory Characteristics (Mean ± SD)

| Study part | Part A: Moderate AH (MELD 11 – 20) | | Part B: Severe AH (MELD 21 – 20) | | | Overall (N=19) |
|---|---|---|---|---|---|---|
| **Study Cohort (dosage)** | 1A (30 mg) N=4 | 2A (90 mg) N=3 | 1B (30 mg) N=4 | 2B (90 mg) N=4 | 3B (150 mg) N=4 | |
| **AST** (IU/L) | 113.0 ± 112.0 | 112.7 ± 24.6 | 116.8 ± 30.1 | 89.5 ± 43.3 | 82.0 ± 18.6 | **102.3 ± 54.1** |
| **ALT** (IU/L) | 36.0 ± 38.1 | 67.3 ± 9.7 | 44.3 ± 15.4 | 30.5 ± 10.7 | 35.5 ± 20.3 | **41.4 ± 23.1** |
| **T. Bilirubin** (mg/dL) | 5.5 ± 1.9 | 10.6 ± 5.7 | 18.7 ± 6.5 | 16.3 ± 10.5 | 19.1 ± 10.2 | **14.2 ± 8.7** |
| **Creatinine** (mg/dL) | 0.63 ± 0.14 | 0.58 ± 0.34 | 0.86 ± 0.27 | 0.91 ± 0.43 | 0.68 ± 0.23 | **0.74 ± 0.29** |
| **WBC** (10^3/uL) | 6.6 ± 8.0 | 9.9 ± 5.7 | 10.2 ± 3.2 | 6.2 ± 2.4 | 9.6 ± 4.7 | **8.4 ± 4.7** |
| **Platelets** (K/uL) | 113.8 ± 100.7 | 126.7 ± 7.8 | 179.0 ± 89.5 | 83.8 ± 32.5 | 173.0 ± 30.5 | **135.7 ± 69.4** |
| **INR** | 1.7 ± 0.27 | 1.3 ± 0.22 | 1.8 ± 0.31 | 1.9 ± 0.29 | 2.1 ± 0.34 | **1.8 ± 0.35** |
| **Maddrey's Discriminant Function** | 41.0 ± 12.2 | 25.7 ± 16.5 | 59.3 ± 18.5 | 63.3 ± 5.9 | 71.0 ± 20.0 | **53.4 ± 21.1** |
| **MELD** | 18.5 ± 2.38 | 18.0 ± 3.61 | 24.5 ± 3.51 | 24.5 ± 2.89 | 25.0 ± 1.83 | **22.3 ± 4.06** |

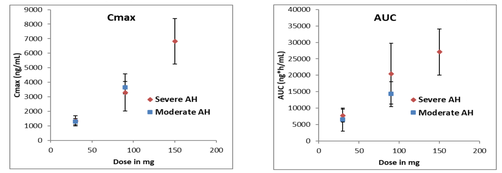
### Mean (SD) Concentration vs. Time Profile of DUR-928

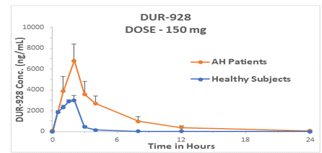



### Mean (SD) Pharmacokinetic Parameters of DUR-928 Following Dosing

| Cohort (Dose) | N | Tmax (h) | Cmax (ng/mL) | T½ (h) | AUCinf (ng*h/mL) | V (L) | CL (L/h) |
|---|---|---|---|---|---|---|---|
| Moderate AH | | | | | | | |
| Cohort 1A (30 mg) | 3 | 2.2 (0.2) | 1277 (214) | 3.7 (1.8) | 6542 (3509) | 24.8 (1.6) | 5.9 (3.7) |
| Cohort 2A (90 mg) | 3 | 2.0 (0) | 3627 (418) | 2.7 (0.8) | 14264 (3759) | 25.8 (10.5) | 6.6 (1.5) |
| | | | | | | | |
| Severe AH | | | | | | | |
| Cohort 1B (30 mg) | 4 | 1.8 (0.5) | 1343 (343) | 1.8 (0.5) | 7721 (1945) | 26.1 (4.9) | 4.1 (1.2) |
| Cohort 2B (90 mg) | 4 | 2.3 (0.5) | 3290 (1277) | 5.1 (1.9) | 20447 (9236) | 35.3 (10.8) | 5.5 (3.3) |
| Cohort 3B (150 mg) | 4 | 2.1 (0.3) | 6820 (1577) | 3.4 (0.4) | 27062 (6998) | 27.8 (5.9) | 5.8 (1.2) |

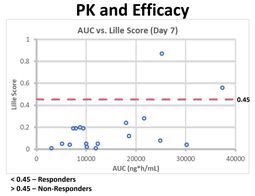
### Plot of Mean (SD) Cmax & AUC Across All Cohorts and Severity of AH




| | Cmax (ng/mL) | T½ (h) | AUCinf (ng*h/mL) | V (L) | CL (L/h) |
|---|---|---|---|---|---|
| AH Patients (N=4) | 6820 (1577) | 3.4 (0.4) | 27062 (6998) | 27.8 (5.9) | 5.8 (1.2) |
| Healthy Subjects (N=5) | 3102 (294.2) | 1.6 (0.9) | 6192 (730) | 55.0 (4.3) | 24.5 (3.1) |
| Fold Change in PK | ↑ 2x | ↑ 2x | ↑ ~5x | ↓ 0.5x | ↓ 0.25x |

### PK and Efficacy




### DUR-928 is safe and well-tolerated at all doses

- Adverse events possibly or probably related to DUR-928:
  - 1 occurrence of moderate generalized pruritus (cohort 1A)
  - 1 occurrence of mild rash (cohort 2B)
  - 1 occurrence of grade 2 Alkaline Phosphatase (cohort 1A)
- No discontinuations, early withdrawal or termination of study drug or study participation due to AEs
- No Serious Adverse Events were related to study drug
- 100% patients survived through 28-day follow-up period

## SUMMARY

- DUR-928 is safe and well-tolerated at all doses (30, 90 or 150 mg) in patients with AH, including severe AH
- Pharmacokinetics of DUR-928 in moderate and severe AH patients are similar for the dose administered and are dose proportional
- For a given dose, the systemic clearance of DUR-928 is about 5 fold lower in AH patients as compared to healthy subjects
- Based on the study, the 30 and 90 mg doses are selected to be tested in an upcoming Phase 2b study.
- **With only 1 or 2 injections of DUR-928:**
  - Significant early reduction of bilirubin from baseline by Day 7
  - 100% treatment response rate (Lille score <0.45) in patients receiving 30 or 90 mg doses; 89% response rate in all patients
  - Significant reduction of MELD by Day 28

**DUR-928 appears to be an innovative and potentially efficacious new therapy for AH**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## REFERENCES

1. C. McClain et. al., J. Hepatology, 2019; 70(1), S834A
2. T. Hassanein et. al., AASLD -2019 – Late Breaker A09



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