Reduction of plasma glycine- and taurine-conjugated bile acids correlated with histological improvements in denifanstat-treated MASH patients in Phase 2b FASCINATE-2 trial

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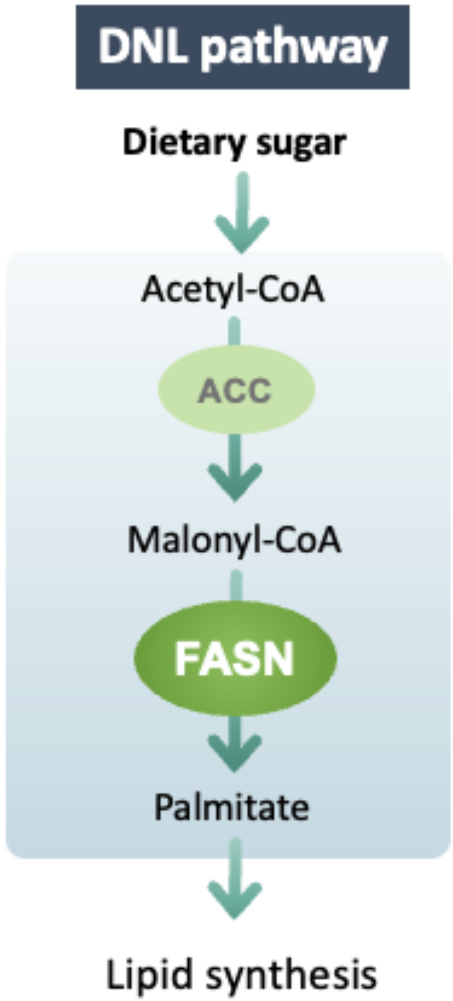
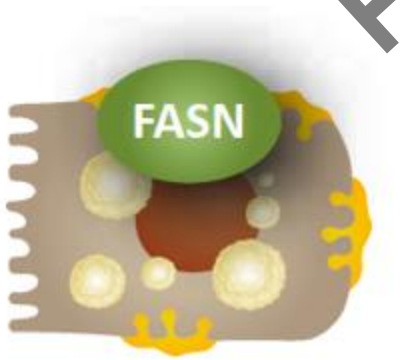
Outline

- Introduction of fatty acid synthase (FASN) and denifanstat MOAs
- Denifanstat histological results in Phase 2b FASCINATE-2 trial in F2/F3 MASH
- Correlation between bile acid changes and histological responses

FASN Plays a Key Role in Three Major Cell Types in MASH



Denifanstat

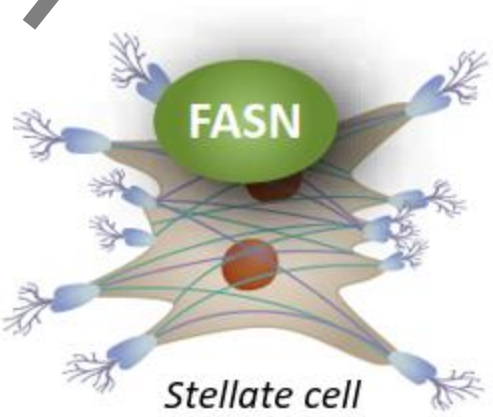


Hepatocyte

<u>Increases</u>
Fatty acids
Triglycerides
Lipotoxins

Immune cell

<u>Increases</u>
Cytokines
Chemokines
Cell activation



Stellate cell

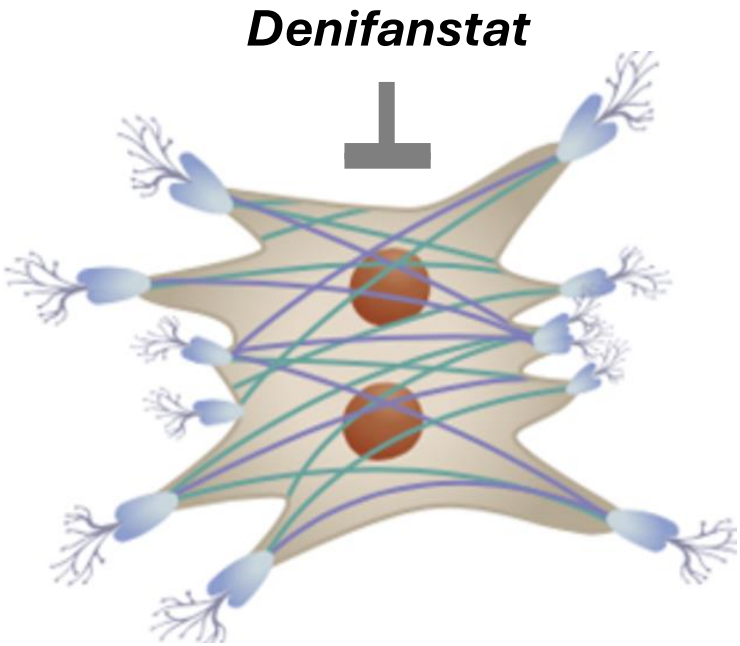
<u>Increases</u>
Fibrogenesis
Cell activation

DNL: *de novo* lipogenesis

FASN Inhibition Directly Blocks Human Liver Stellate Cell Function

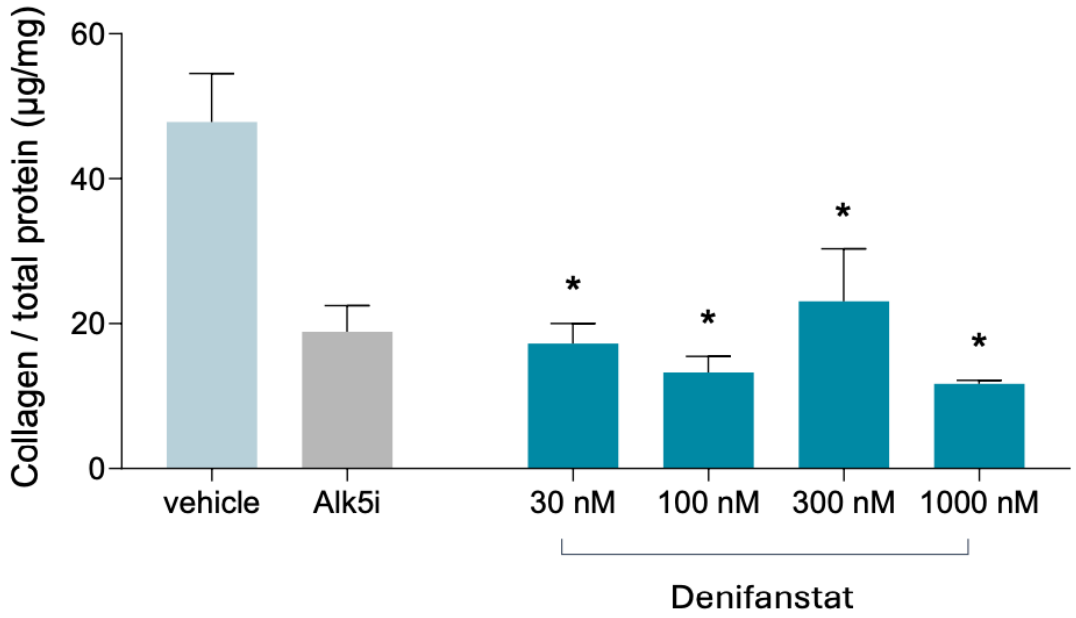
Stellate cells require DNL for fibrogenesis

Denifanstat blocks stellate cell activation



Primary human stellate cell assay

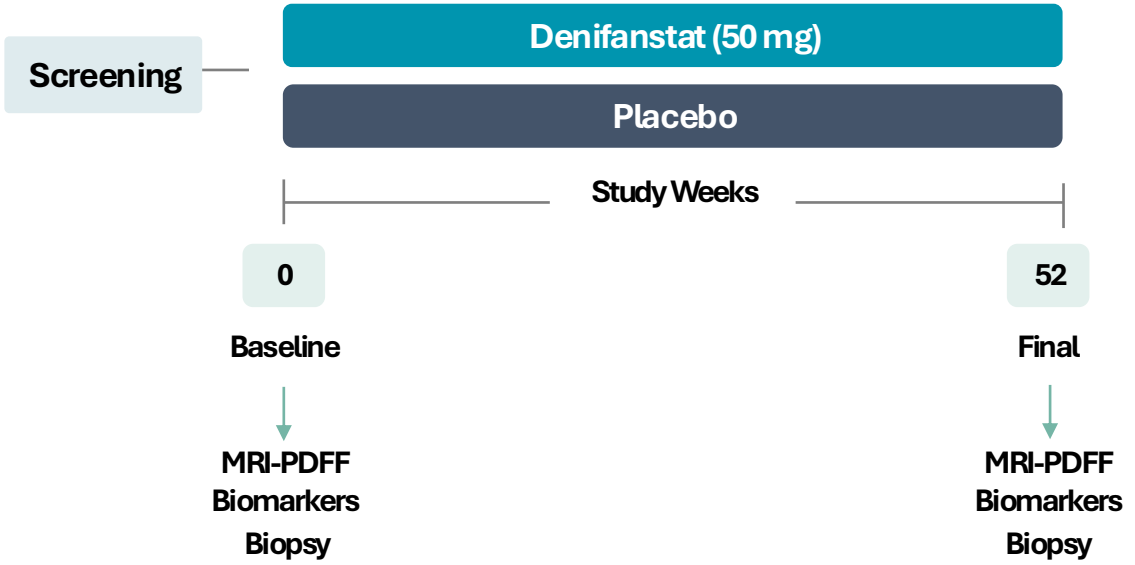
Denifanstat directly inhibits fibrogenic activity



- Stimulated by TGF-beta to activate fibrogenesis
- Denifanstat showed similar inhibition to positive control ALK5 inhibitor

*p<0.05. FASNi directly inhibits fibrosis. O'Farrell et al.,2022. Scientific Reports. 12:15661

FASCINATE-2: Biopsy Trial Design Focused on Histological Endpoints



- Biopsy confirmed F2-F3 MASH patients
- 52 weeks, 2:1 randomization to 50mg or placebo, double-blind
- Single pathology reader: Dr. Pierre Bedossa
- AI digital pathology: HistoIndex

Primary endpoints

- NAS ≥2 points improvement w/o worsening of fibrosis
- MASH resolution + NAS ≥2 improvement w/o worsening of fibrosis

Selected secondary endpoints

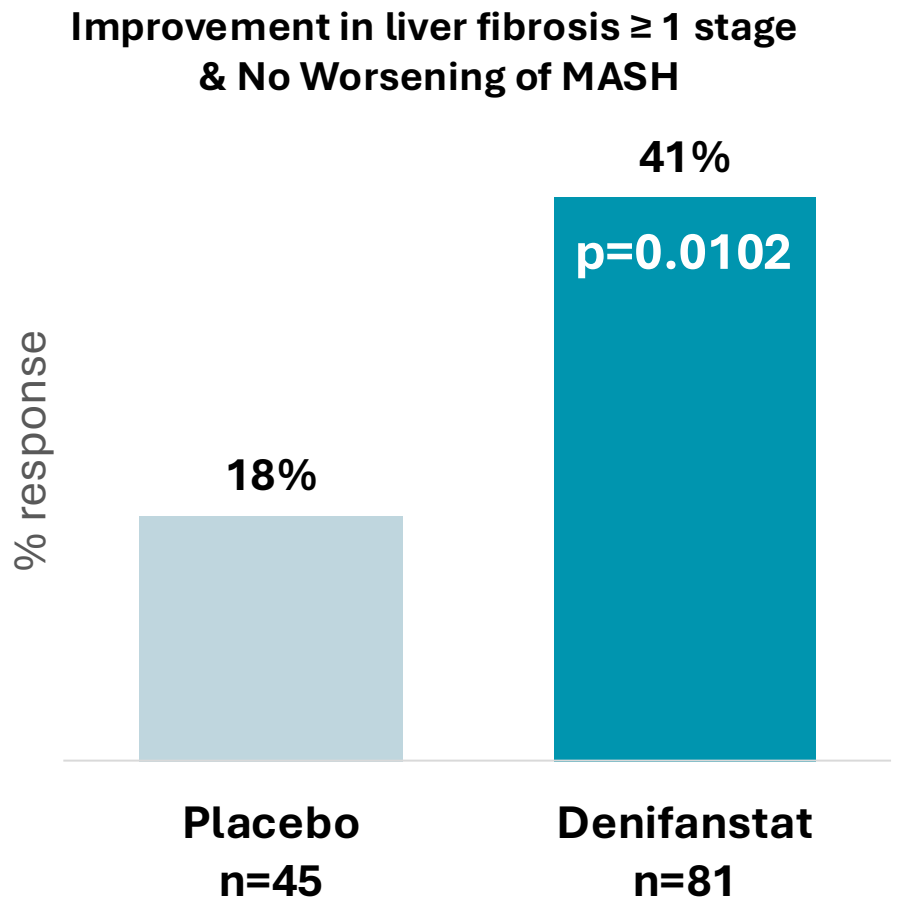
- **Improvement in liver fibrosis ≥1 stage without worsening of MASH as assessed by biopsy**
- **MASH resolution w/o worsening of fibrosis**
- Digital AI pathology
- MRI-PDFF: absolute decrease, % change from baseline, % pts ≥30% reduction from baseline (responders)

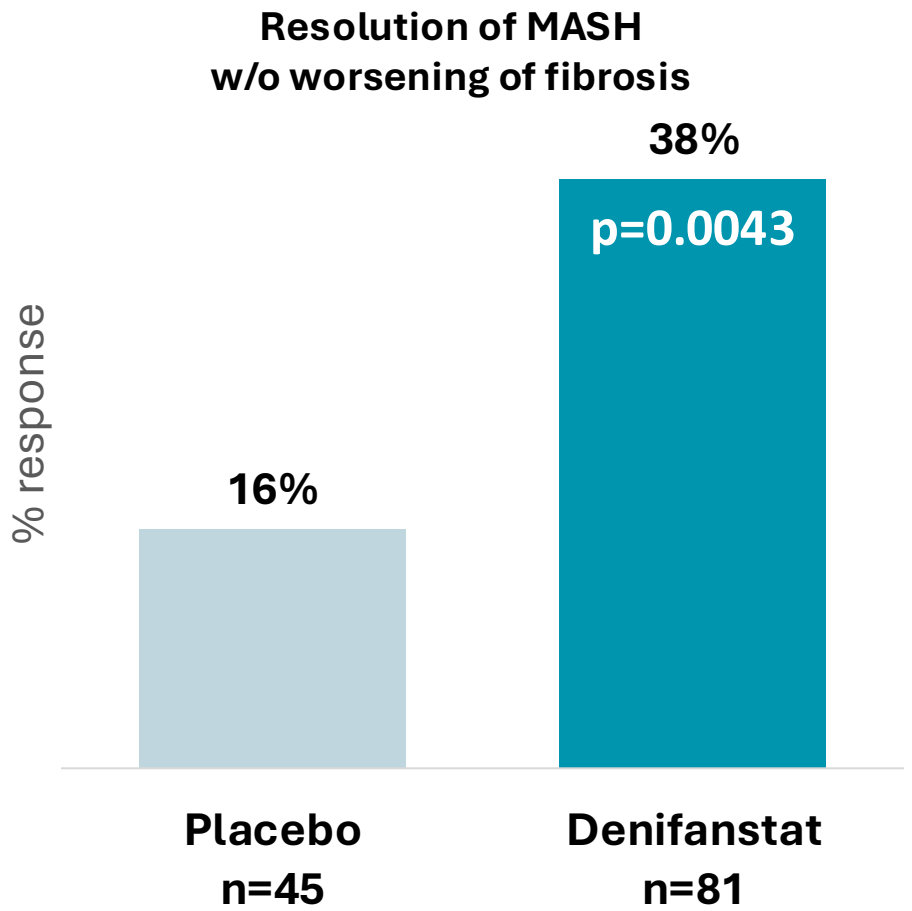
AI: Artificial Intelligence, MRI-PDFF; magnetic resonance imaging derived proton density fat fraction, NAS; NAFLD Activity Score.

Loomba et al., 2024. The Lancet Gastroenterology & Hepatology. doi:10.1016/S2468-1253(24)00246-2

Histology Endpoints of MASH Resolution and Liver Fibrosis at Week 52

Denifanstat Achieved Statistical Significance (Endpoints per FDA Draft Guidance 2020)





Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level. mITT population. Statistical significance also reached for ITT population.

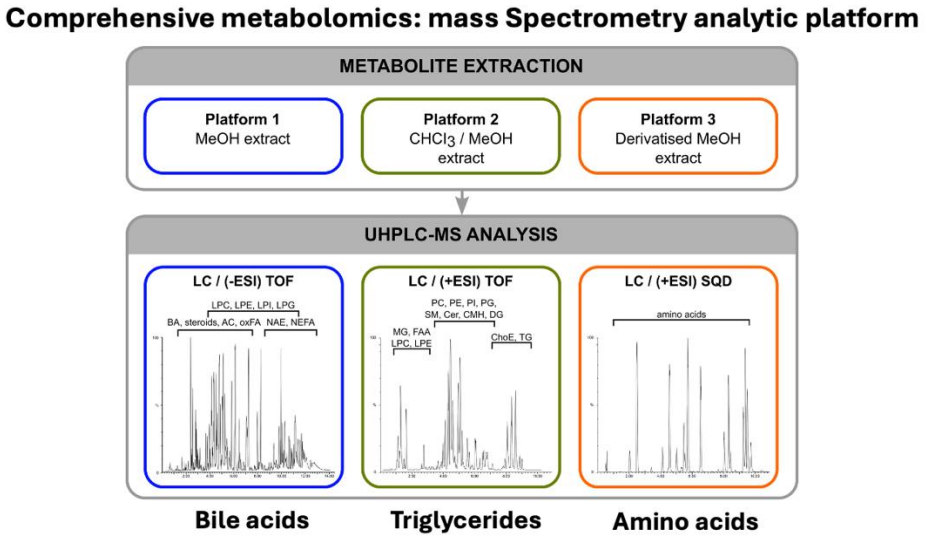
Additional Fibrosis Endpoint Analysis at Week 52

Denifanstat Achieved Strong Improvement in F3 Population

Fibrosis Endpoints	Subgroup	Placebo	Denifanstat	p-value
≥1 stage improvement in fibrosis w/o worsening of MASH	All pts	18%	41%	0.0102**
	F3 only	**13%**	**49%**	**0.0032****
≥2 stage improvement in fibrosis w/o worsening of MASH	**All pts**	**2%**	**20%**	**0.0065****
	F3 only	**4%**	**34%**	**0.0065****
Progression to cirrhosis (F4)	**All pts**	**11%**	**5%**	**0.0386***

mITT population; *One sided at the 0.05 significance level, **Two sided at the 0.05 significance level .

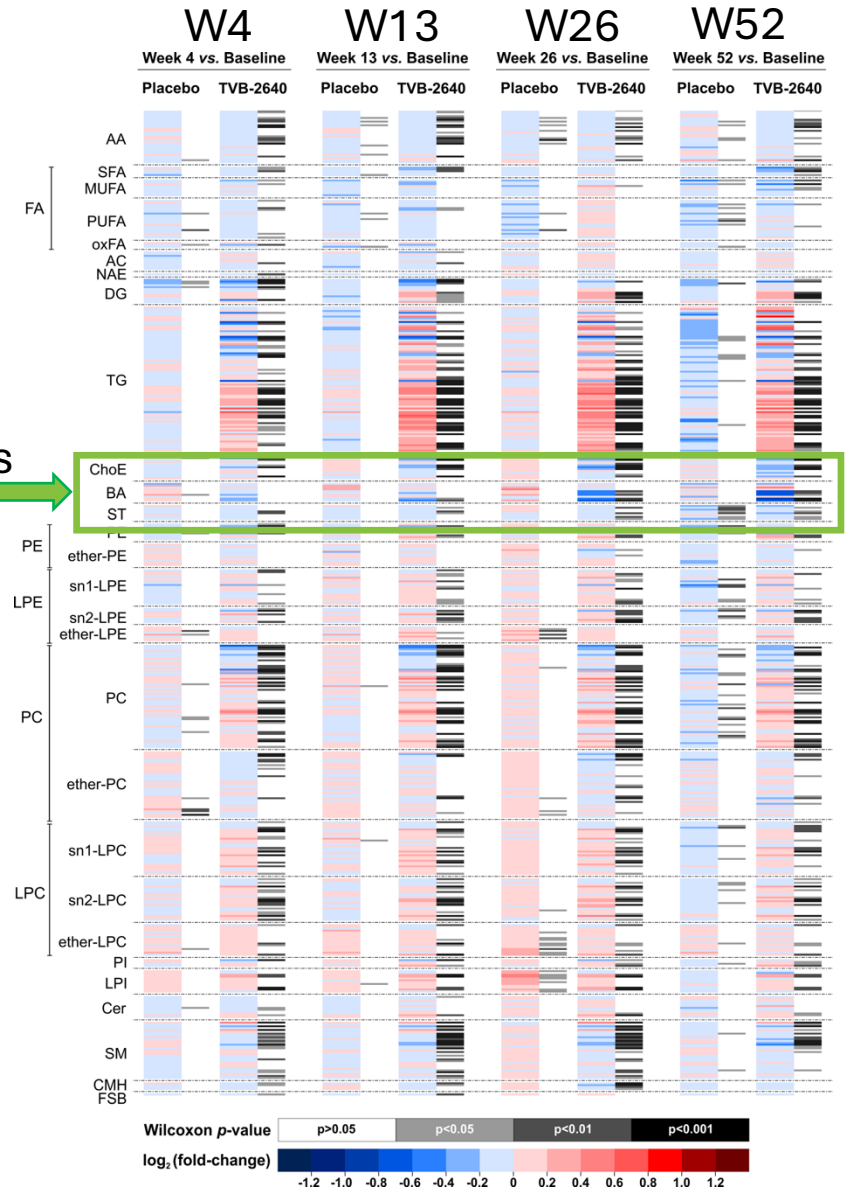
Denifanstat Decreased Conjugated Bile Acids Over Time in MASH Patients



Changes from baseline to W52

	Change from baseline to week 52			
	Placebo		Denifanstat	
	% change	p values	% change	p values
Bile Acids	**0**	0.95	**-5**	0.136
Free bile acids	**7**	0.80	**10**	0.803
Glycine-conjugated bile acids	**5**	0.89	**-27**	0.002
Taurine-conjugated bile acids	**7**	0.82	**-45**	<0.001

Bile acids



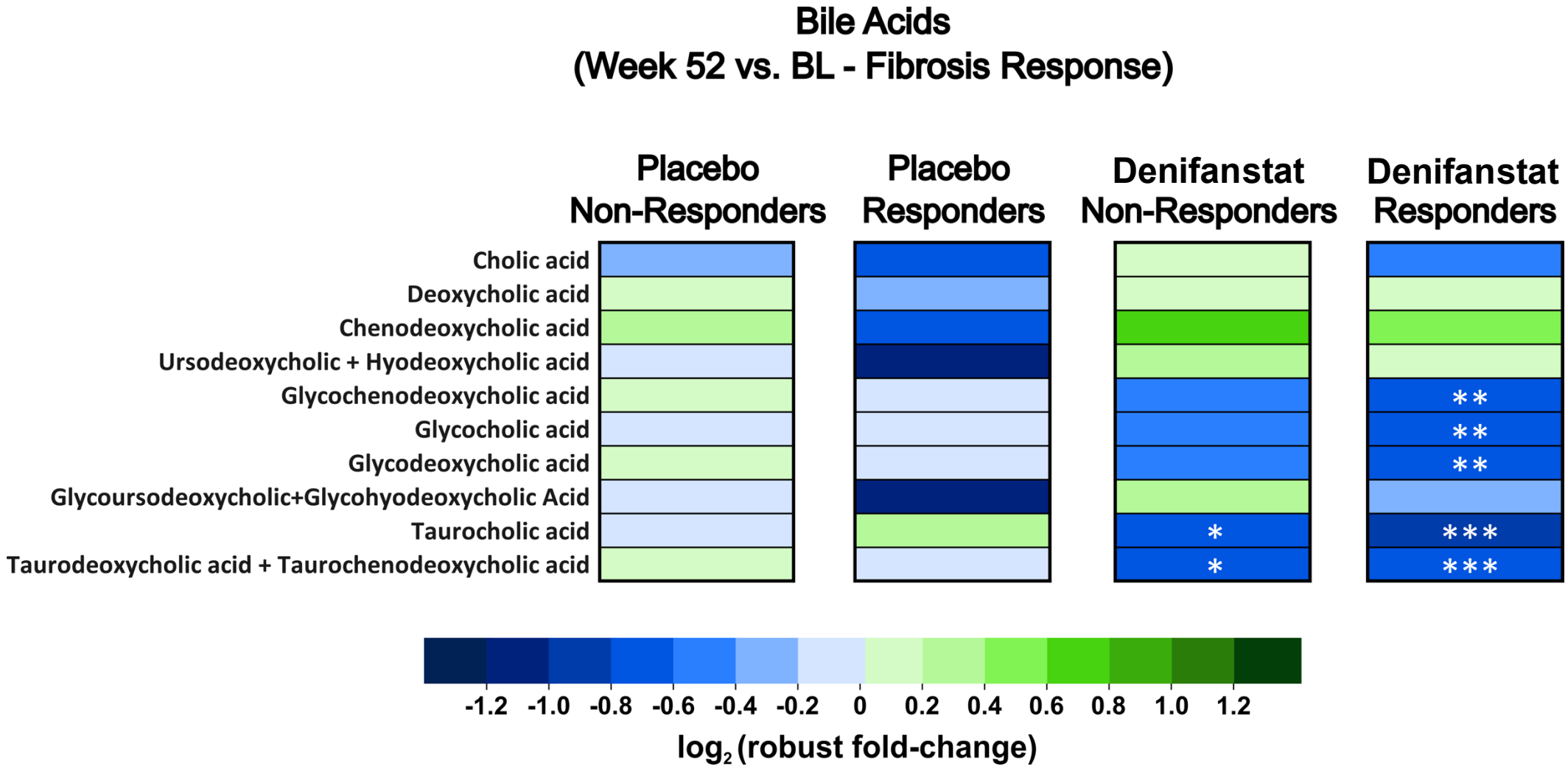
Wilcoxon-signed rank test

Denifanstat Specifically Decreased Glycine- and Taurine-Conjugated Bile Acids at Week 52 in MASH Patients

Bile acids	Week 52 vs Baseline					
	Placebo			Denifanstat		
	log(rob. FC)	% Change	p-val	log(rob. FC)	% Change	p-val
Cholic acid	-0.34	-21	0.278	-0.24	-15	0.956
Deoxycholic acid	0.02	1	0.949	0.05	3	0.409
Chenodeoxycholic acid	0.23	17	0.623	0.54	46	0.363
Ursodeoxycholic + Hyodeoxycholic acid	-0.04	-3	0.369	0.11	8	0.730
Glycochenodeoxycholic acid	-0.11	-7	0.759	-0.47	-28	0.001
Glycocholic acid	-0.18	-12	0.977	-0.67	-37	0.005
Glycodeoxycholic acid	0.02	1	0.570	-0.64	-36	0.025
Glycoursodeoxycholic+Glycohyodeoxycholic Acid	-0.32	-20	0.435	0.08	6	0.539
Taurocholic acid	-0.04	-3	0.822	-0.77	-42	0.000
Taurodeoxycholic acid + Taurochenodeoxycholic acid	-0.08	-5	0.885	-0.69	-38	0.000

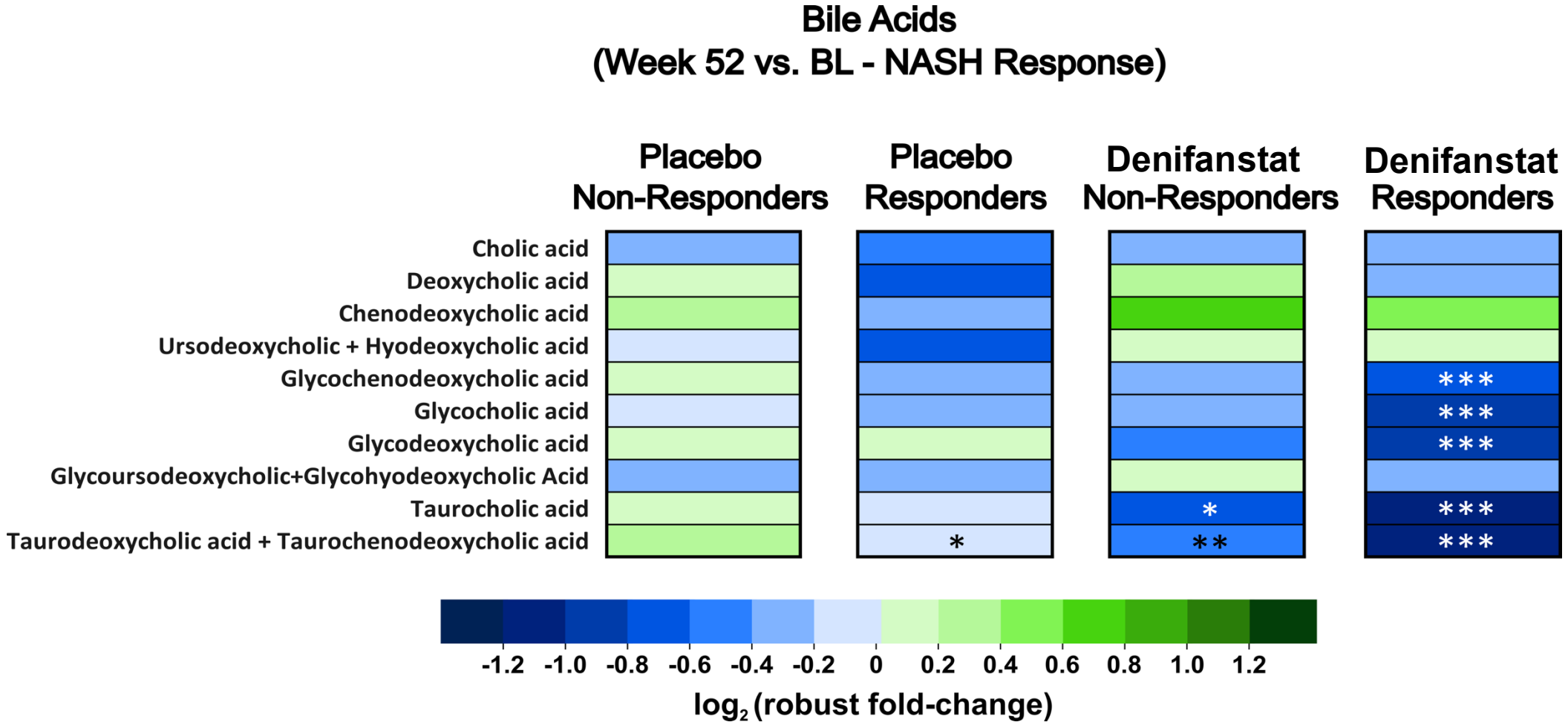
Log2 (robust fold-changes) and Wilcoxon-signed rank test

G/T-BAs Were Reduced at Week 52 in Denifanstat-Treated Fibrosis Responders



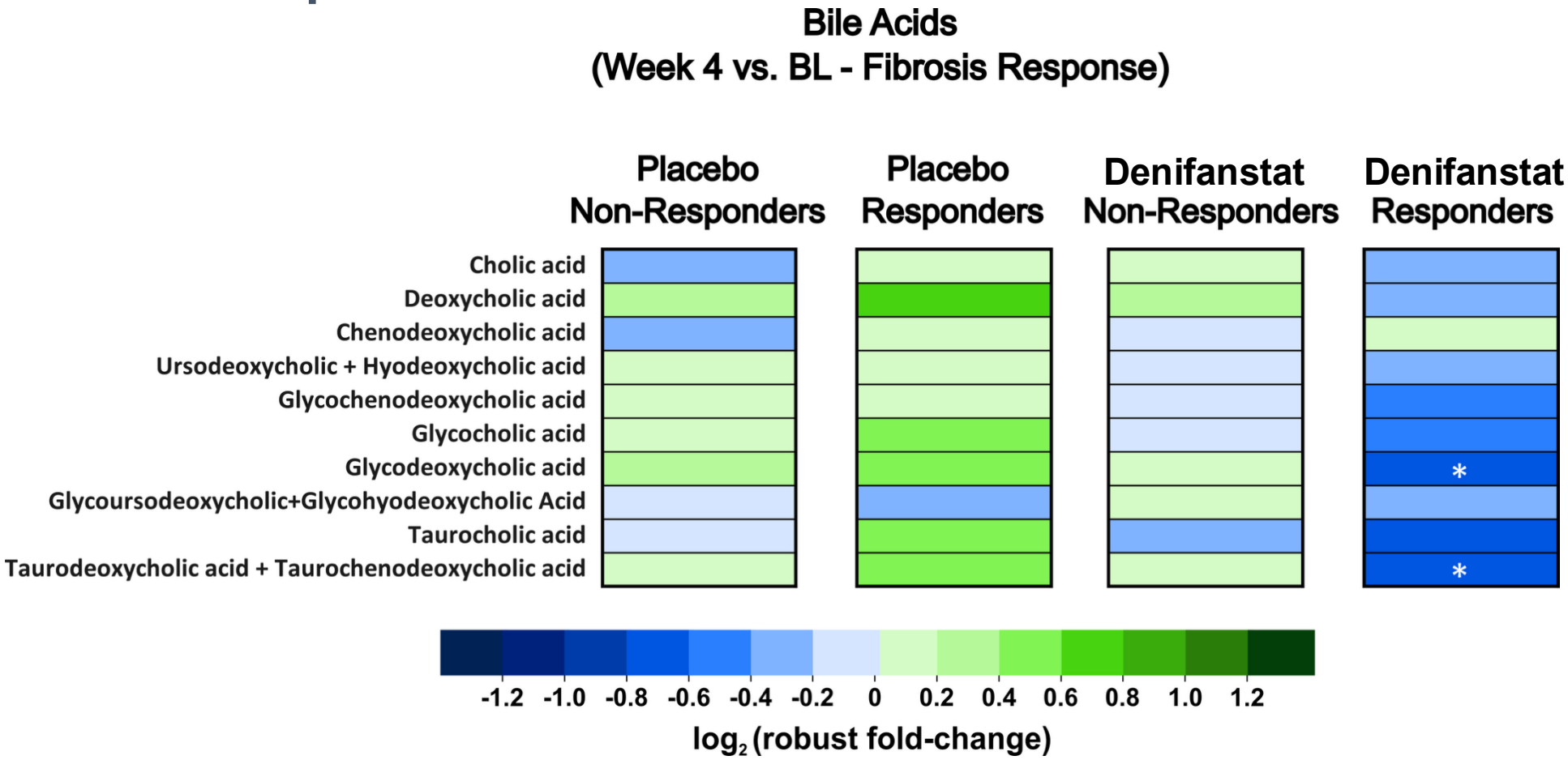
G/T-BAs: glycine- and taurine-conjugated bile acids; Wilcoxon signed-rank test p-values: *p<0.05; **p<0.01; ***p<0.001.

G/T-BAs Were Reduced at Week 52 in Denifanstat-Treated MASH Resolution Responders



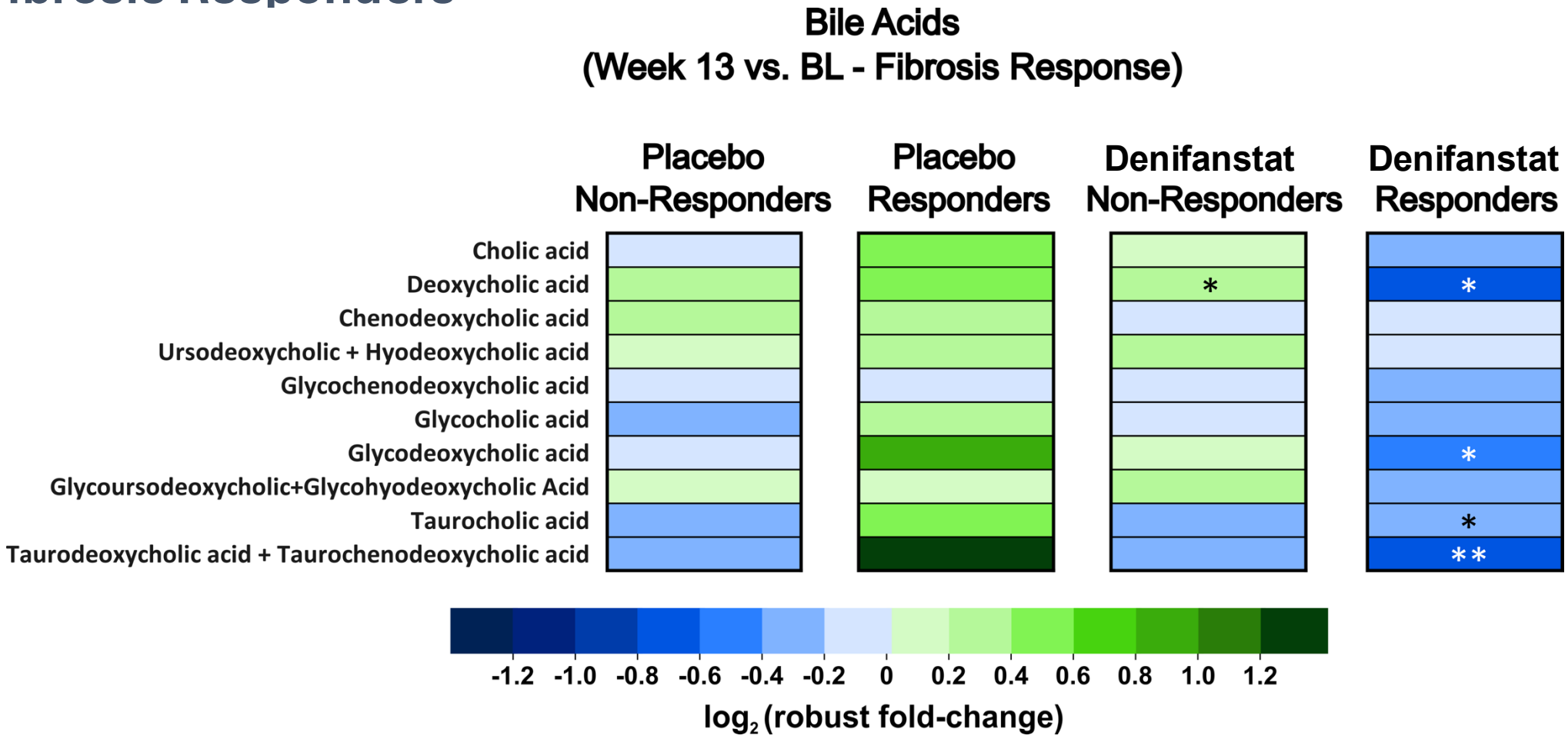
G/T-BAs: glycine- and taurine-conjugated bile acids; Wilcoxon signed-rank test p-values: *p<0.05; **p<0.01; ***p<0.001.

Two G/T-BAs Were Significantly Reduced at Week 4 in Denifanstat-Treated Fibrosis Responders



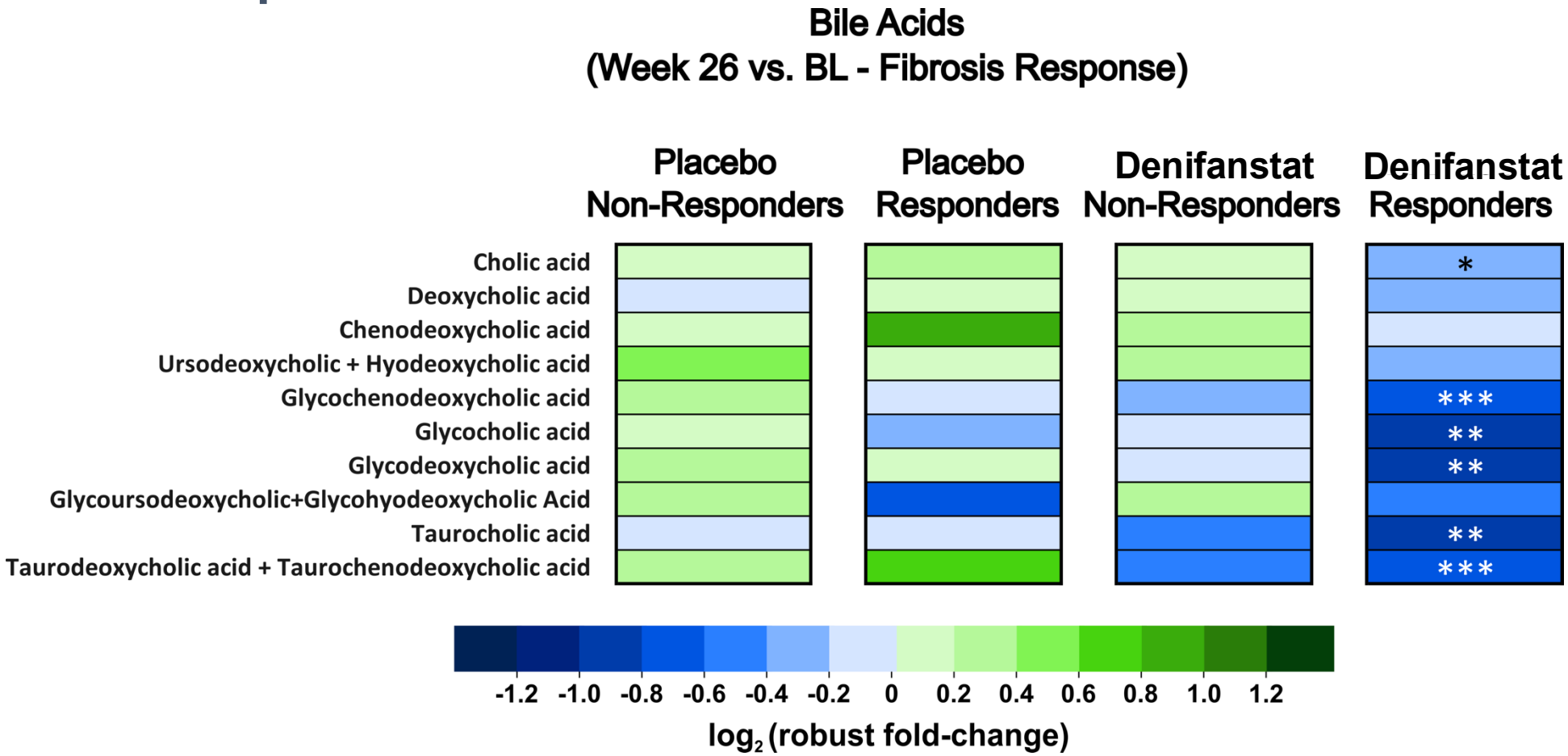
G/T-BAs: glycine- and taurine-conjugated bile acids; Wilcoxon signed-rank test p-values: *p<0.05.

Three G/T-BAs Were Significantly Reduced at Week 13 in Denifanstat-Treated Fibrosis Responders



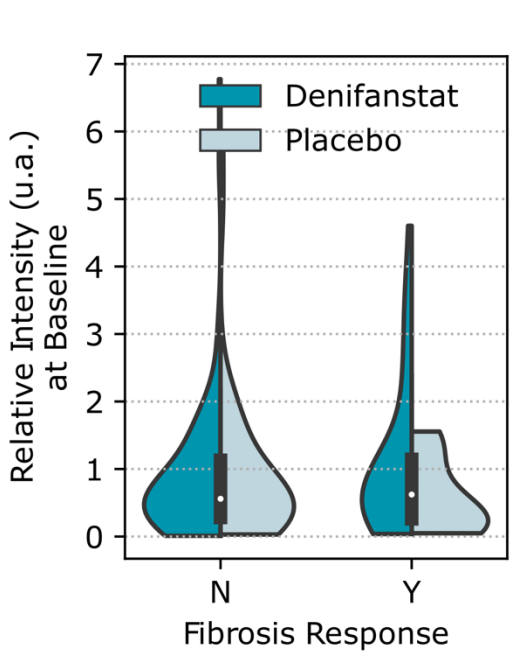
GG/T-BAs: glycine- and taurine-conjugated bile acids; Wilcoxon signed-rank test p-values: *p<0.05; **p<0.01.

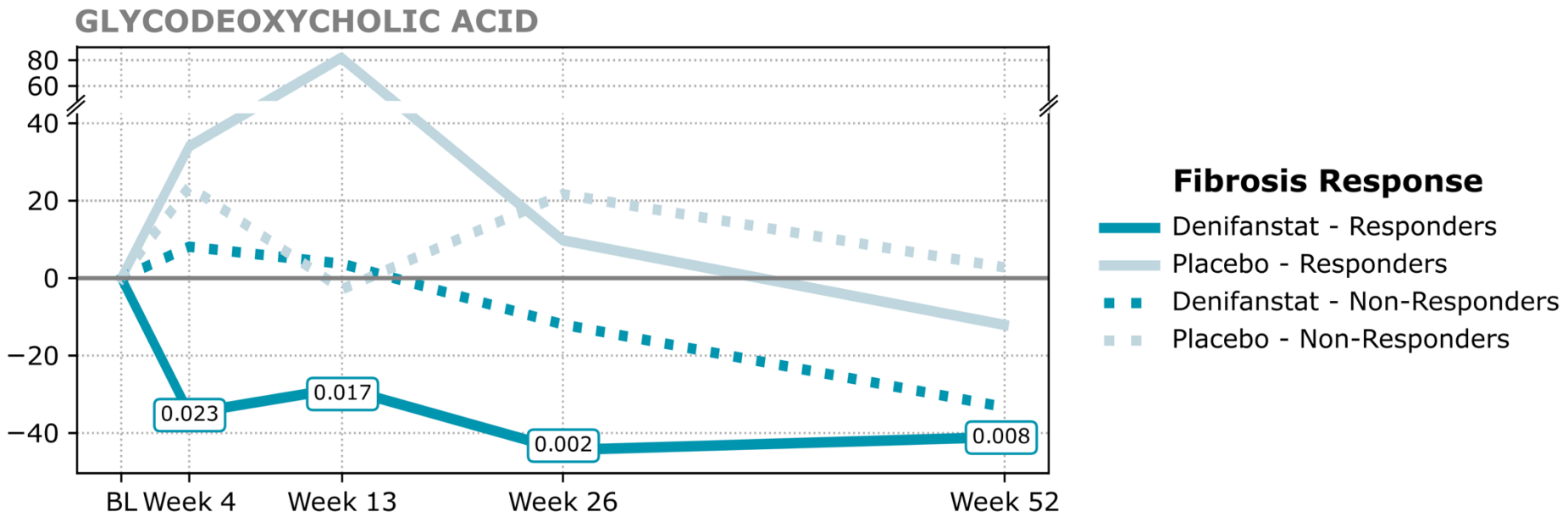
Five G/T-BAs Were Significantly Reduced at Week 26 in Denifanstat-Treated Fibrosis Responders



G/T-BAs: glycine- and taurine-conjugated bile acids; Wilcoxon signed-rank test p-values: *p<0.05; **p<0.01; ***p<0.001.

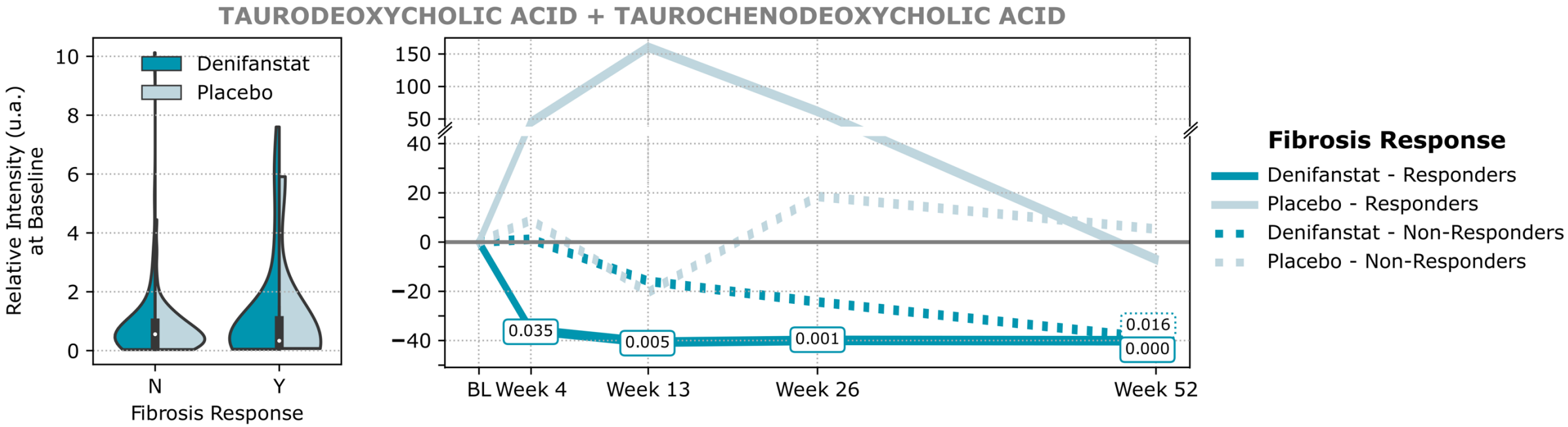
Glycodeoxycholic Acid Was Reduced at Week 4 in Fibrosis Responders





Wilcoxon signed-rank test compared to baseline.

Tauro-Deoxycholic/Chenodeoxycholic Acids Were Reduced at Week 4 in Fibrosis and MASH Responders



Wilcoxon signed-rank test compared to baseline.

Acknowledgements

- Investigators, sites and patients involved in FASCINATE-2 trial
- Sagimet team
- Sagimet advisors
- Rubio Metabolomics team