Targeting VAP-1 Inhibition in NASH

Erin Quirk, M.D.
President and Chief Medical Officer
Terns Pharmaceuticals

NASH-TAG
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Introduction

- NAFLD/NASH prevalence is increasing and is associated with life-threatening complications including cirrhosis and hepatocellular carcinoma[1]
- New treatments for NASH are urgently needed, including treatments targeting inflammatory and fibrotic mechanisms in the liver that contribute to disease
- Vascular adhesion protein-1 (VAP-1, SSAO, AOC3) is a cellular adhesion protein with amine oxidase activity that may play a role in hepatic inflammation and fibrosis that has been identified as a potential target for the treatment of NASH[2]

[1]Liu et al. *Lancet Gastroenterol Hepatol* 2019
[2]Weston et al. *Journal of Clinical Investigation* 2015

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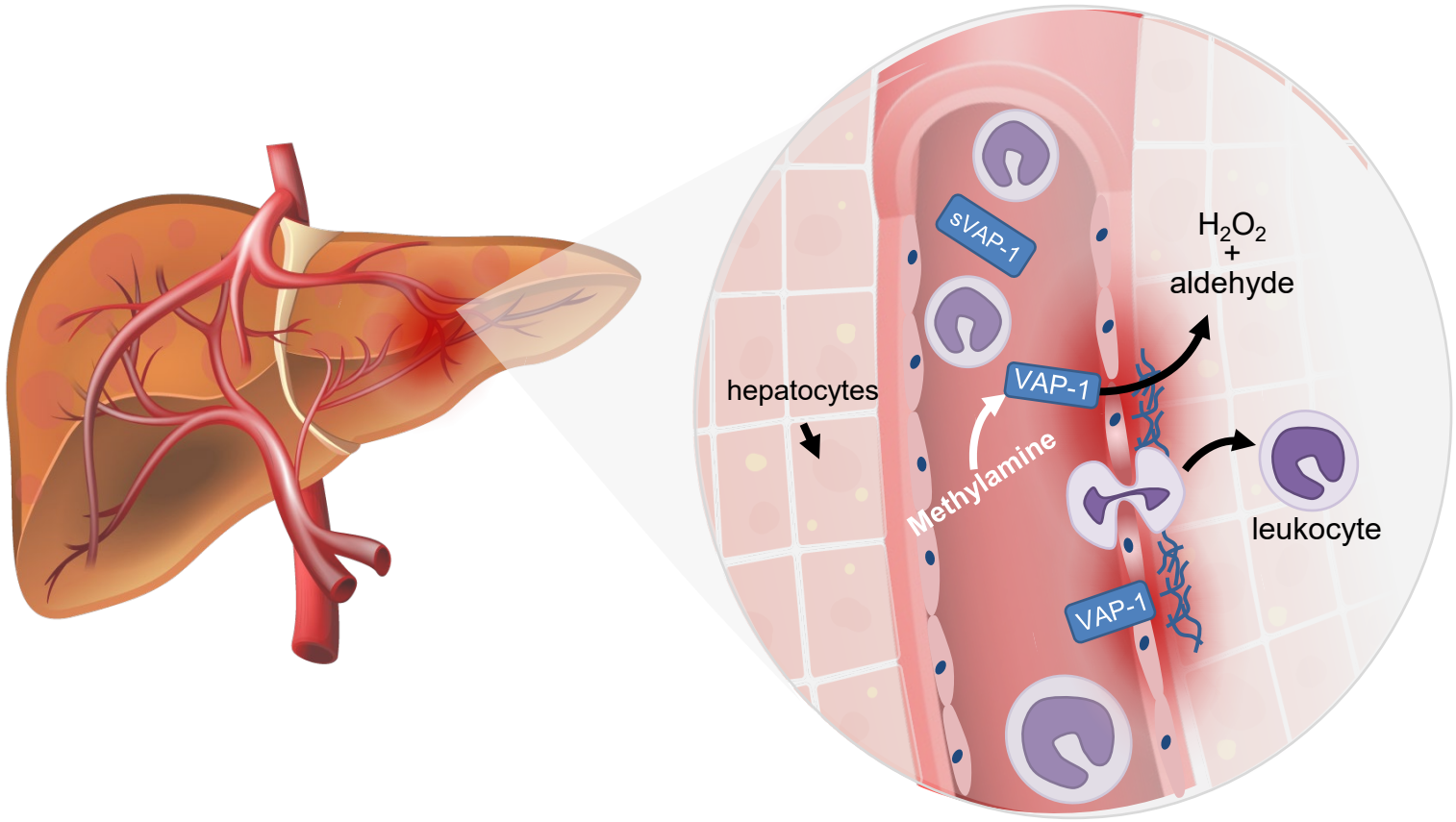
Role of VAP-1 in NASH

- VAP-1 may contribute to hepatic inflammation and fibrosis in NASH by:
  - Converting amines to aldehyde and hydrogen peroxide in the liver, leading to local oxidative stress
  - Recruitment of inflammatory leukocytes to the liver



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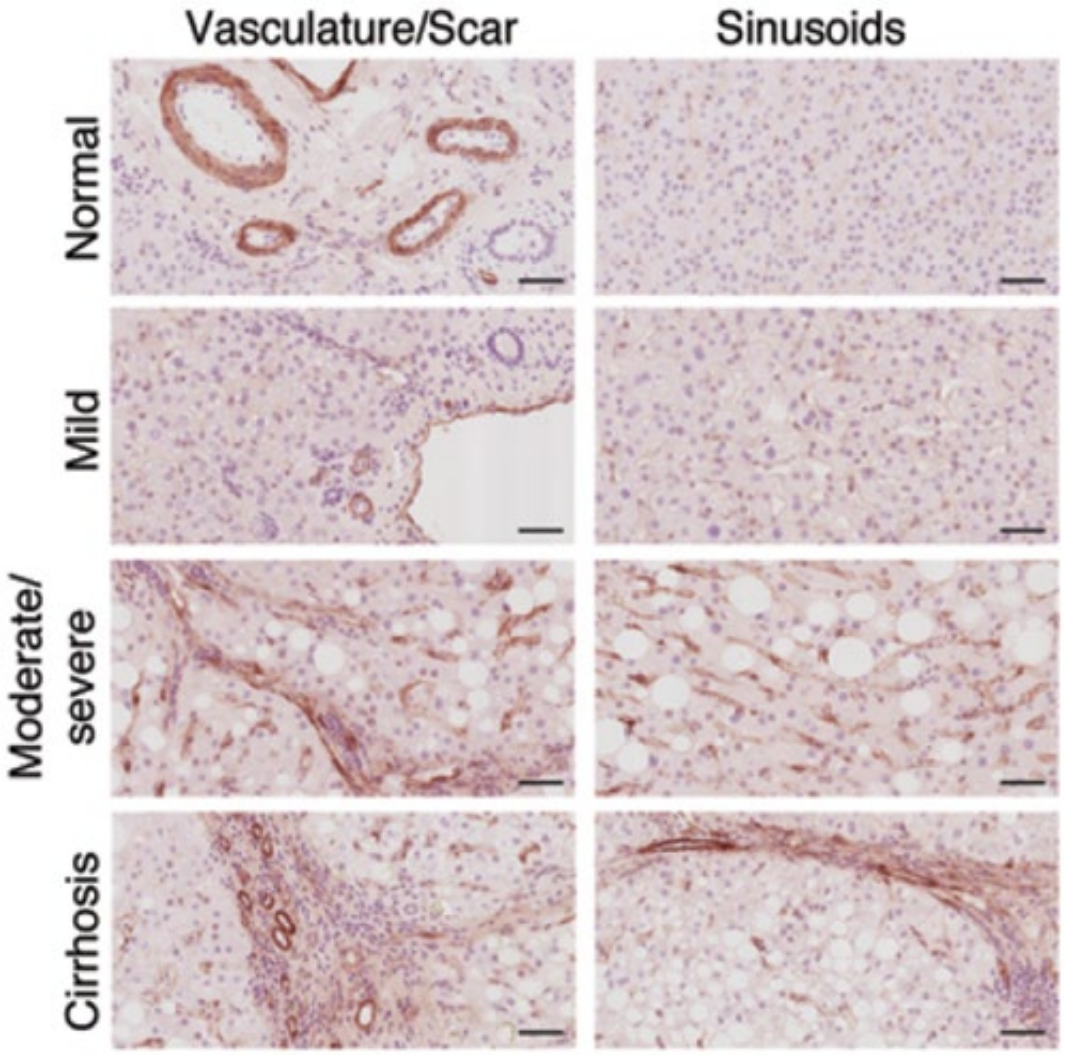
VAP-1 Expression is Increased in NASH Patients with Liver Fibrosis



Scale bars: 50 µm. Adapted from Weston et al, JCI, 2015

- VAP-1 is significantly and broadly over-expressed starting in moderate-severe fibrotic livers

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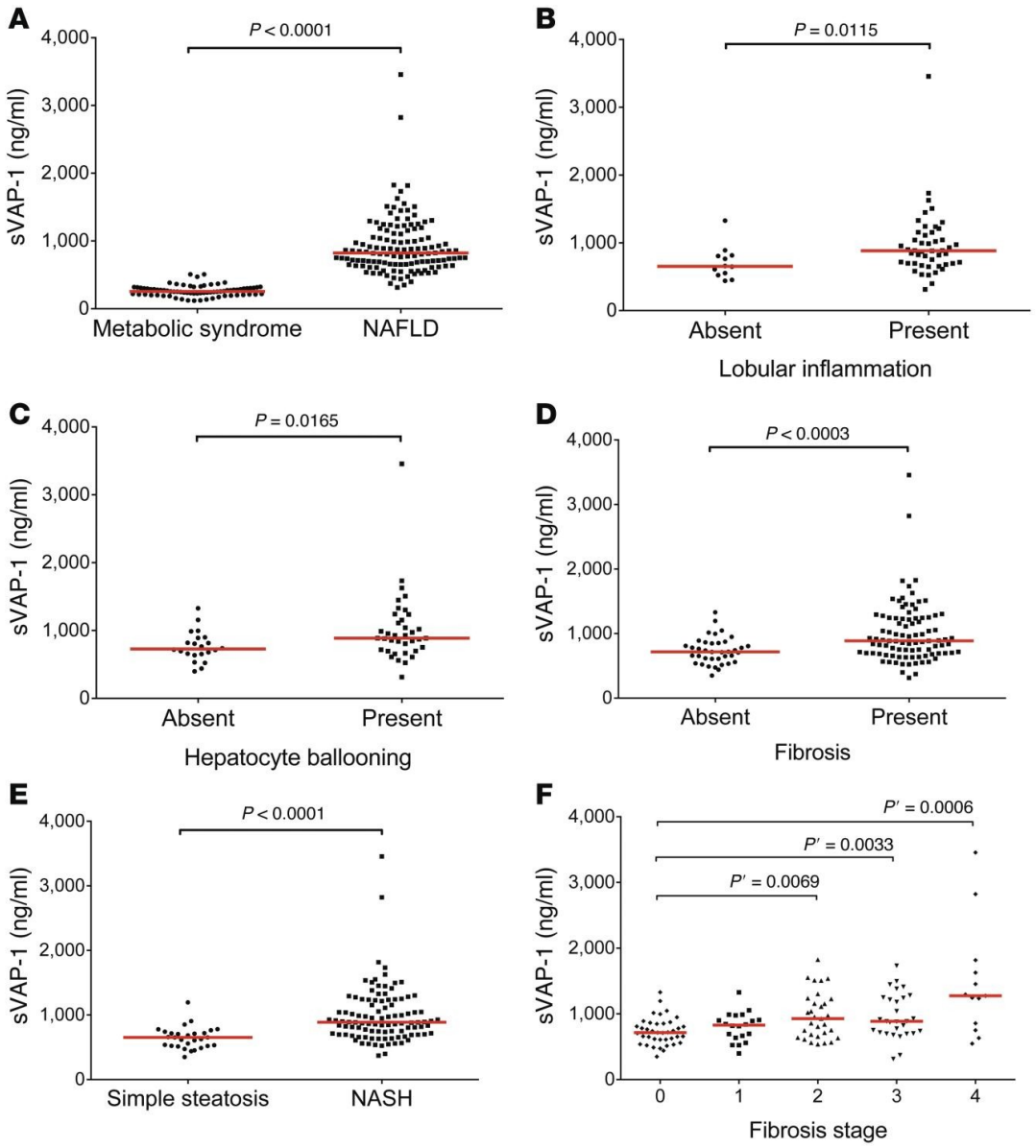
Soluble VAP-1 is Elevated in NASH Patients



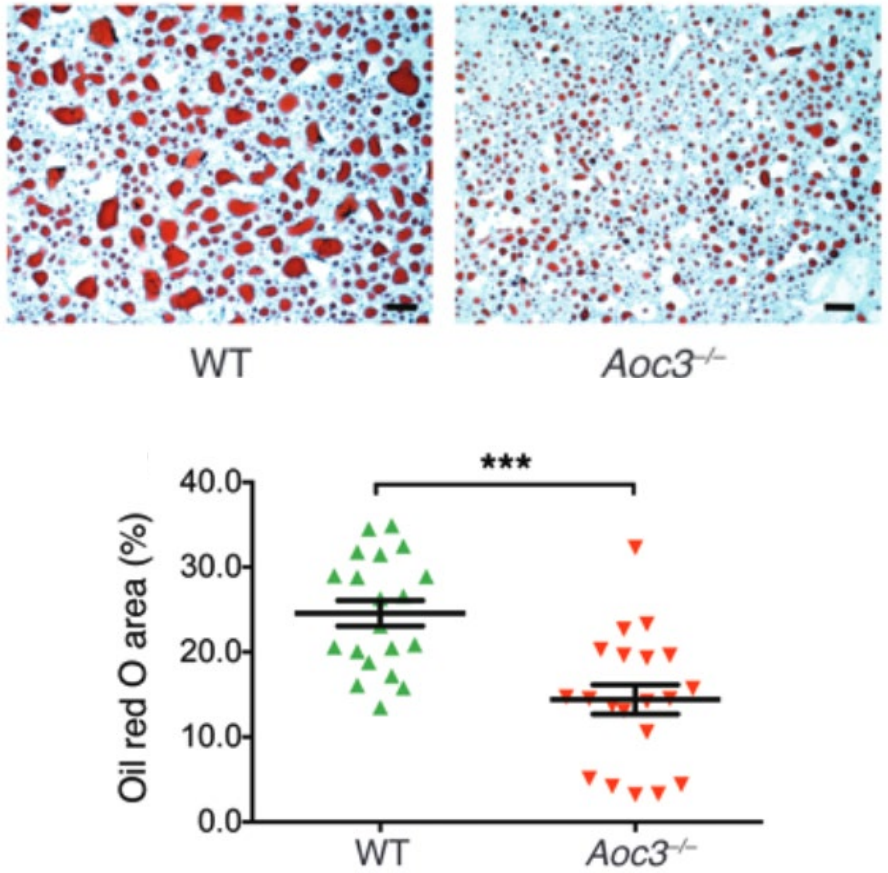
- Plasma VAP-1 concentration increased in NAFLD and NASH patients
- Increasing fibrosis stage correlates with increasing plasma VAP-1 concentrations

Adapted from Weston et al, JCI, 2015

Potential role of VAP-1 in Steatosis

- Genetic deletion of VAP-1 ($AOC3^{-/-}$) protects against high fat diet induced steatosis in mice[1]
- Anti-VAP-1 antibody can reduce steatosis in methionine choline deficient mice[1]
- Methylamine (endogenous VAP-1 substrate) increases BMI and abdominal fat in transgenic mice overexpressing VAP-1[2]
- VAP-1 activity reduces triglyceride secretion and increases steatosis in human liver tissue[3]
- VAP-1 activity in human liver tissue upregulates lipid transporter molecule gene expression including fatty acid binding proteins (FABP 2 and 4)[3]

Liver steatosis in Western diet fed mice[1]
(oil red staining for lipid droplets)



[1]Weston et al. 2015 J Clin Invest
[2]Stolen et al. 2004 FASEB J
[3]Shepherd et al. 2020 World J Hepatol

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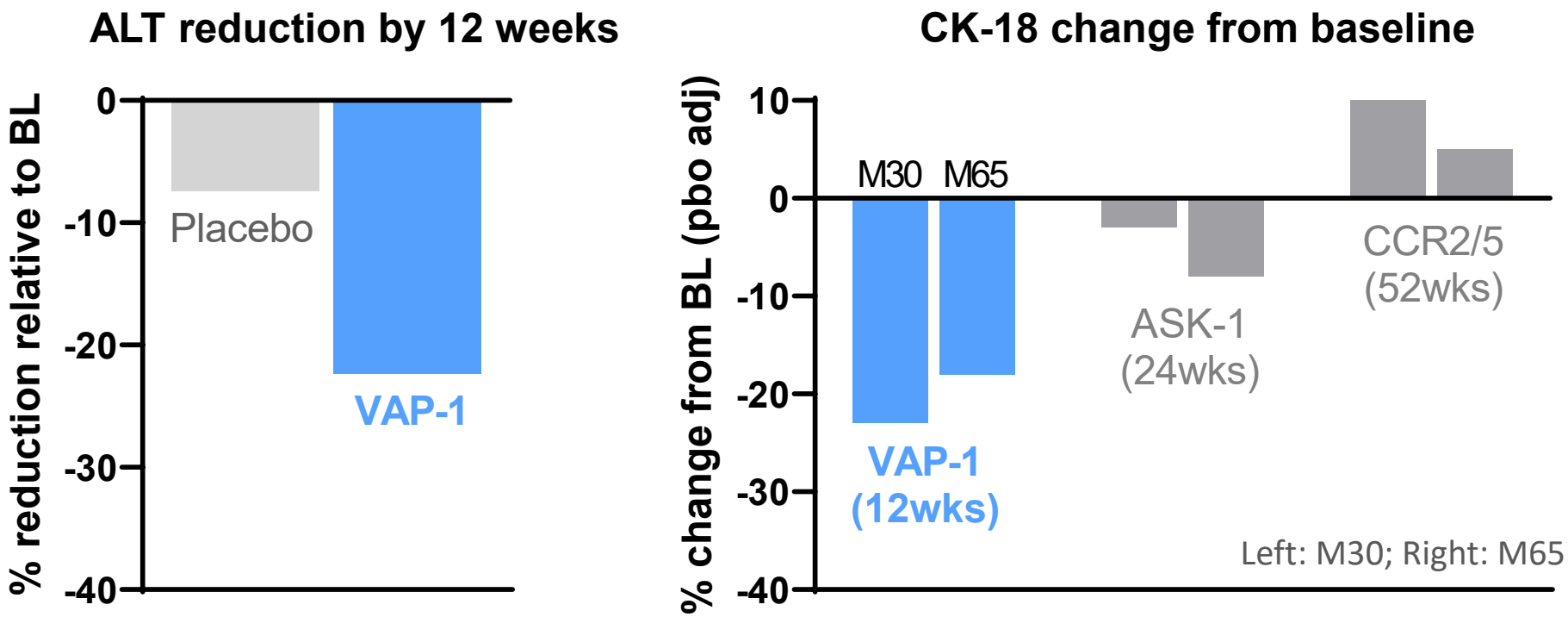
VAP-1 Inhibition Reduces ALT and CK-18 in NASH Patients

ALT and CK-18 decrease with VAP-1 inhibitors in NASH patients indicating potential for decreased inflammation and liver injury



Source: (LEFT) VAP-1 data from BI 1467335 (10mg) Phase 2a, 12-week NASH study from clinicaltrials.gov (NCT03166735; (RIGHT) CK-18: cytokeratin 18; M30 measures apoptosis and M65 measures apoptosis and necrosis. VAP-1 data from BI 1467335 (10mg) Phase 2a, 12-week NASH study from clinicaltrials.gov (NCT03166735), ASK1 data from selonsertib (18mg) Phase 2, 24-weeks NASH study from Hepatology. 2018; 67(2): 549–559; CCR2/5 data from cenicriviroc (150mg) Phase 2, 52-week NASH study from Hepatology. 2018; 67(5): 1754-1767

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TERN-201: Highly selective VAP-1 inhibitor in development for the treatment of NASH

- TERN-201 is a novel, potent VAP-1 inhibitor with high liver distribution in Phase 1 development for the treatment of NASH
- TERN-201 is a highly selective inhibitor of VAP-1 with minimal potential to inhibit other human amine oxidases

Biochemical activity (IC_{50}, μM)

Inhibitor	VAP-1	MAO-A	MAO-B
TERN-201	0.0065	>50	>50
BI 1467335	0.005	>100	2.7

IC_{50}: 50% inhibitory concentration; MAO: monoamine oxidase

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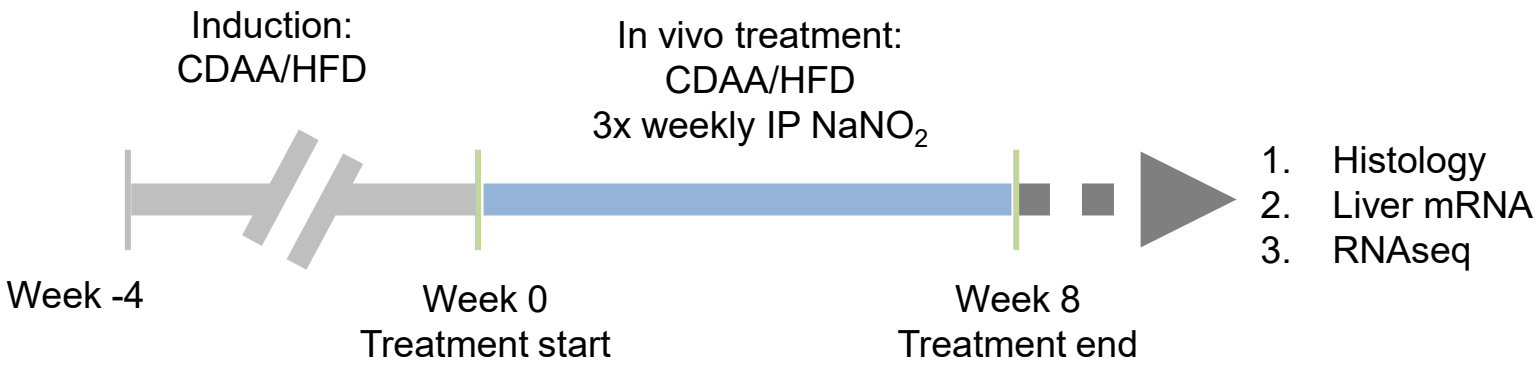
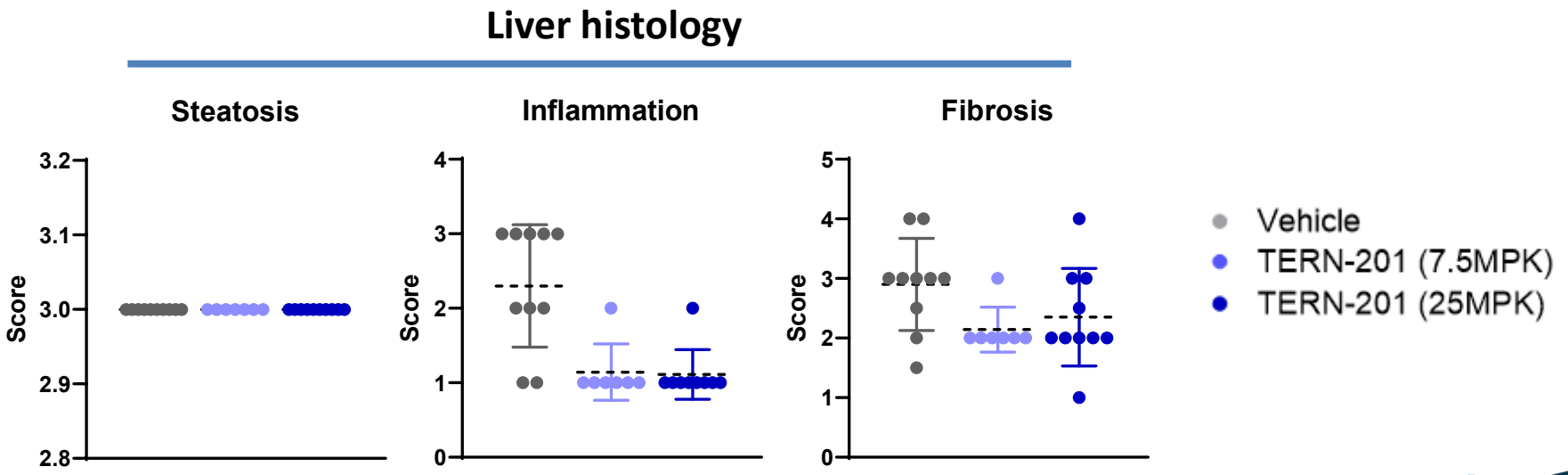
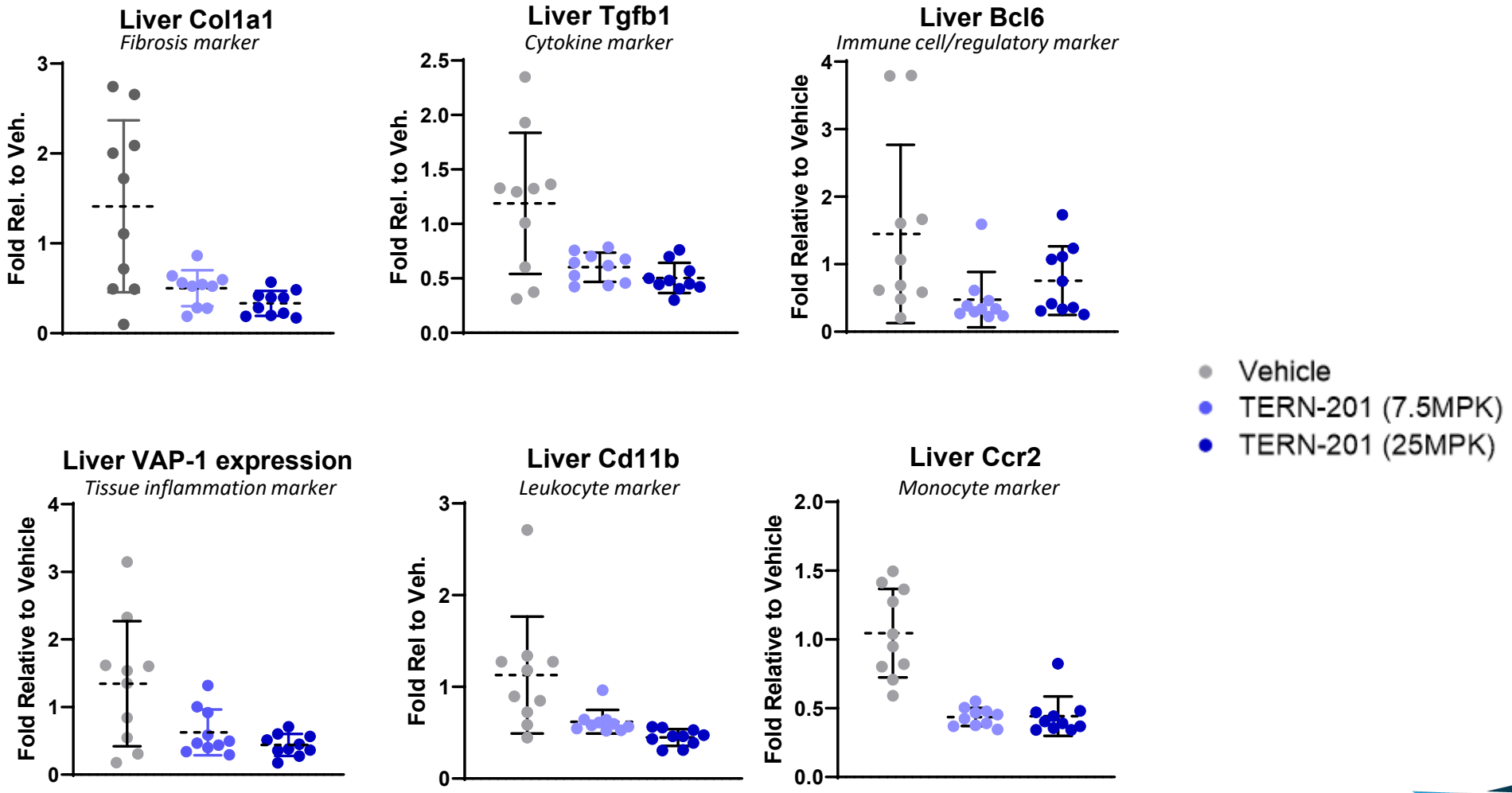
TERN-201 Improved Inflammation and Fibrosis in a Rat CDAA/HFD NASH Model





TERN-201 Rat CDAA/HFD NASH Model

Reduced expression of fibrosis and inflammation markers



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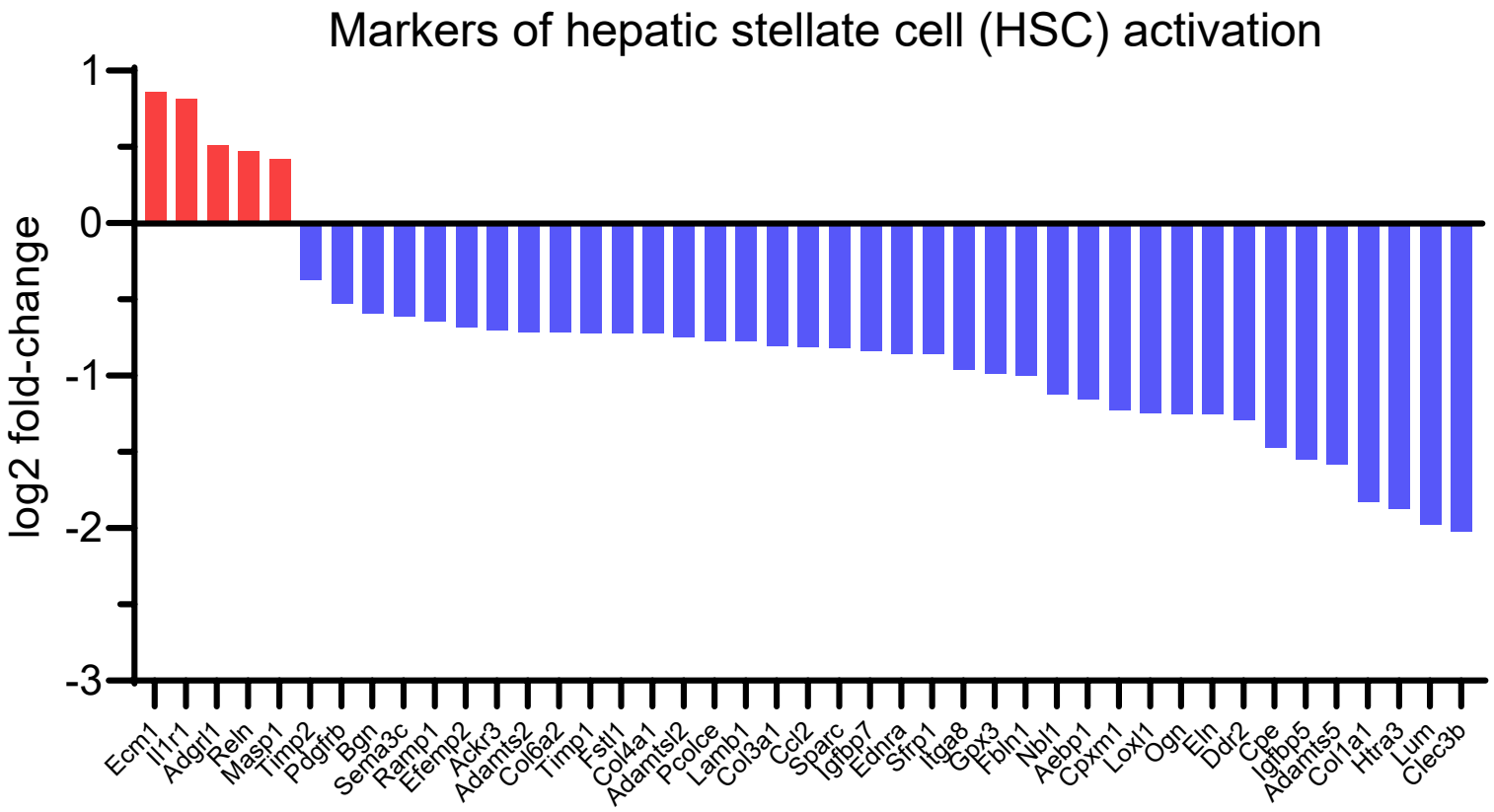
TERN-201 Rat CDAA/HFD NASH Model

Reduced expression of hepatic stellate cell activation markers



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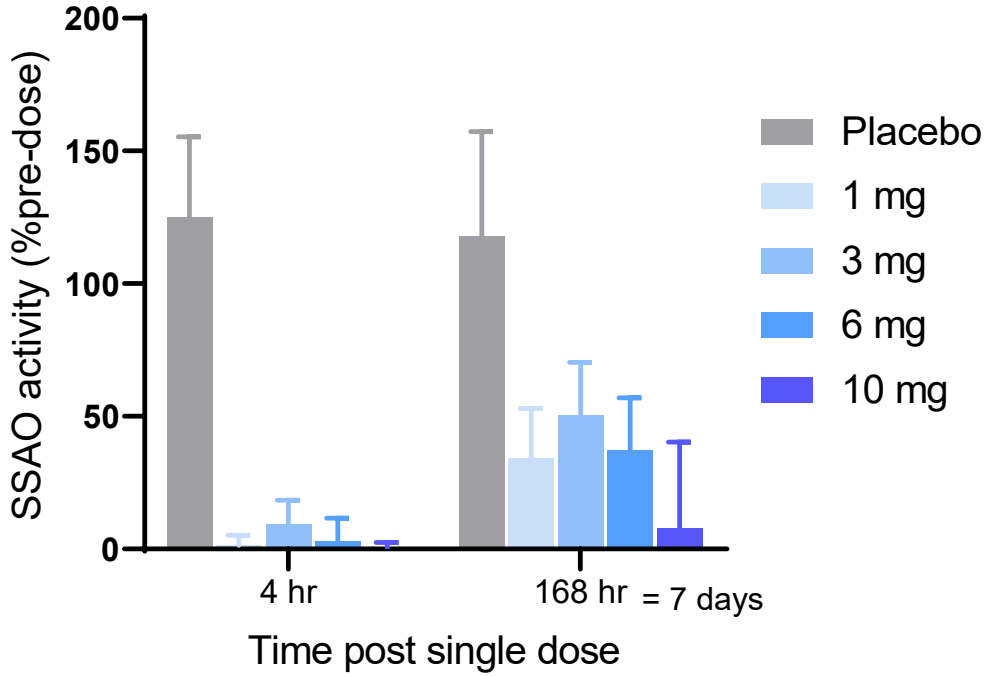
TERN-201 Single Ascending Dose Phase 1 Study

Generally well tolerated; sustained, near complete VAP-1 inhibition with once daily dosing

Plasma VAP-1/SSAO-specific activity (% pre-dose)



All TERN-201 dose levels were generally well tolerated

Jones et al, NASH-TAG 2020

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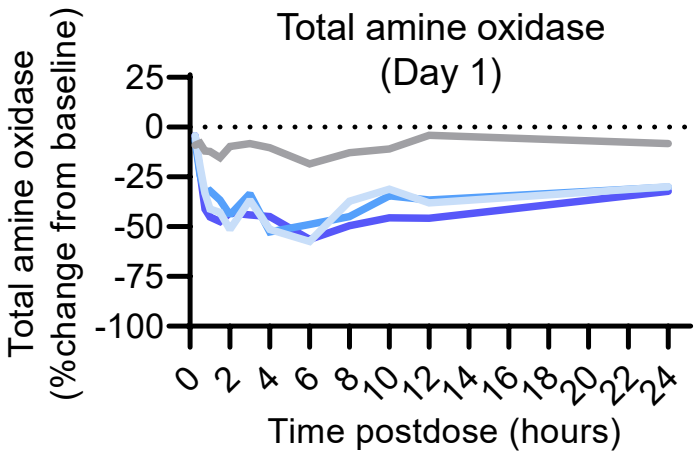
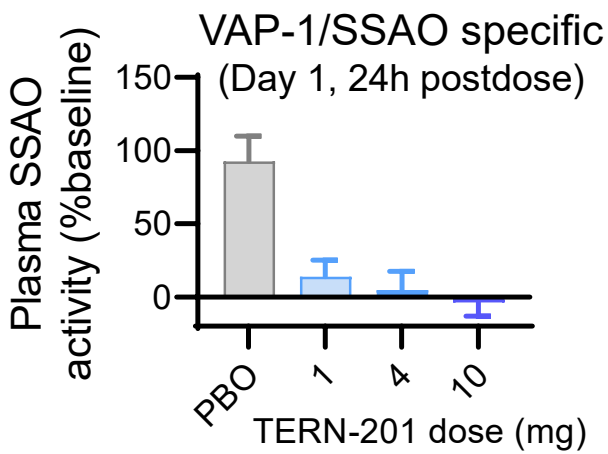
TERN-201 Multiple Ascending Dose Phase 1 Study

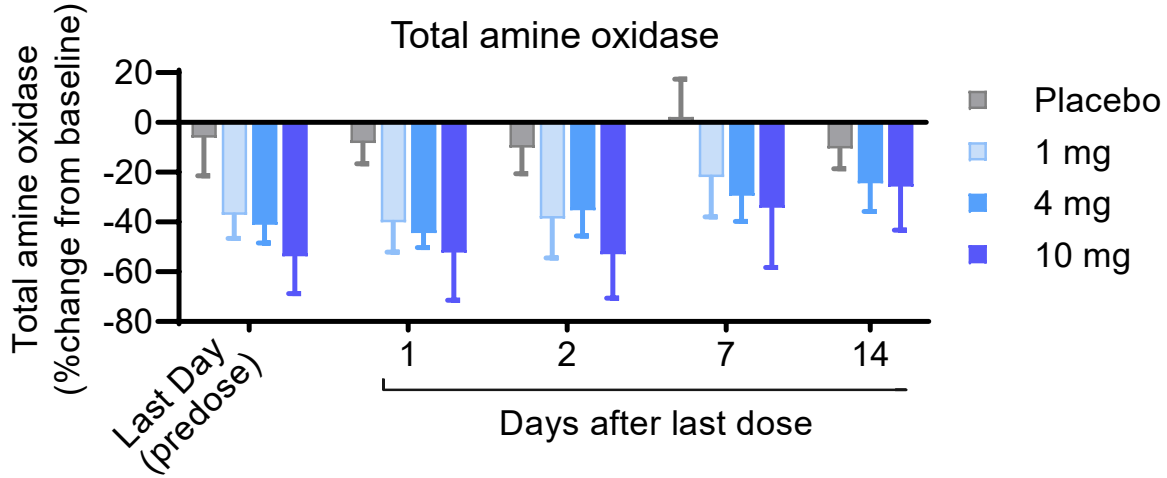
Sustained suppression of plasma VAP-1-specific activity

Inhibition of plasma amine oxidase activity





Sustained suppression after last dose



Jones et al, AASLD 2020

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TERN-201 Development Status

✓ Preclinical NASH Model

- ✓ Improved liver inflammation and fibrosis
- ✓ Reduced gene expression and biomarkers of liver inflammation, fibrosis and stellate cell activation

✓ Phase 1 in Healthy Subjects

- ✓ Generally well-tolerated
- ✓ Inhibited plasma VAP-1 activity

Next step: 12-week Phase 1b study in NASH patients to assess

- TERN-201 safety and tolerability
- Biomarkers of liver inflammation, fibrosis and steatosis

Data expected in 1H 2022 → **Inform TERN-201 subsequent development, potentially in combination with metabolically active NASH treatment**

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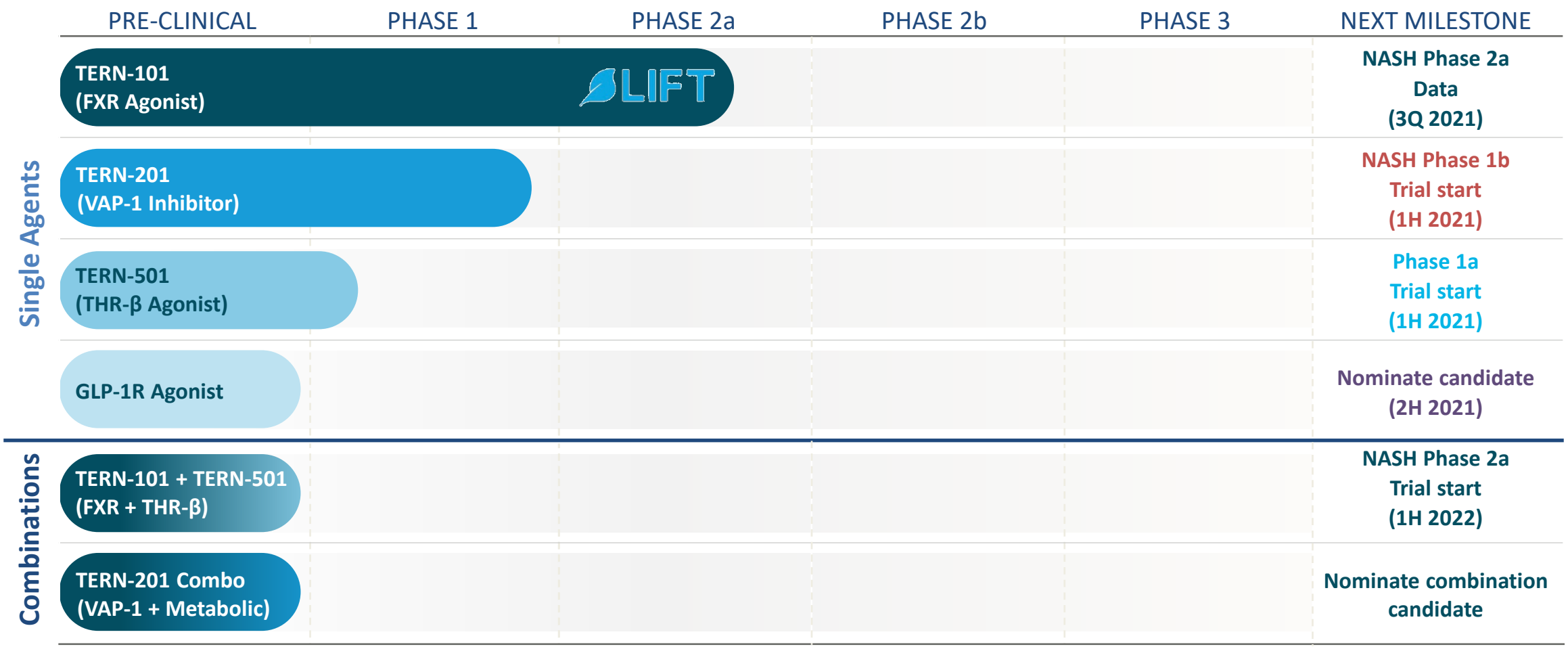
TERN-201 and Terns' NASH Pipeline

Combination opportunities



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Summary

- VAP-1 is a cellular adhesion protein with ectoenzyme amine oxidase activity
- NASH patients have hepatic VAP-1 overexpression which may contribute to hepatic inflammation and fibrosis
- VAP-1 may also potentiate hepatic steatosis in NAFLD/NASH
- VAP-1 inhibition resulted in reduced plasma VAP-1 activity, transaminase levels and biomarkers of liver inflammation in a 12-week clinical trial in NASH patients

- TERN-201 is a VAP-1 inhibitor in clinical development
  - high liver penetration
  - high selectivity for VAP-1 inhibition and minimal potential for off-target monoamine oxidase inhibition
- TERN-201 was generally well-tolerated in Phase 1 clinical trials and exhibited near complete and sustained inhibition of plasma VAP-1 specific activity
- Further studies of TERN-201 as a potential treatment for NASH are warranted
  - 12-week Phase 1b study in NASH patients to initiate in 1H2021
  - Data expected in 1H2022