Analysis of non-invasive biomarker tests in the Phase 2 FASCINATE-1 study of FASN inhibitor TVB-2640

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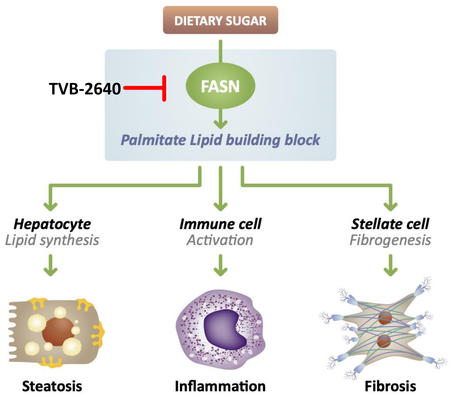
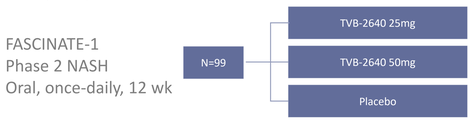
INTRODUCTION

- TVB-2640 is a potent and selective FASN inhibitor
- Directly tackles 3 hallmarks of NASH: inhibits liver fat accumulation (hepatocytes), inhibits fibrosis (stellate cells require DNL for activation) and decreases inflammation (inflammasome activation by palmitate)



OBJECTIVE

Explore correlations between liver fat efficacy and non-invasive tests (NITs) in FASCINATE-1



- Multicenter, randomized, placebo-controlled trial
- Primary endpoint: liver fat reduction by MRI-PDFF and safety
- Secondary endpoint: % pts ≥30% reduction of liver fat
- Serum markers included ALT, AST, tripalmitin, adiponectin, PRO-C3

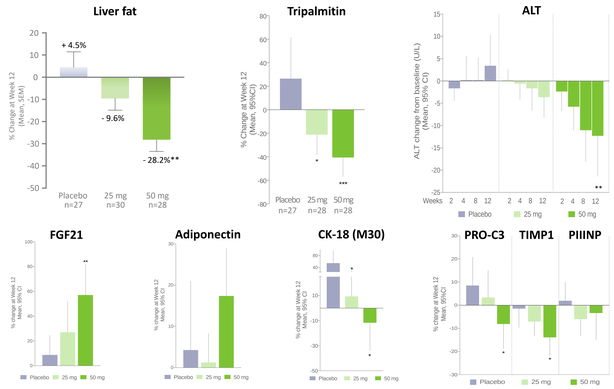
METHODS

Study design, demographics and top line results have been described[1,2]. Population shown is from US cohorts. All results shown are week 12 as change from baseline. Tripalmitin, and lipidomic profiling and correlative analysis were performed by OWL[3]. Biomarker assays used established methods: PRO-C3 (Nordic), TIMP1 and PIIINP (Siemens), FGF21 (Precision for Medicine), CK-18 and adiponectin (BARC/Cerba).

RESULTS

1 Liver fat and biomarker results at Week 12.

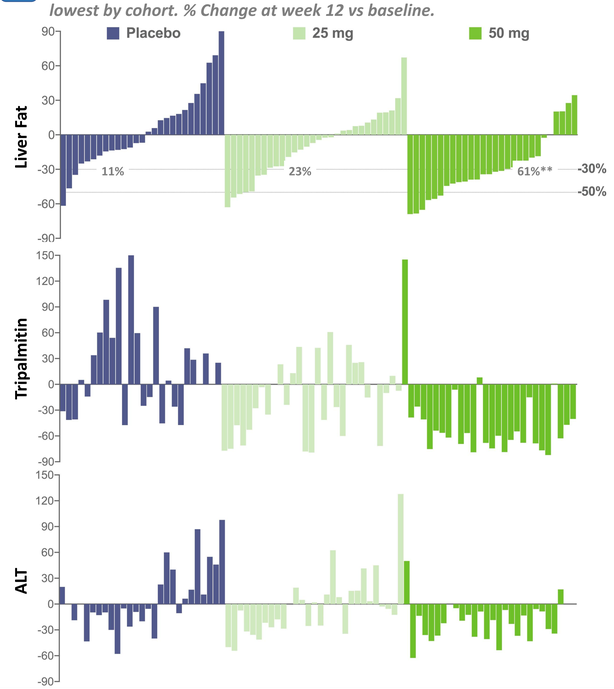
TVB-2640 significantly decreases liver fat, and biomarkers of fibrosis and inflammation at 50 mg



*p<0.05, **p<0.005, ***p<0.001. LSM difference versus placebo for liver fat, ANCOVA. Mann Whitney U test for biomarkers.

2 Liver fat, ALT, and tripalmitin. % change per patient

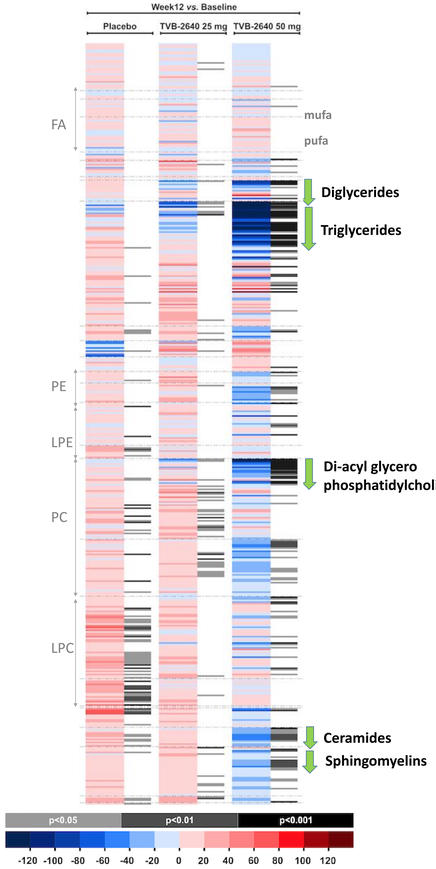
Patients are ranked by relative liver fat decrease in all 3 graphs, from highest to lowest by cohort. % Change at week 12 vs baseline.



3 Heat map of lipidomic analysis

Classes decreased at 50 mg

- *Ceramides*
- *Sphingomyelins*
- *DAGs and TAGs, notably shorter chain and unsaturated*



Paired Wilcoxon ranked test. Log2 fold change is shown. Similar results for % change. n of 27 (25 mg), 28 (50 mg) and 25 (placebo). FA: fatty acids, mufa: monounsaturated FA, pufa: polyunsatured FA, PE; phosphatidylethanolamines, LPE; lyso-PE, PC: phosphatidylcholines, LPC: lyso-PC.

- *Tripalmitin decrease in TVB-2640 treated patients confirms mechanism-based effect. At 25 mg, pts with LF response have higher rate of TP decrease (p=0.016), while at 50 mg majority of patients showed LF and TP response (p=0.002 and p<0.001 for LF decrease <30% and ≥30%).*
- *ALT decrease is associated with liver fat response for TVB-2640 (p=0.016 at 25mg, and p=0.003 at 50 mg).*
- *Body weight did not meaningfully change and no association with liver fat change was apparent (not shown).*

4 Correlation of biomarker changes with liver fat response (decrease ≥30%)

Significant associations with ALT, tripalmitin, TIMP1, FGF21.
Next steps include continuous analysis of LF change.

	Placebo		TVB-2640 25mg				TVB-2640 50mg			
	LF decrease <30%		LF decrease ≥30%		LF decrease <30%		LF decrease ≥30%		LF decrease <30%	
	%Change	p-value	%Change	p-value	%Change	p-value	%Change	p-value	%Change	p-value
ALT (U/L)	-0.07	0.61	-0.36	0.016	0.03	0.69	-0.21	**0.003**	-0.13	0.10
Adiponectin (ug/ml)	-0.01	0.63	0.00	1.00	-0.01	0.86	0.19	0.15	0.19	0.13
BW (kg)	0.01	0.21	-0.03	0.16	0.00	0.73	0.00	0.60	0.00	0.58
ELF Score	-0.01	0.96	-0.06	0.036	0.02	0.24	-0.03	0.08	-0.04	0.08
FGF21 (pg/ml)	-0.03	0.99	-0.29	0.31	0.35	0.017	0.34	0.045	0.89	**0.007**
HA (ng/ml)	0.01	0.74	-0.30	0.08	0.27	0.016	-0.16	0.039	-0.17	0.16
IP10 (ng/ml)	-0.01	0.24	-0.29	0.031	0.01	0.49	-0.01	0.89	-0.10	0.17
PIIINP (ng/ml)	0.04	0.39	-0.22	0.08	0.02	0.95	-0.11	0.44	-0.10	0.54
ProC3 (ng/ml)	0.07	0.21	-0.01	0.84	0.08	0.28	-0.08	0.46	-0.25	0.019
TIMP1 (ng/ml)	-0.03	0.99	-0.25	0.016	0.01	0.59	-0.15	0.044	-0.22	0.027
Tripalmitin	0.25	0.56	-0.53	0.016	-0.09	0.37	-0.57	**6.56E-04**	-0.63	**0.002**

p<0.05 p<0.01 p<0.001

Paired Wilcoxon signed-rank test p-values are indicated. LF decrease ≥ 30% are "responders". For LF decrease ≥30%/<30%, n of 7/20 (25 mg), 17/11 (50 mg) and 23 (placebo). Placebo >30% LF decrease not included as insufficient number of patients). Greyscale indicates significance.

CONCLUSIONS

1. TVB-2640 led to a significant decrease in LF with a 61% response rate vs 11% in placebo.
2. TVB-2640 significantly decreased biomarkers of liver inflammation and fibrosis.
3. Correlative analyses showed a significant association between liver fat, tripalmitin and ALT changes at 12 weeks.
4. TVB-2640 reduced lipotoxic species associated with NASH.
   - Including ceramides, sphingolipids, di- and triacylglycerols notably with shorter chains and lower saturation.
5. Overall biomarker results from FASCINATE-1 confirm the expected MOA and indicate that FASN inhibition has potential to be a foundational treatment for NASH.

ACKNOWLEDGEMENTS

We are grateful to the patients, their families and investigators that participated in this study.

REFERENCES

1. AASLD 2020, Loomba et al., Abstract 0067.
2. EASL ILC 2020, Loomba et al., Abstract S074.
3. Barr et al., J Proteome Research, 2012: 11, 2521.

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