Assessment of metabolic dysfunction-associated steatohepatitis resolution index and component biomarkers in prediction of histology response to denifanstat in the FASCINATE-2 trial

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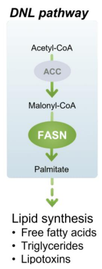
Introduction

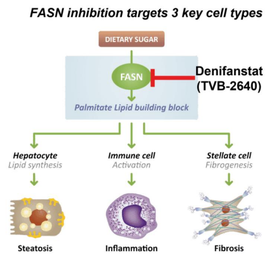
- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH
- FASN inhibition targets 3 hallmarks of MASH:

  - inhibits liver fat synthesis & accumulation (hepatocytes)

  - **inhibits fibrosis (hepatic stellate cells require DNL for activation)**

  - decreases inflammation (inflammasome activation by palmitate)[1]

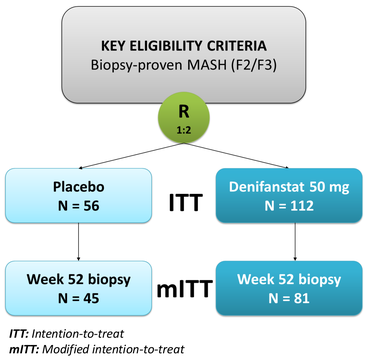




Background and Aims

- The phase 2b FASCINATE-2 trial (see study design below) met its primary and multiple secondary endpoints, including fibrosis improvement without worsening of MASH, and MASH resolution without worsening of fibrosis[2]
- This analysis tested the performance of the MASH Resolution Index[3] in predicting MASH resolution by denifanstat by retrospective analysis of FASCINATE-2

Methods



ITT: Intention-to-treat
mITT: Modified intention-to-treat

FASCINATE-2 was a 52-week randomized, double-blind, placebo-controlled phase 2b trial

Primary Endpoints

- NAS ≥2 points improvement without worsening of fibrosis
- MASH resolution + NAS ≥2 improvement without worsening of fibrosis

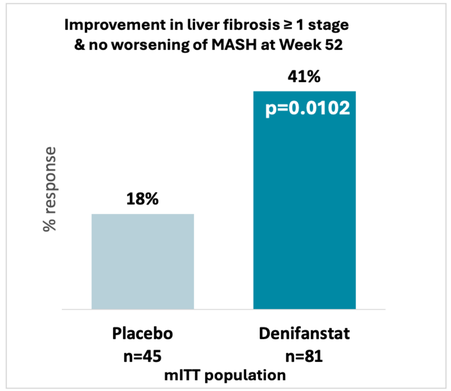
Selected Secondary Endpoints

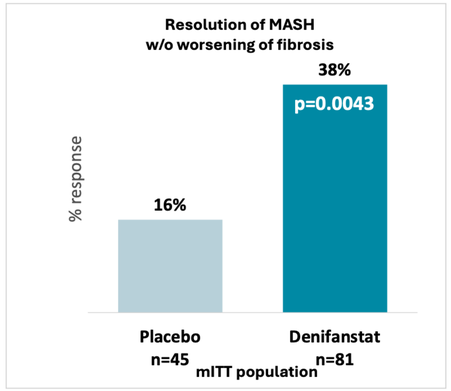
- Improvement in liver fibrosis ≥1 stage without worsening of MASH
- Digital artificial intelligence (AI) pathology

- MASH Resolution Index (MR-I) score[3] = 0.520–0.003×baseline ALT (U/L) −0.024×(latest ALT [U/L]- baseline ALT (U/L)) − 0.048×baseline MRI-PDFF − 2.571×((latest MRI-PDFF - baseline MRI-PDFF) / baseline MRI-PDFF) − 0.039×baseline AST (U/L)
- Logistic regression (LR) models were used for analysis versus MASH resolution

Results

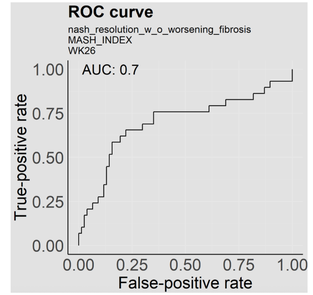
Denifanstat significantly improved liver fibrosis and MASH resolution in FASCINATE-2

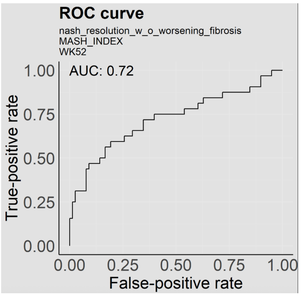




Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level

Prediction of MASH resolution by change in MASH Resolution Index score at week 26 and week 52



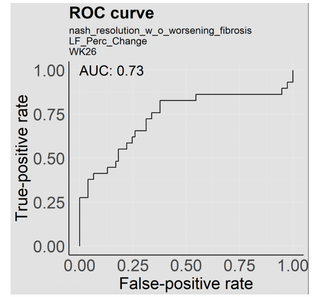


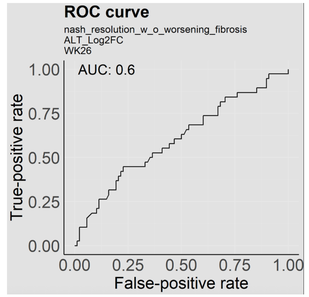
Performance comparison of changes in ALT, liver fat and MASH Resolution Index to predict MASH resolution

Input Variable	Modeled Variable	Method	Time Point	N	AUC	P-value in logistic regression model	Best Threshold selected from ROC	Sensitivity	Specificity	NPV	PPV
ALT	ALT_Log2FC	Regression	WK04	126	0.6	0.0356	0.42	0.26	0.94	0.75	0.67
ALT	ALT_Log2FC	Regression	WK13	123	0.68	0.0033	0.24	0.78	0.55	0.86	0.42
ALT	ALT_Log2FC	Regression	WK26	126	0.6	0.0804	0.33	0.45	0.77	0.76	0.46
ALT	ALT_Log2FC	Regression	WK52	125	0.62	0.0102	0.44	0.29	0.94	0.75	0.69
Liver_Fat_%	LF_Perc_Change	Regression	WK26	106	0.73	0.4515	0.28	0.83	0.62	0.91	0.45
Liver_Fat_%	LF_Perc_Change	Regression	WK52	111	0.73	0.0056	0.40	0.47	0.94	0.81	0.75
MASH_Index	MASH_Index	Regression	WK26	106	0.7	0.2349	0.30	0.66	0.78	0.86	0.53

MASH resolution was determined by conventional histology approaches; NPV: negative predictive value, PPV: positive predictive value

Prediction of MASH resolution by change in liver fat or ALT at week 26





Conclusions

- Denifanstat demonstrated a statistically significant improvement in liver fibrosis and MASH resolution in FASCINATE-2 study
- This retrospective analysis of FASCINATE-2 indicated that the MASH Resolution Index score and its components have potential application to enrich for histology responders to denifanstat

References
(1) O'Farrell et al., 2022. Scientific Reports. doi:10.1038/s41598-022-19459-z
(2) Loomba et al., 2024. The Lancet Gastroenterology & Hepatology. doi:10.1016/S2468-1253(24)00246-2
(3) Loomba R, et al. Gut 2024;0:1–7. doi:10.1136/gutjnl-2023-331401

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