AASLD THE LIVER MEETING® NOVEMBER 8-12 2019 BOSTON

Safety and Efficacy of DUR-928: A Potential New Therapy for Acute Alcoholic Hepatitis

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Disclosure Slide

Tarek Hassanein

I disclose the following financial relationship(s) with a commercial interest:

- **Research Grants:** AbbVie, Afimmune, Allergan, Assembly, BeiGene, Boehringer-Ingelheim, Bristol-Myers Squibb, Cymabay, **DURECT Corporation**, Dova, Eisai, Enanta, Genetech, GenFit, Gilead, Grifols, Intercept, Mallinckrodt, Medicinova, Merck, Novartis, Obalon, Synlogic, Sundise, Salix, Shire, Valeant, Vital Therapies
- **Speaker and sponsored lectures:** AbbVie, Baxter, Bristol-Myers Squibb, Dova, Gilead, Merck, Salix
- **Advisory Board:** AbbVie, Bristol-Myers Squibb, Gilead, Mallinckrodt, Merck, Organovo

This presentation contains the discussion of off-label/investigative use of DUR-928.

Background

- ❑ Alcoholic Hepatitis (AH) attributed to 117,000 hospitalizations in a 2016 report
- ❑ Results in the loss of 22.2 million disability-adjusted life years annually
- ❑ Medical costs are high because of hospitalization and transplantation
- ❑ Current Treatment for AH are not satisfactory
- ❑ **The need for new and innovative therapies is urgent**

Source: Crabb, DW et al. AASLD Alcohol-Related Practice Guidance 2019 ; doi: 10.1002/hep.30866

DUR-928

- **Naturally occurring endogenous newly discovered regulatory Molecule**

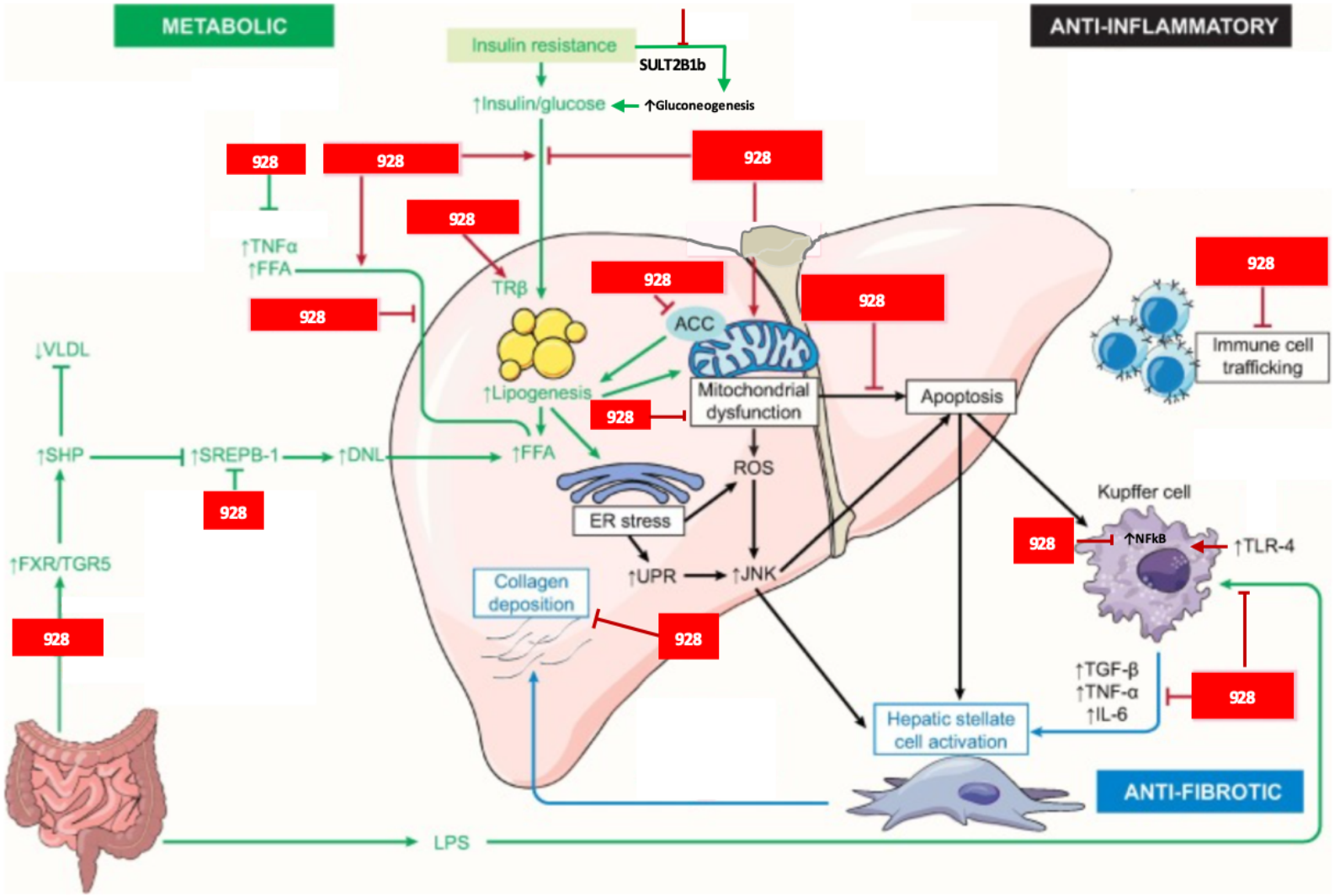
- **Sulfated oxysterol,** small molecule:
  - Produced in the cytoplasm and acts intracellulary
  - Highly conserved across 7 mammalian species studied to date, including humans (*Important in the regulation of cell function*)

- **Epigenetic regulator with broad activity**
  - Modulates gene activities
  - Regulates metabolism, inflammation, cell survival, and tissue regeneration

- **Well tolerated in multiple Phase 1 studies**

Biological Pathways Potentially Influenced by DUR-928

DUR-928 modulates multiple biological pathways involved in metabolic homeostasis, inflammatory response, cell survival and tissue regeneration

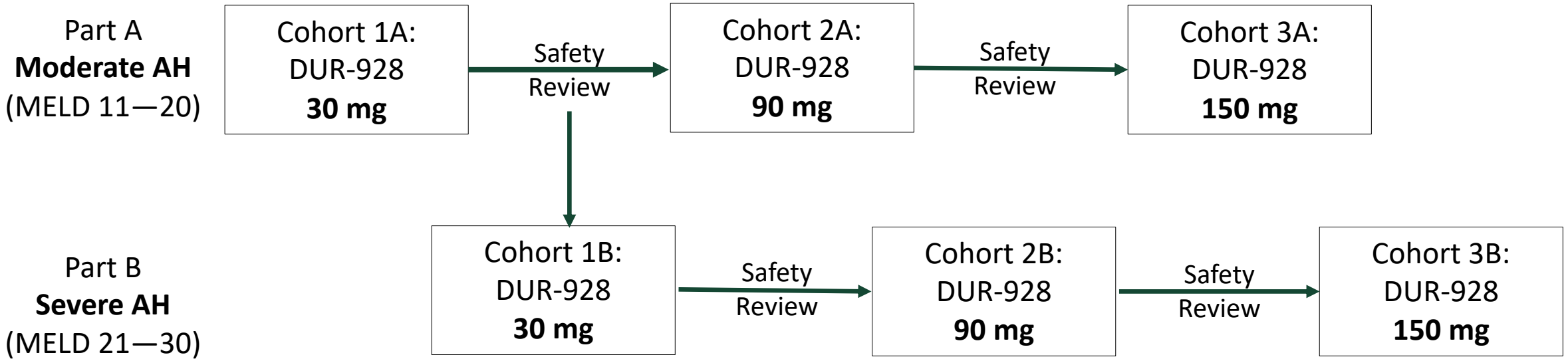


Source: modified from Konerman M et al., J. Hepatol 2018; 68:362-75

Phase 2a Study: DUR-928 for Alcoholic Hepatitis

- Open label, multi-center dose escalation clinical trial (NCT 03432260)
- Objectives and endpoints:
  1. Assess the safety and tolerability of DUR-928 (IV formulation)
  2. Determine pharmacokinetics of DUR-928
  3. Assess the pharmacodynamics signals (biochemical and biomarkers) of DUR-928
- Key eligibility criteria:
  - Age 21 or older
  - Clinical diagnosis of Alcoholic Hepatitis consistent with AASLD's 2019 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

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	*Did not need to enroll in. Completed enrollment in Cohort 3B first*	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 21-30)			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 ± 112.9	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 ± 4.9**
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**

RESULTS

DUR-928 Dosing and hospitalization

- 14 (74%) of the 19 enrolled subjects were discharged ≤ 4 days of Day 1

  Number of subjects who received 1 dose: 14

  Number of subjects who received 2 doses: 5

  - 1 each in Cohorts 1A, 1B, and 2B
  - 2 in Cohort 3B

- 67% of subjects with MELD 21-30 were discharged in ≤4 days after a single dose of DUR-928

Treatment Emergent Adverse Events

		All	30 mg	90 mg	150 mg
Number of AE occurrences*		37	22 (59.5%)	7 (18.9%)	8 (21.6%)
AEs with a frequency of >= 2 occurrences **	Nausea	4 (10.8%)	2	0	2
	Insomnia	3 (8.1%)	1	1	1
	Abdominal Pain	2 (5.4%)	2	0	0
	Ascites	2 (5.4%)	1	1	0
	Dehydration	2 (5.4%)	0	1	1
	Diarrhea	2 (5.4%)	2	0	0

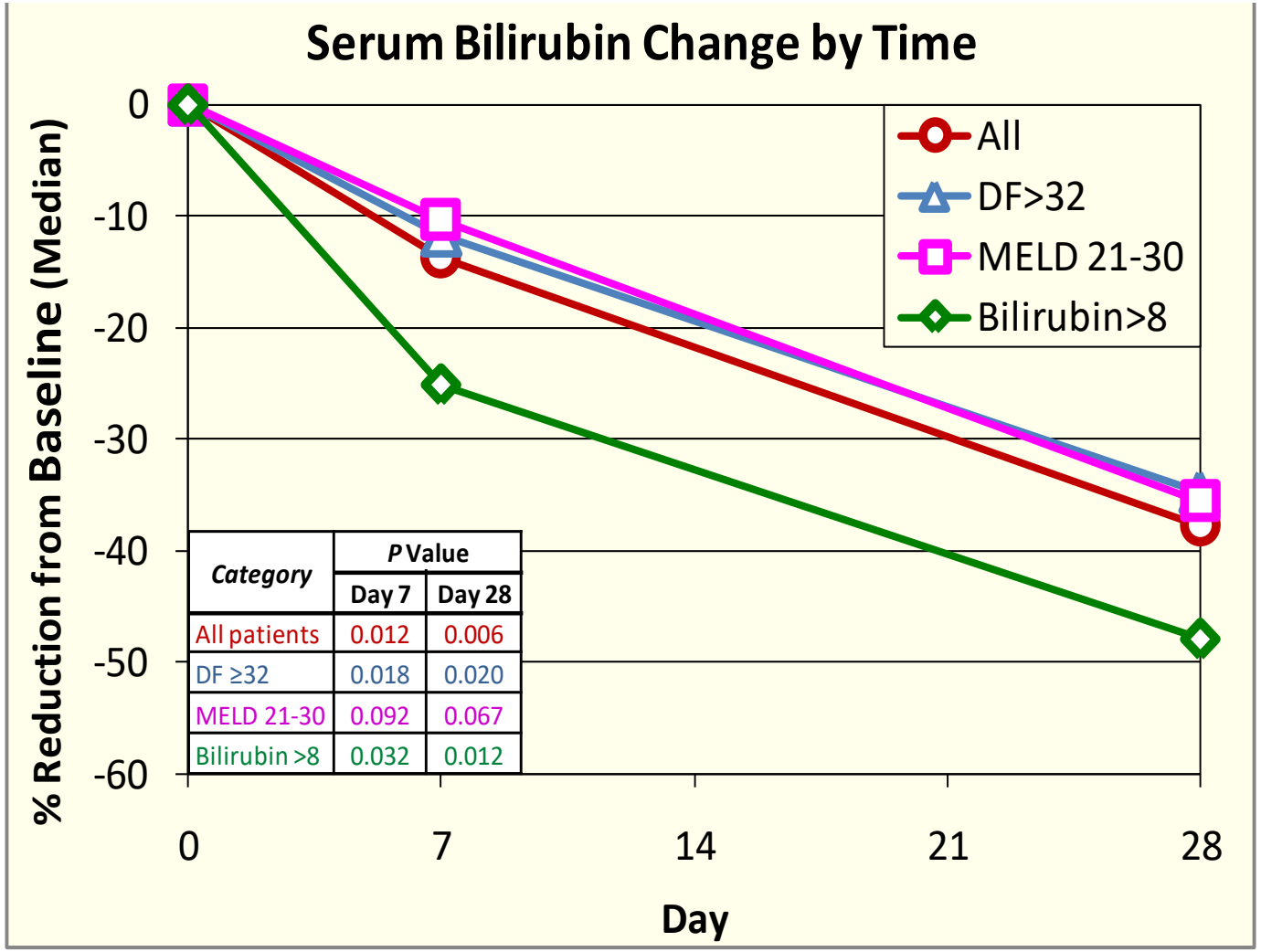
*There was only 1 severe AE reported: fluid overload (cohort 1B), not related to DUR-928

**All AEs were either mild or moderate

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

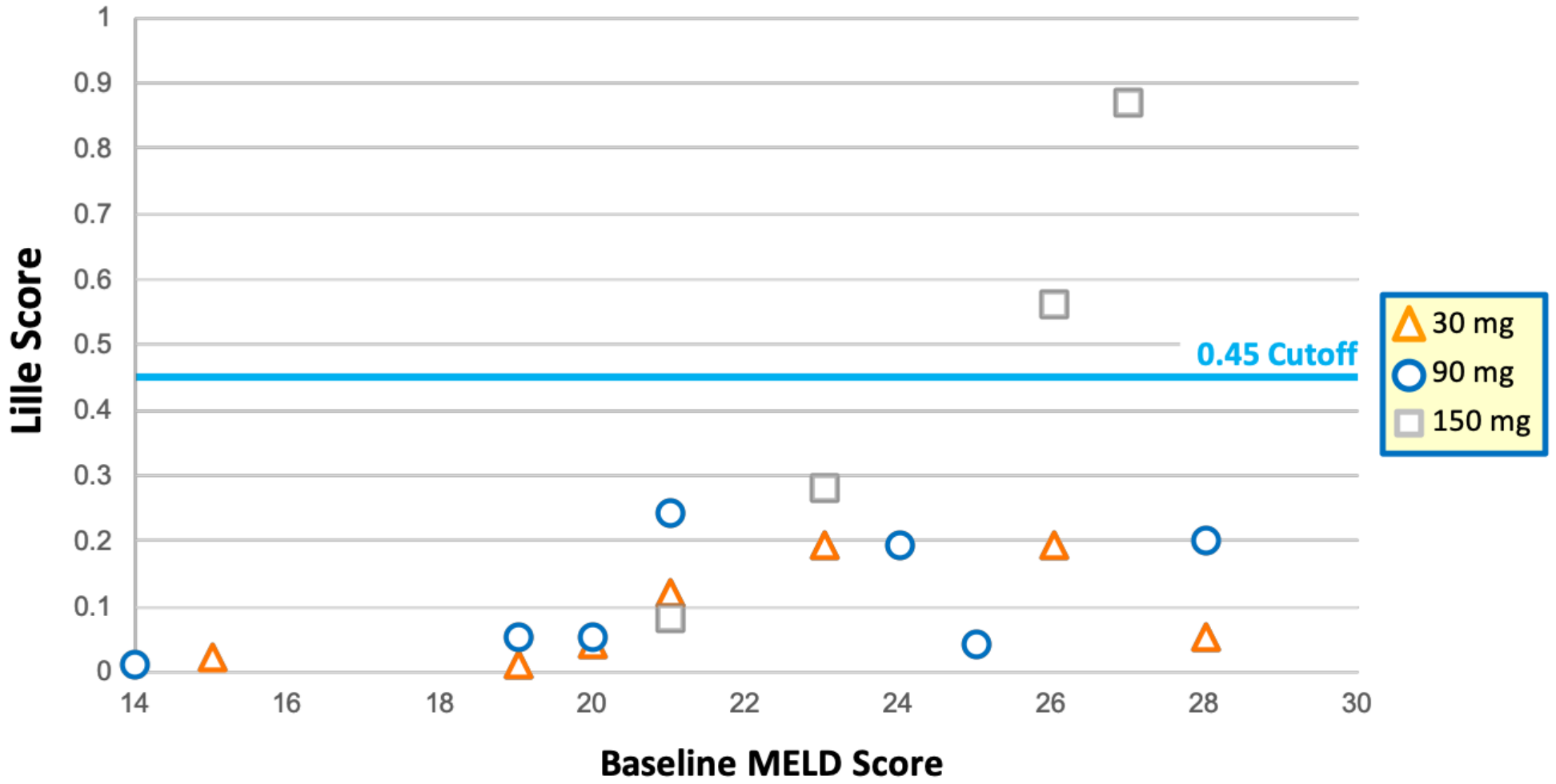
Results



Category	P Value	
	Day 7	Day 28
All patients	0.012	0.006
DF ≥32	0.018	0.020
MELD 21-30	0.092	0.067
Bilirubin >8	0.032	0.012

One of the 19 patients did not return for the follow-up visits on Day 7 and Day 28. All data were analyzed based on those 18 who completed visits.

Lille Score on Day 7

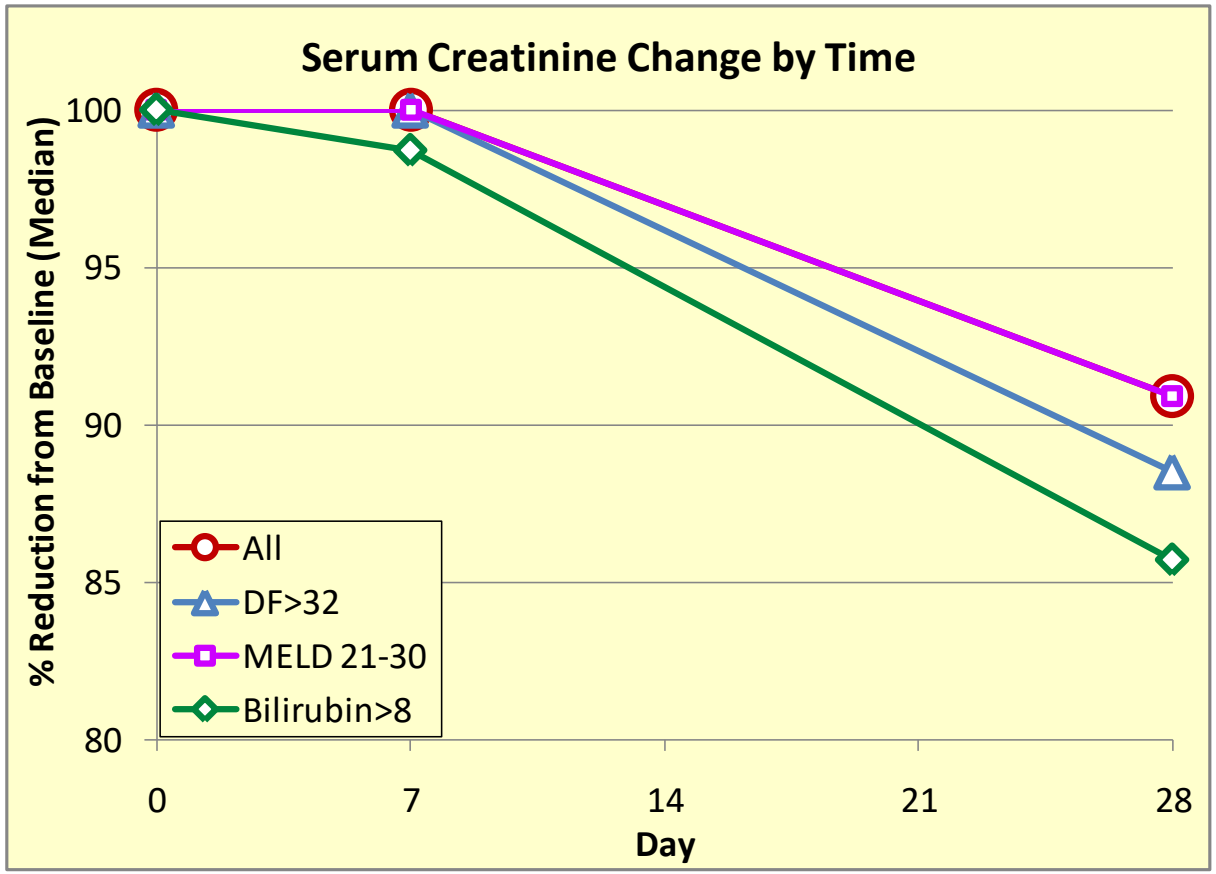


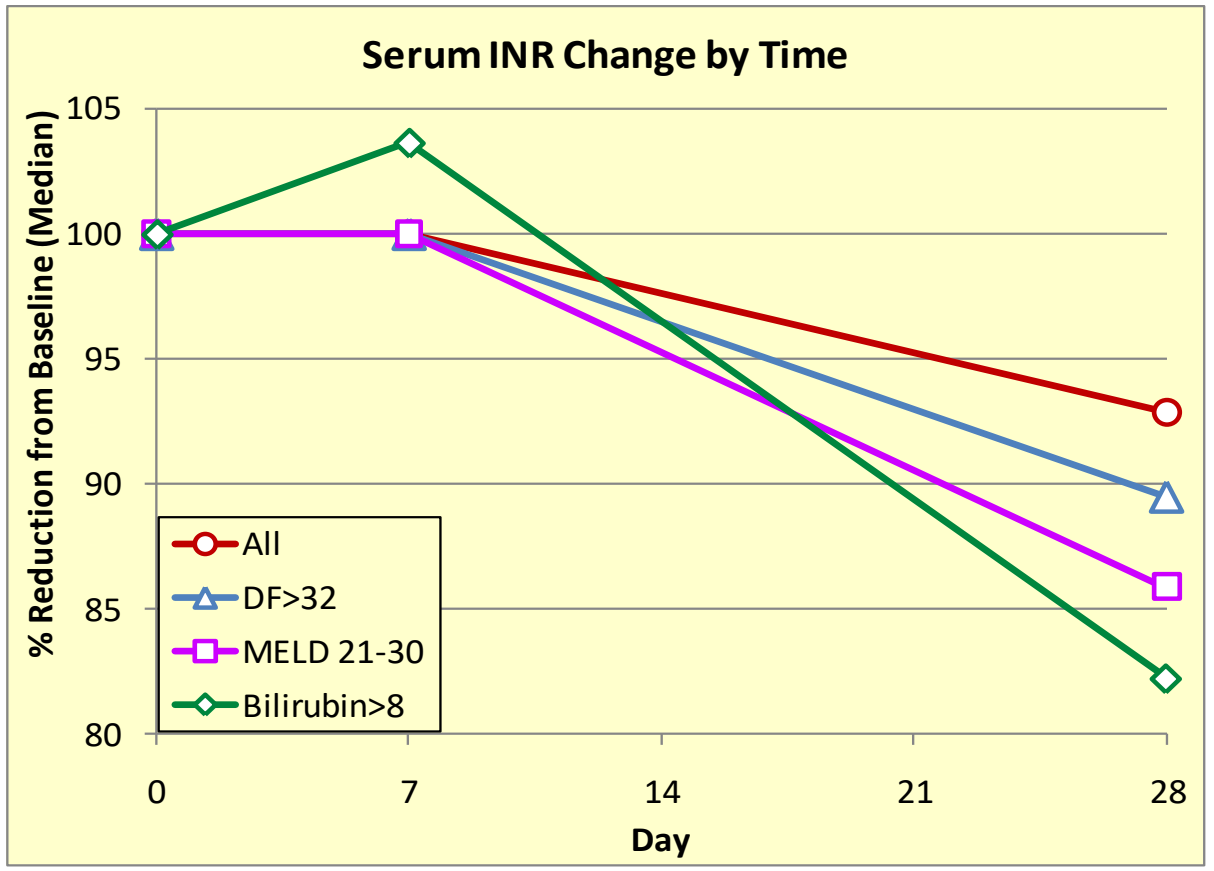
Treatment Response Rate by Lille Score

AH Patient Category	n[1]	Responders	Lille Median (Quartile)
All Patients[2]	18	89%	0.10 (0.04, 0.20)
30 or 90 mg DUR-928[3]	14	100%	0.05 (0.04, 0.19)
DF >32 (SAH)[2]	15	87%	0.19 (0.05, 0.22)
30 or 90 mg DUR-928[3]	11	100%	0.12 (0.05, 0.19)
MELD 21-30[2]	12	83%	0.19 (0.11, 0.25)
30 or 90 mg DUR-928[3]	8	100%	0.19 (0.10, 0.19)
Baseline bilirubin >8 mg/dL[2]	11	82%	0.10 (0.05, 0.20)
30 or 90 mg DUR-928[3]	8	100%	0.10 (0.05, 0.19)

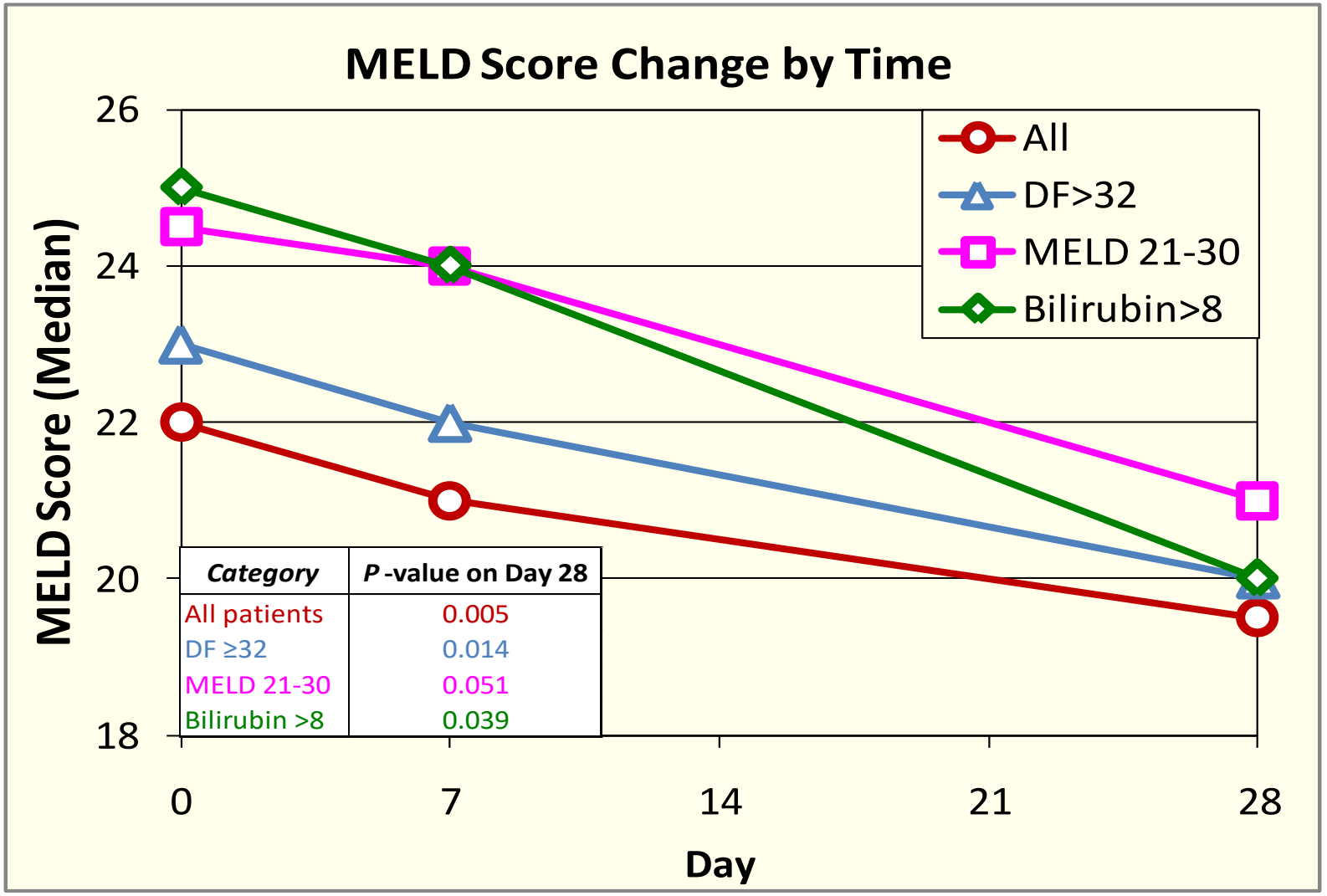
1. One patient did not return for Day 7 visit
2. Including patients receiving 30, 90, or 150 mg DUR-928
3. Excluding patients receiving 150 mg
4. SAH: Severe AH Patients

Results





Results



Summary

- DUR-928 is safe and well-tolerated at all doses (30, 90 or 150 mg) in patients with AH, including severe AH

- **With only 1 or 2 injections of DUR-928:**
  - Significant early reduction of bilirubin from baseline by Day 7
  - Patients with higher baseline bilirubin (>8 mg/dL) had higher bilirubin reduction, 25% decrease by Day 7 and 48% decrease by Day 28
  - 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

Key Take-Away Message

- ❑ AH is on the rise with high mortality rates and a huge unmet need
- ❑ DUR-928 is a **naturally occurring** endogenous sulfated oxysterol. It modulates inflammatory responses, promotes cell survival, stimulates hepatic regeneration, and reduces lipotoxicity.
- ❑ In this Phase 2a trial, DUR-928:
  - Was well tolerated up to 150 mg by all AH patients, including SAH patients.
  - Significantly reduced serum bilirubin levels by Day 7 and MELD scores at Day 28.
  - Lille scores of DUR-928 treated patients were significantly better than comparative published historic data (AASLD 2019 poster 1376)
- ❑ Further studies of DUR-928 are needed for patients with AH, including SAH.

Acknowledgments

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