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Efficacy Signals of 4-Week Oral DUR-928 in NASH Subjects

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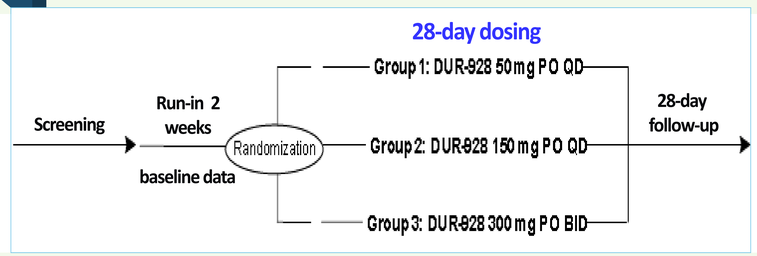
Background

1. The pathogenesis of Non-alcoholic Steatohepatitis (NASH) involves numerous dysregulated pathways
2. Lipotoxicity, oxidative stress, and mitochondrial toxicity in the setting of an active innate immune response are likely contributors to the development of NASH
3. **DUR-928,** 5-cholesten-3β, 25-diol 3-sulfate, is
   - **Endogenous,** highly conserved across all 7 mammals tested to date
   - **Epigenetic regulator,** inhibiting DNA methyltransferase (DNMT) 1, 3a & 3b, regulating expression of genes involved in multiple critical cell signaling pathways:
     - stabilizes mitochondria
     - reduces lipotoxicity
     - modulates inflammatory or stress responses
     - promotes cell survival and tissue regeneration
   - **Well tolerated in nearly 300 subjects** in multiple Phase 1 & 2 studies at all doses tested via oral, IM and IV administration
4. We previously reported that daily oral DUR-928 for 4 weeks in subjects with NASH resulted in overall improvement in liver enzymes, liver fat content by MRI-PDFF, serum lipid profiles, and certain biomarkers. Here we present additional data of efficacy signals from this trial.

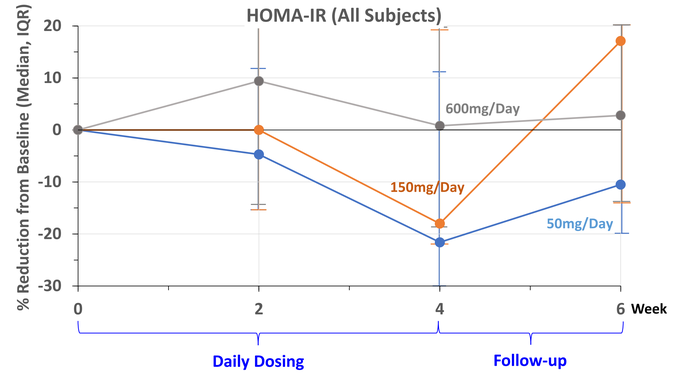
Trial Scheme



Methods

- Multi-center in US, open-label, Phase 1b trial
- 28 days daily oral dosing of DUR-928 at 50 mg QD, 150 mg QD, and 300 mg BID (or 600 mg/day)
- NASH (fibrosis stage 1-3), N=65
- Key endpoints:
  1. Safety / PK
  2. Clinical chemistry and biomarkers (e.g., ALT, AST, GGT, triglycerides, Non-HDL-C, CRP, CK-18s, PAI-1, inflammatory cytokines)
  3. Imaging (e.g., MRI-PDFF, TE by FibroScan®, and MRE)

Results: Insulin Resistance



Median (% from Baseline)	50 mg / day			150 mg / day			600 mg / day		
	Daily Dosing		Follow-up	Daily Dosing		Follow-up	Daily Dosing		Follow-up
	2 Week	4 Week	6 Week	2 Week	4 Week	6 Week	2 Week	4 Week	6 Week
All Subjects	-4.7	-21.6	-10.5	0	-18.0	17.1	9.4	0.8	2.8
n	23	21	20	21	21	20	21	20	21
Subjects with ≥ -10% in PDFF	-12.8	-20.9	8.9	-13.8	-10.9	22.7	15.2	2.4	20
n	9	9	9	9	9	9	9	9	9

Results: Biochemical and Imaging

Overall Improvement in Liver Enzymes[1], Liver fat[1], Serum Lipids[1], Cell Death Markers[1], Liver Stiffness, and Liver Fibrosis Markers

% Change from baseline (median) at the end of dosing (Day 28)

	Median at Day 28	All Subjects			Subjects with ≥ 10% Reduction in MRI-PDFF		
		50 mg QD (n=21-23)	150 mg QD (n=20-21)	300 mg BID (n=20-21)	50 mg QD (n=9)	150 mg QD (n=8)	300 mg BID (n=9)
Liver Enzymes	ALT	**-16%***	-10%	**-17%*****	**-21%****	**-19%***	**-32%*****
	AST	-14%	-9%	**-18%****	**-24%****	-21%	**-39%*****
	GGT	-6%	-1%	**-8%***	**-13%*****	**-16%***	-14%
Liver Fat & Stiffness	MRI-PDFF	-7%	-7%	-4%	**-18%*****	**-19%*****	**-23%*****
	FibroScan®	**-10%****	-9%	-1%	-7%	**-9%****	-9%
	MRE	-6%	4%	0%	-8%	2%	0%
	Pro-C3	-8%	-1%	-5%	**-8%***	-4%	**-12%***
	ELF	-2%	-1%	-1%	-2%	-2%	-3%
Serum Lipids	LDL-C	-6%	**-11%***	-7%	-7%	-11%	**-8%***
	Non-HDL-C	-8%	-5%	-1%	-10%	**-8%***	**-12%***
	Triglycerides	**-13%***	-3%	-2%	-9%	0%	-8%
	24% reduction in serum triglycerides in patients with elevated baseline triglycerides (≥200 mg/dL; n=16) across all dose groups at day 28 from baseline (p <0.01)						
Cell Death Marker	CK18, M30	-14.6%	-8.6%	-16.1%	**-22.8%*****	-3.8%	**-42.1%***
	CK18, M65	-18.1%	-9.9%	-35.0%	**-28.1%*****	-8.7%	**-55.8%***

** p < 0.05; ** p < 0.01; *** p < 0.001*

1. Lawitz et al.: Safety and Efficacy Signals of Daily Oral DUR-928 for 4-Weeks in F1-F3 NASH. AASLD 2020 Poster No. 1693

Summary

- As previously reported, DUR-928 was well tolerated by all subjects with F1-F3 NASH in the study. There was an overall improvement in liver enzymes, liver fat content by MRI-PDFF, serum lipid profiles, liver fat by MRI-PDFF, and cell death markers
- Here we show additional data of an overall improvement in liver stiffness by TE, MRE, and the liver fibrosis marker, pro-C3, as well as insulin resistance by HOMA-IR
- The results, together with a previously reported study in F1-F4 NASH subjects*, suggest that epigenetic regulation of gene expression and their signaling pathways is an attractive approach to treat NASH
- The results warrant further study of DUR-928 in subjects with metabolic disorders, such as NASH

* Kemp et al., Safety and pharmacokinetics of DUR-928 in patients with non-alcoholic steatohepatitis – A Phase 1b study. EASL 2017 Poster

Acknowledgement

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