Denifanstat and resmetirom combination therapy rapidly decreased atherogenic lipids in healthy adults in Phase 1 open-label trial

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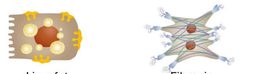
Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor. Denifanstat (Deni) demonstrated MASH resolution and fibrosis improvement in the Phase 2b MASH trial, FASCINATE-2 (NCT04906421)[1]
- In preclinical models, FASN inhibitors improved 3 hallmarks of MASH: inhibited liver fat synthesis & accumulation (hepatocytes), inhibited fibrosis (hepatic stellate cells require DNL for activation) and decreased inflammation (inflammasome activation by palmitate)[2]
- Thyroid hormone receptor-beta (THR-β) agonists increase lipid oxidation which decreases liver fat; resmetirom (Res) demonstrated MASH resolution and fibrosis improvement in Phase 3 trial[3]



Denifanstat Reduces de novo Lipogenesis	Sugar → FASN → Fatty acids	**Direct** - decreases de novo lipogenesis	**Direct** – decreases fibrogenesis in stellate cells, liver fat and lipotoxicity
Resmetirom Increases mitochondrial beta-oxidation	Fatty acids → THR-β → Metabolized	**Direct** - increases fatty acid oxidation and improves mitochondrial function	**Indirect** – decreases fibrosis due to decreased liver fat and lipotoxicity

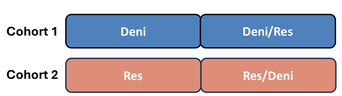
Background and Aim

- In preclinical MASH models, combination of a FASN inhibitor and Res increased efficacy to improve liver histology versus monotherapy through complementary mechanisms of liver fat reduction and Deni's direct anti-fibrotic effect
- This Phase 1 trial evaluated safety, PD and PK of the Deni/Res combination therapy in healthy adults

Methods

- Forty healthy adults (20/cohort) received 50 mg Deni and weight-based Res (80/100 mg)
- Cohorts 1 and 2 completed 7 days of monotherapy lead-in for Deni (cohort 1) or Res (cohort 2) respectively followed by 7 days of combination therapy
- Blood was analyzed for multi-omic profiling, and Deni and Res plasma concentrations

Phase 1 trial design

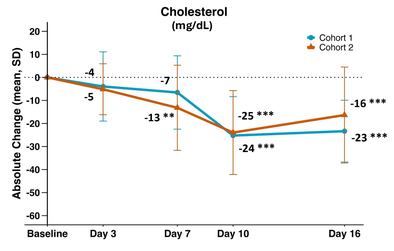


Results

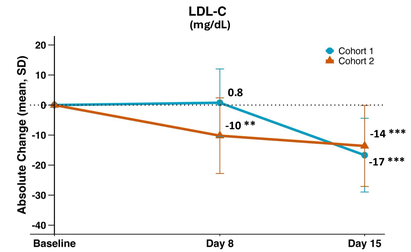
Demographics

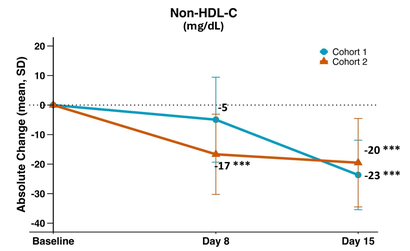
Mean (SD)	Cohort 1	Cohort 2
Age (yr)	44 (9)	34 (7)
Gender (M/F)	12/8	15/5
White/Hispanic (n)	19	16
Black/African American (n)	1	4
BMI	31.7 (4.7)	30.1 (3.7)
BW (kg)	93.8 (18.9)	92.5 (14.9)
80 mg resmetirom	77.7 (9.9)	80.7 (12.4)
100 mg resmetirom	109.9 (8.7)	104.2 (3.1)

Total cholesterol, LDL-C and non-HDL-C were rapidly decreased in both cohort 1 and 2 with two weeks treatment



Cholesterol was measured in clinical laboratory
** p<0.01, *** p<0.001, Mixed Model for Repeated Measures (MMRM)





LDL-cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C) were measured by NMR-based lipoprotein fractionation
** p<0.01, *** p<0.001, MMRM

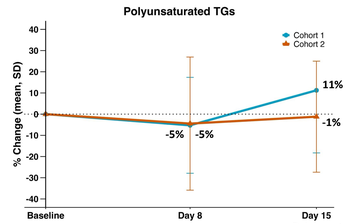
Treatment-Emergent Adverse Event (TEAE) frequency by cohort

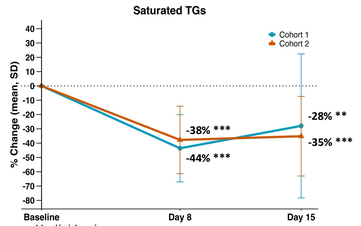
- Overall the combination was well tolerated
- No Serious Adverse Events (SAEs) occurred, no clinically significant laboratory results, and no treatment discontinuations

Adverse Event	Cohort 1 (N = 20)	Cohort 2 (N = 20)	Overall (N = 40)
Number of Participants with TEAEs	8 (40%)	5 (25%)	13 (33%)
Number of TEAEs	22	11	33
Ear and labyrinth disorders	1 (5%) [4]	0 (0%) [0]	1 (3%) [4]
Eye disorders	2 (10%) [2]	0 (0%) [0]	2 (5%) [2]
Gastrointestinal disorders	3 (15%) [10]	1 (5%) [2]	4 (10%) [12]
General disorders and administration site conditions	1 (5%) [1]	2 (10%) [2]	3 (8%) [3]
Infections and infestations	1 (5%) [1]	0 (0%) [0]	1 (3%) [1]
Musculoskeletal and connective tissue disorders	0 (0%) [0]	1 (5%) [1]	1 (3%) [1]
Nervous system disorders	3 (15%) [3]	1 (5%) [1]	4 (10%) [4]
Respiratory, thoracic and mediastinal disorders	1 (5%) [1]	3 (15%) [4]	4 (10%) [5]
Skin and subcutaneous tissue disorders	0 (0%) [0]	1 (5%) [1]	1 (3%) [1]

Most TEAEs were Grade 1, and 6 events were Grade 2

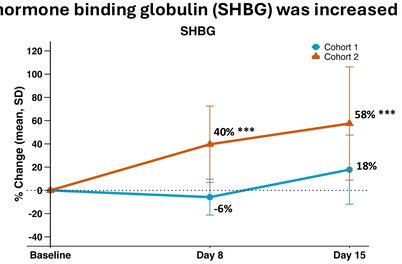
Polyunsaturated TGs were increased by 2-week Deni treatment, while saturated TGs were decreased by Deni and Res





Polyunsaturated and saturated TGs were measured by lipidomics
** p<0.01, *** p<0.001, MMRM

Sex hormone binding globulin (SHBG) was increased by Res



Serum SHBG was measured by Olink proteomics
*** p<0.001, MMRM

Deni and Res PK parameters in Cohorts 1 and 2

		Monotherapy (End of Period 1)		Combination (End of Period 2)	
		$AUC_{0\text{-}tau}$ (hr*ng/mL)	$C_{max,ss}$ (ng/mL)	$AUC_{0\text{-}tau}$ (hr*ng/mL)	$C_{max,ss}$ (ng/mL)
Cohort 1 Deni exposure (N=19)	Mean	13110	928	14970	1137
	SD	5386	402	6189	462
Cohort 2 Res exposure (N=20)	Mean	7054	1736	4580	1142
	SD	6066	984	2883	539

1 subject in cohort 1 was excluded due to minimal drug exposure

Conclusions

- The Phase 1 trial results showed that all treatments were generally well tolerated, and the combination therapy rapidly reduced atherogenic lipids, suggesting a potential cardiovascular benefit
- Strong target engagement was observed with both denifanstat and resmetirom as monotherapy and in combination
- Together with prior clinical results of fibrosis improvement in monotherapy of denifanstat or resmetirom, the Phase 1 safety, PD biomarker and PK results support further clinical evaluation of denifanstat and resmetirom combination for the treatment of MASH and liver fibrosis

References

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3. Harrison et al., 2024. N Engl J Med 2024;390:497-509