



**GANNEX**  
*A Member of the Asclepis Group*

# Corporate Presentation

A Biotech Dedicated to NASH

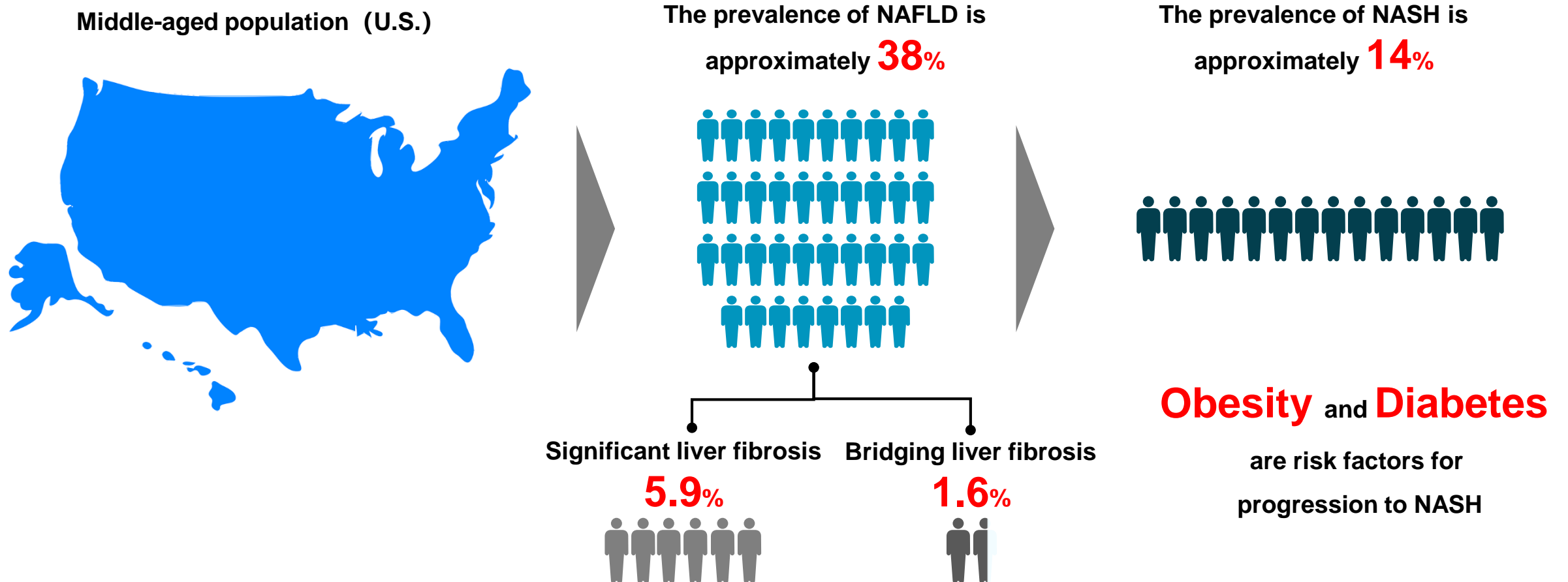
# About Gannex



Gannex, a wholly-owned company of Ascletis, is dedicated to the R&D and commercialization of new drugs in the field of NASH. Gannex has three clinical stage drug candidates against three different targets – FASN, THR $\beta$  and FXR, and three fixed-dose combinations.

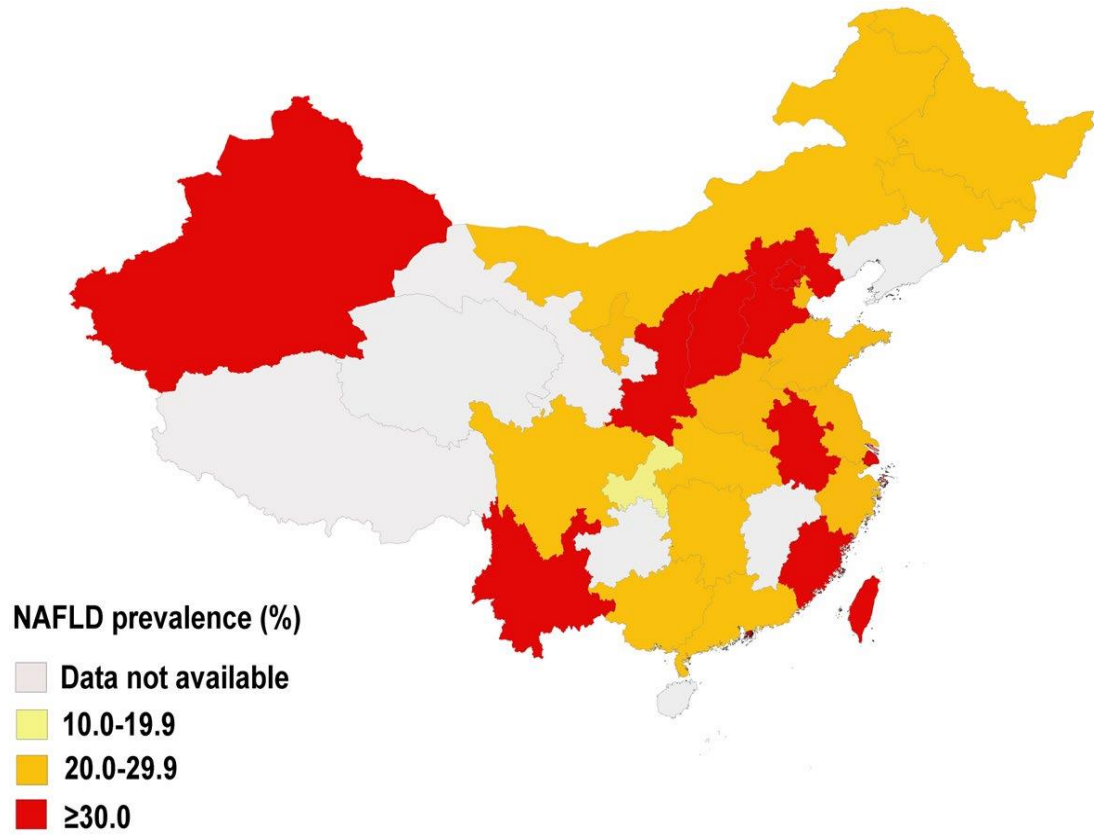
# NAFLD and NASH Represent a Large and Growing Health Problem

- A large prospective study evaluated the prevalence and severity of NAFLD/NASH in an asymptomatic middle-aged population attending outpatient colonoscopy in the United States.



# NAFLD and NASH Represent a Large and Growing Health Problem

- A large meta-analysis revealed that the prevalence of NAFLD in China was as high as **29.2%** from various perspectives.



NAFLD prevalence statistics in China

## Highest NAFLD prevalence age group

- Age 50~59 (**32.9%**; 95% CI, 30.3-35.5)

## Prevalence of NAFLD in people with obesity

- **51.6%**, 5 times higher than non-obese population (10.8%)

## The prevalence of NAFLD in China is **increasing rapidly**

- 2008 ~ 2010 (25.4%) vs. **2015 ~ 2018 (32.3%)**
- Twice as high as in Western countries, and already exceeds the average prevalence (29.2% vs. 25.2%)

# Significant Unmet Medical Needs for the Treatment of PBC

## China

- The prevalence of PBC in China was 49.2 cases per 100,000 persons and as high as 155.8 cases per 100,000 in women older than 40 years old, indicating a total of 656,000 PBC patients in China including 440,000 in females over age 40
- Ursodeoxycholic acid (UDCA) is the only drug been approved in China with the effect of delaying disease progression. However, approximately 40% PBC patients have an inadequate response to UDCA or are unable to tolerate UDCA

## US/EU

- 120,000 PBC patients in the US in 2014
- Obeticholic acid (Ocaliva) has been approved by US FDA for the indication of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA
- Significant side effects occurred with Ocaliva, including pruritus (63%) and fatigue (22%)

# NASH/PBC Pipeline

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
FASN	ASC40 (NASH)	Greater China <sup>1</sup>	U.S. FDA Fast Track						<ul style="list-style-type: none"> <li>First-in-class, inhibit de novo lipogenesis</li> <li>US/CN phase II showed significant reduction of liver fat content, and minimal side effects compare to other NASH candidates</li> </ul>
THRβ	ASC41 (NASH)	Global							<ul style="list-style-type: none"> <li>Third-in-class globally, First-in-class in China</li> <li>Triglyceride reduction &gt;30% with 1mg per day dosing</li> <li>No DDI with drugs commonly used by NASH patients</li> </ul>
FXR	ASC42 (NASH)	Global	U.S. FDA Fast Track						<ul style="list-style-type: none"> <li>Potential Best-in-class, no pruritus or LDC-c elevation</li> <li>Higher elevation of FGF-19, an FXR target engagement biomarker</li> </ul>
THRβ + FXR	ASC43F FDC (NASH)	Global							<ul style="list-style-type: none"> <li>First-in-class, dual targets to THRβ and FXR</li> </ul>
FASN + FXR	ASC44F FDC (NASH)	Global							<ul style="list-style-type: none"> <li>First-in-class, dual targets to FASN and FXR</li> </ul>
FASN + THRβ	ASC45F FDC (NASH)	Global							<ul style="list-style-type: none"> <li>First-in-class, dual targets to THRβ and FASN</li> </ul>
FXR	ASC42 (PBC)	Global							<ul style="list-style-type: none"> <li>No pruritus</li> <li>CDE approval for Phase II/III clinical trials</li> </ul>

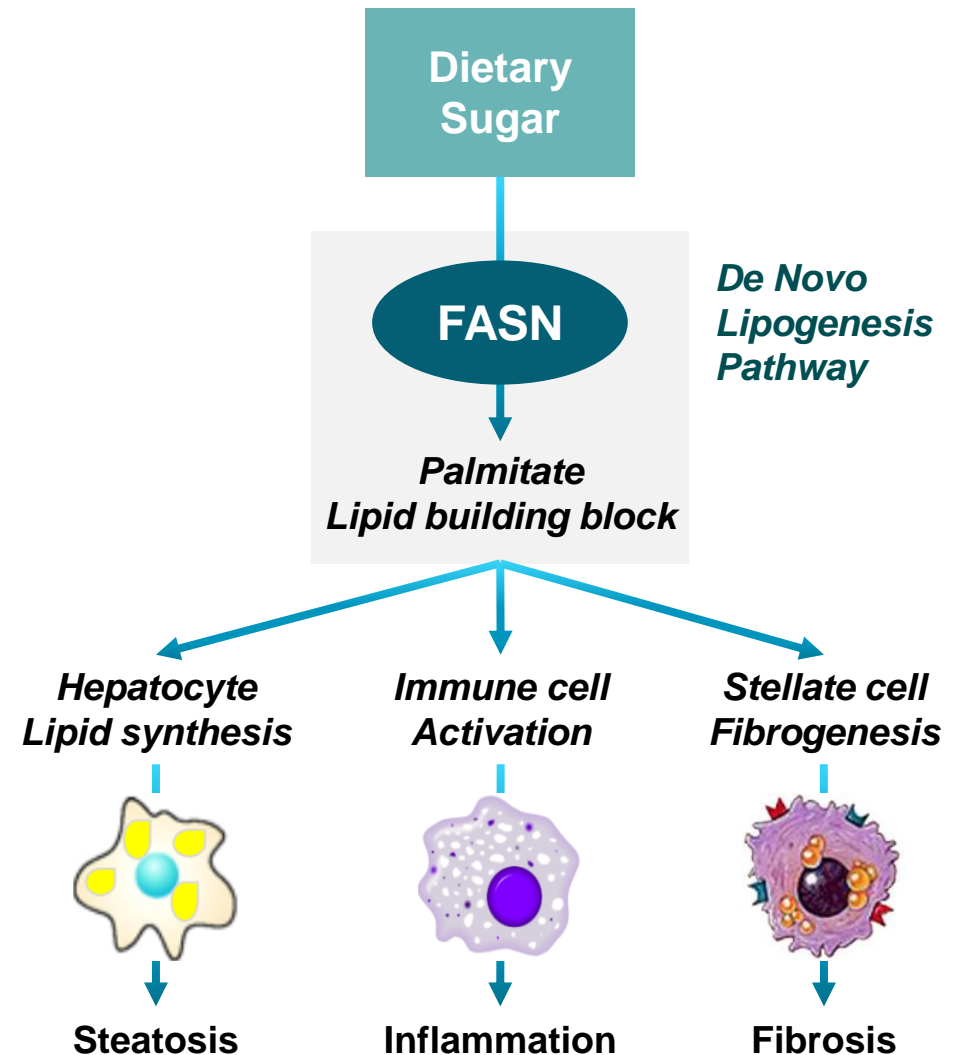
1. ASC40 is licensed from Sagimet Biosciences Inc. for the exclusive rights in the Greater China.



# ASC40: First-in-Class Oral Fatty Acid Synthase (FASN) Inhibitor

**FASN is an important rate-limiting step in intrahepatic fatty acid synthesis as well as De novo lipogenesis (DNL)**

- Reduces steatosis by blocking DNL
- Reduces inflammation by decreasing cytokine secretion and Th17 differentiation
- Blunts fibrosis by reducing procollagen and profibrotic gene expression



# Phase II U.S. Cohort: ASC40 Clinical Trial Design in NASH Patients

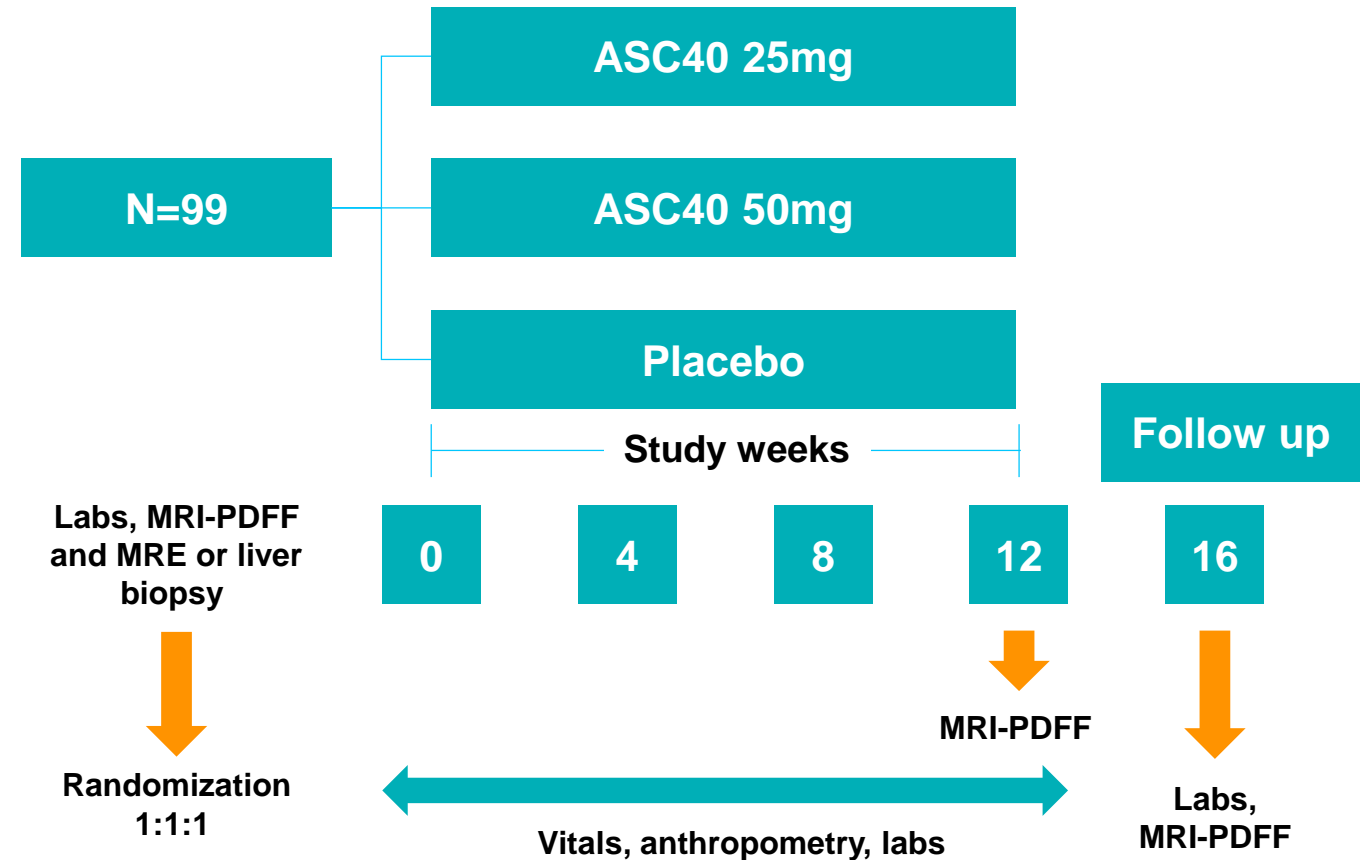
■ Multicenter, randomized, placebo-controlled trial 1:1:1 25mg:50mg:placebo (N=99)

## Criteria

- Inclusion
  - $\geq 8\%$  liver fat
  - MRE  $\geq 2.5\text{kPa}$  or recent biopsy
- Exclusion
  - Evidence of cirrhosis
  - Other chronic liver disease

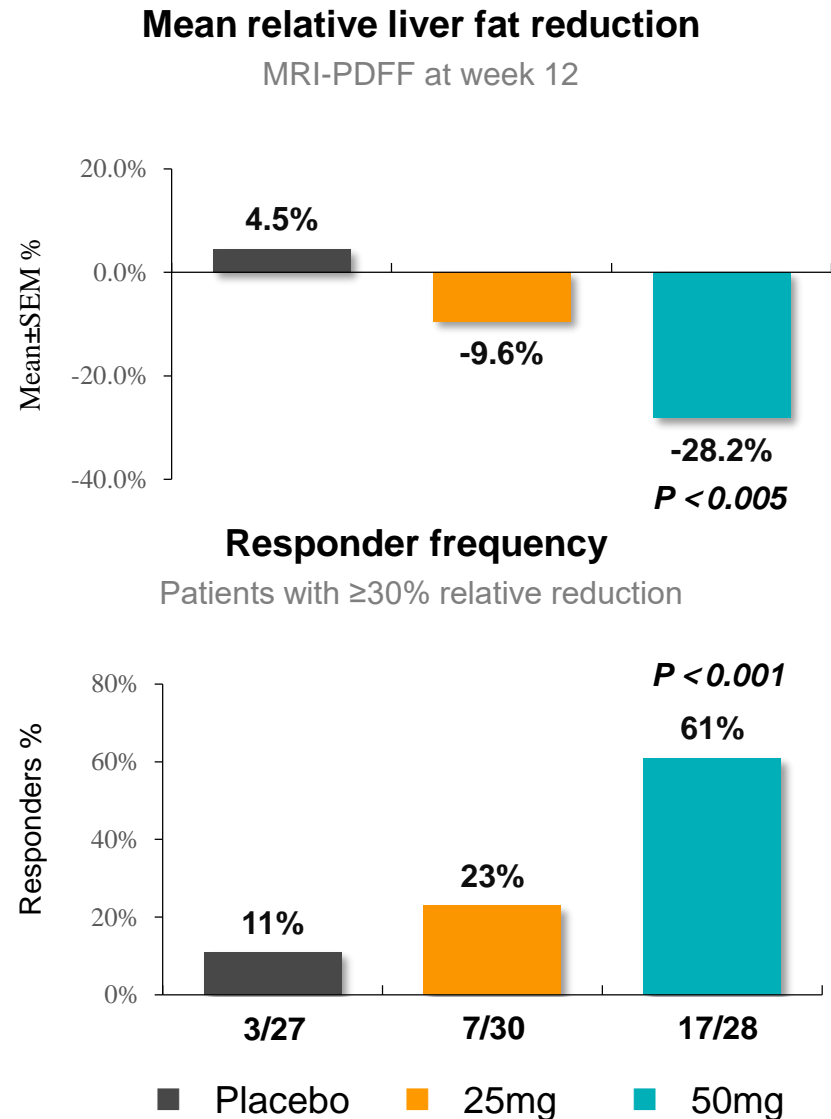
## Endpoints

- Primary
  - Liver fat reduction by MRI-PDFF
  - Safety
- Secondary
  - % pts  $\geq 30\%$  reduction of liver fat
  - ALT, AST
  - Biomarkers

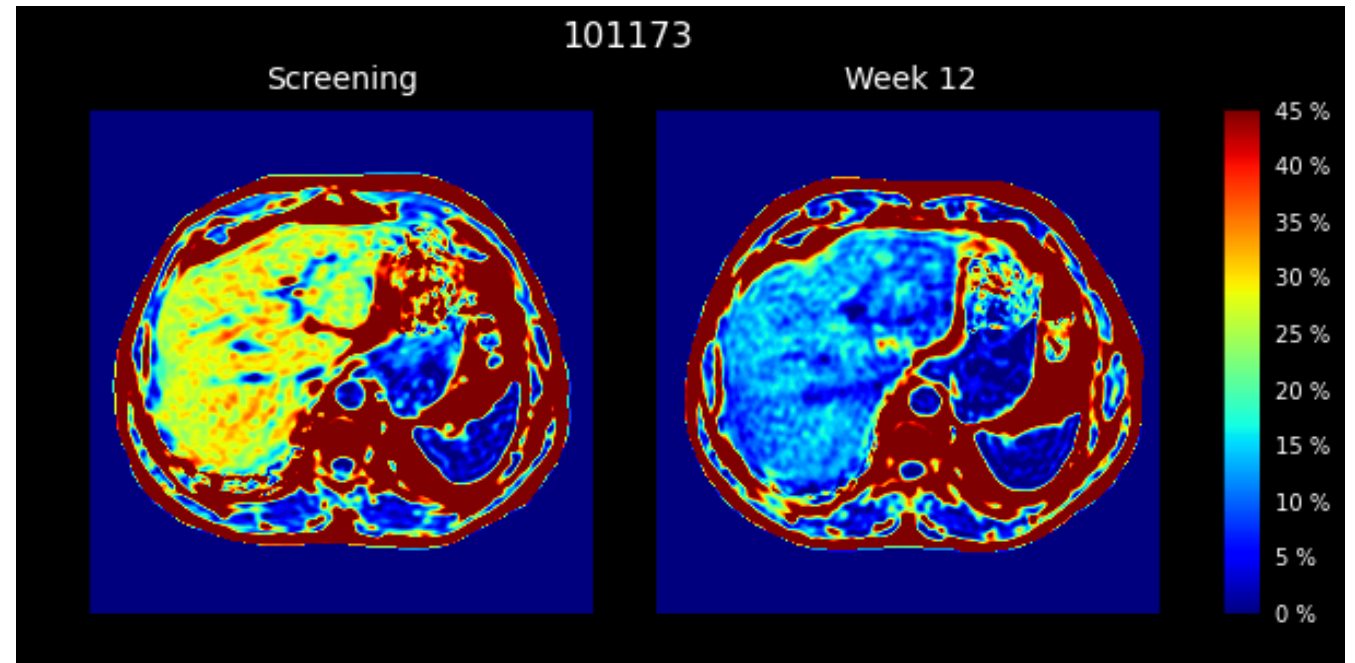




# Phase II U.S. Cohort: ASC40 Significantly Reduces Liver Fat Content



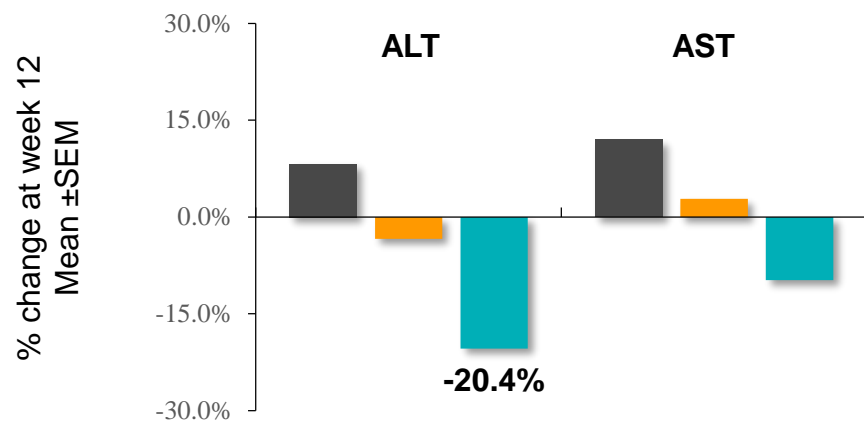
## Significant reduction in liver fat content over 12 weeks of treatment



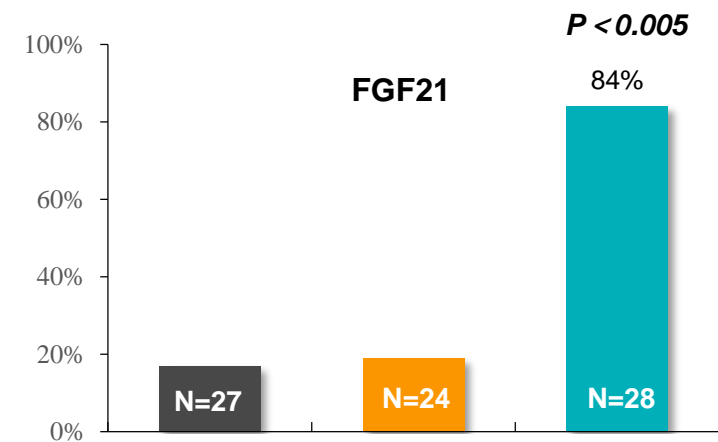
MRI-PDFF responders were defined as those with  $\geq 30\%$  MRI-PDFF decline relative to baseline

# Phase II U.S. Cohort: ASC40 Significantly Improves NASH-related Metrics

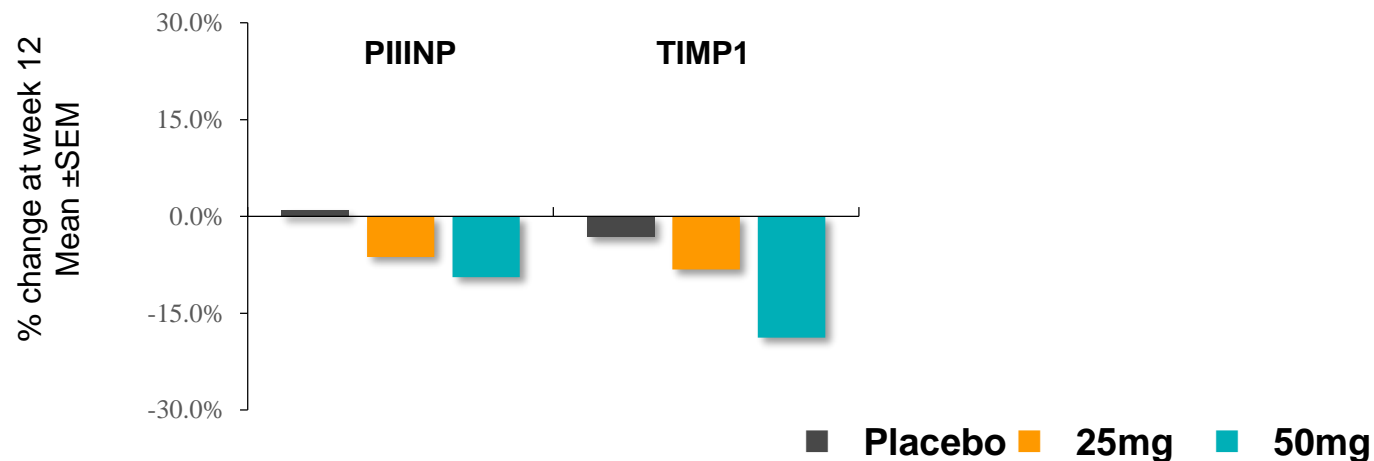
Dose-dependent response in reducing ALT/AST



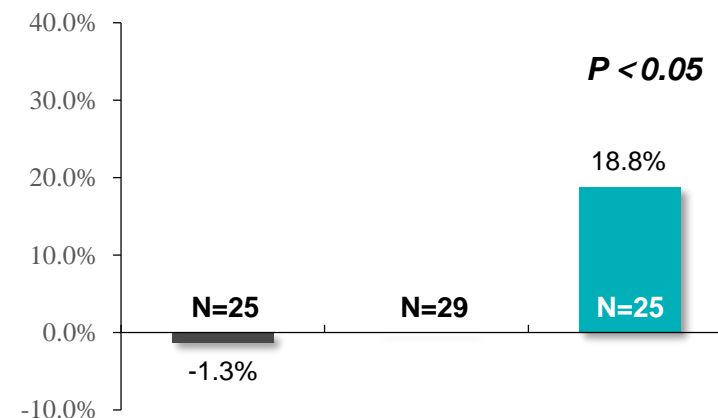
Improves markers of hepatic insulin sensitivity



Decreases fibrosis markers



Adiponectin



# Phase II ASC40 Compares Favorably With Other Phase II/III NASH Drugs

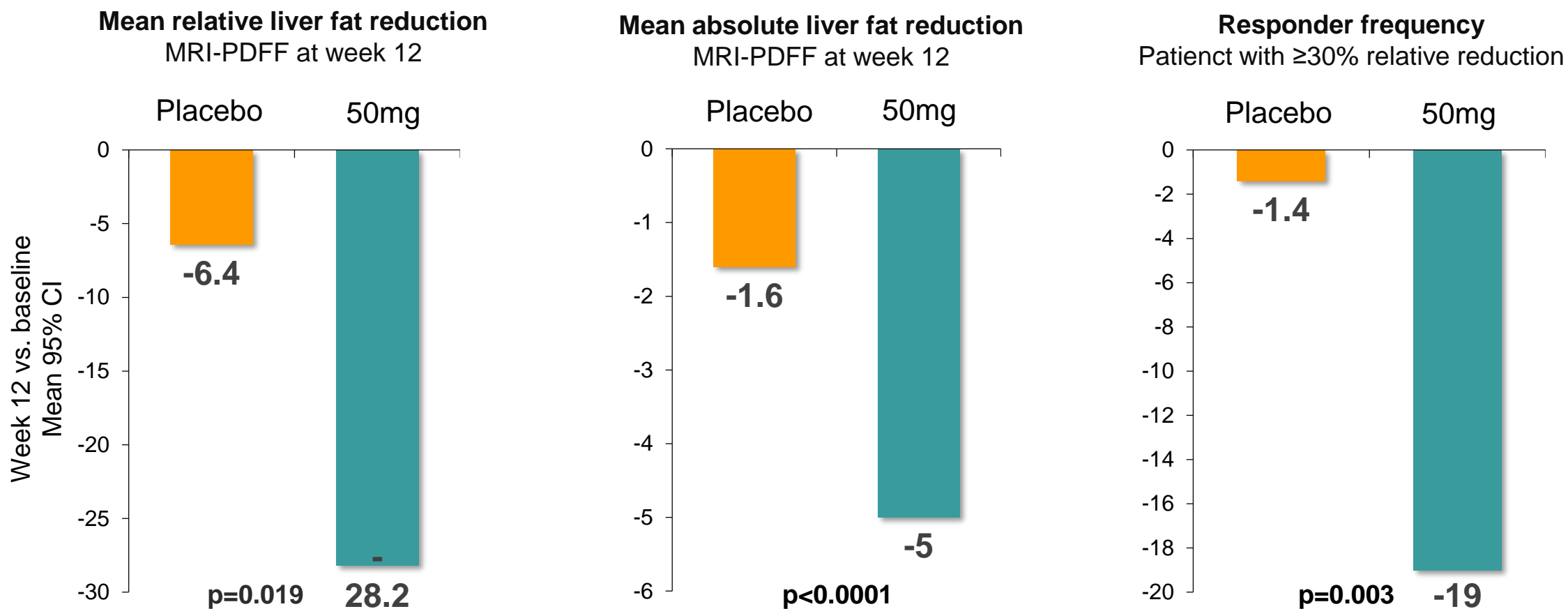
Drug Candidate	Company	Target	Dose	Weeks	≥ 30% liver fat reduction responder rate, %		Placebo adjusted ≥ 30% liver fat reduction responder rate, %	Safety
					Drug	Placebo		
ASC40 <sup>1</sup>	Gannex /Sagimet	FASN	50 mg	12	60.7	11.1	49.6	minimal side effects
Firsocostat <sup>2</sup>	Gilead	ACC	20mg	12	47.8	15.4	32.4	TG ↑
Tropiflexor <sup>3</sup>	Novartis	FXR	200µg	12	64	20	44	LDL-C ↑, pruritus
Resmetirom <sup>4</sup>	Madrigal	THRβ	80mg	36	74.4	29.4	45	diarrhea, nausea

Non-head to head research

- 1、 Rohit Loomba et al. 2020,Hepatology 72;103.EASL 2020 Oral Presentation  
 3、 Marcos Pedrosa et al. Contemp Clin Trials. 2020 Jan;88:105889.

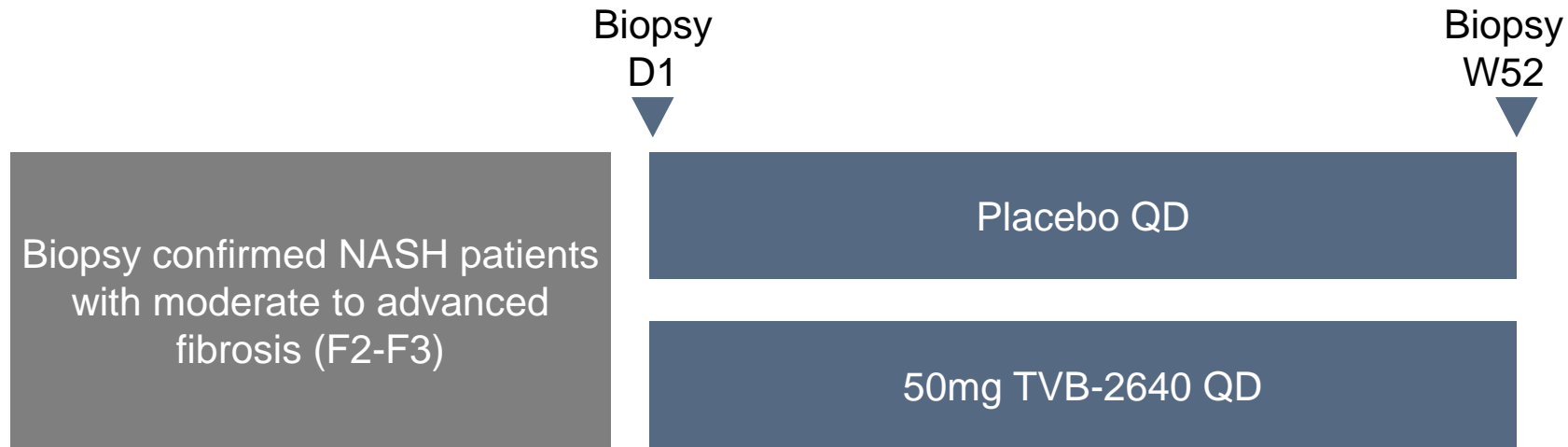
- 2、 Eric J Lawitz et al. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1983-1991  
 4、 Stephen A Harrison et al. Lancet. 2019 Nov 30;394(10213):2012-2024

# Phase II Combined U.S. & China Cohorts: ASC40 Reduces Liver Fat



Source: NOVEL, FIRST-IN-CLASS, FATTY ACID SYNTHASE (FASN) INHIBITOR TVB-2640 DEMONSTRATES ROBUST CLINICAL EFFICACY AND SAFETY IN A GLOBAL PHASE 2 RANDOMIZED PLACEBO-CONTROLLED NASH TRIAL (FASCINATE-1) CONDUCTED IN THE US AND CHINA 72<sup>th</sup> American Association for the Study of Liver Diseases (AASLD) & The Liver Meeting®, November 12-15, 2021. Virtual Conference.

# ASC40 (TVB2640): US Phase IIb Study Design for NASH

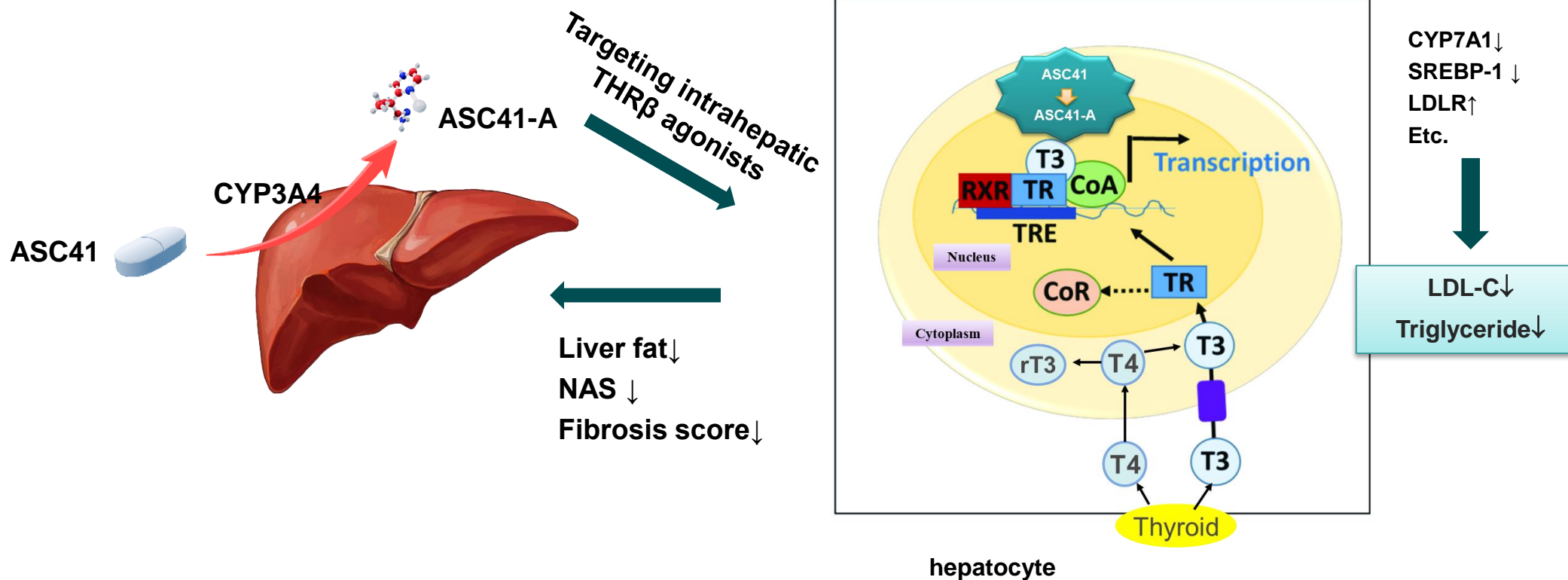


*Primary efficacy endpoints:*

- 1.  $\geq 2$ -point improvement in NAS (Nonalcoholic fatty liver disease (NAFLD) Activity Score) that results from reduction of necro-inflammation (inflammation or ballooning), or*
- 2. improvement in fibrosis.*

# ASC41: A Liver Targeting Thyroid Hormone Receptor Beta (THR $\beta$ ) Agonist

- ASC41 is a liver targeted small molecule which is converted to its active metabolite ASC41-A - a potent and selective THR $\beta$  agonist



# ASC41: Third-in-class THR $\beta$ Agonist in USA

## First-in-class THR $\beta$ Agonist in China

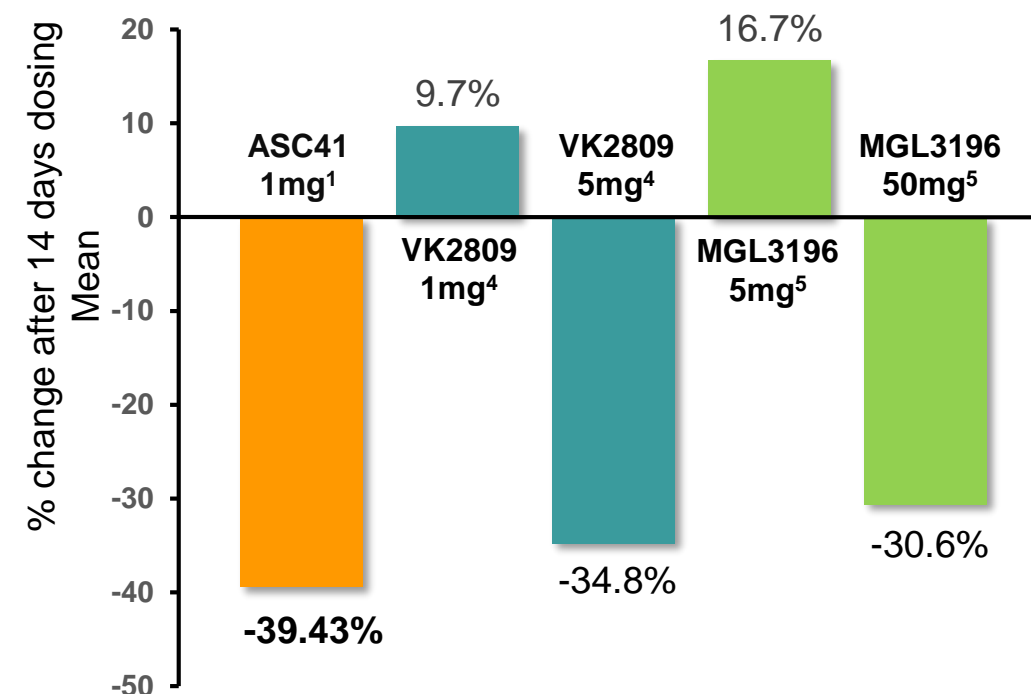
- In two NASH animal models, at 1/10th dose of MGL-3196, ASC41 demonstrated the same improvement in liver steatosis, inflammation and fibrosis.
- Commercially ready oral tablet formulation developed with in-house proprietary technology
- 2 Phase I studies completed
  - Single doses (1, 2, 5, 10, 20 mg) and 14 day multiple doses (1, 2, 5 mg) in 65 subjects with elevated LDL-C > 110 mg/dL
  - Food effect in 12 healthy subjects
- 1 Phase Ib study completed
  - 28 day, 10 mg in 20 overweight and obese subjects with elevated LDL-C > 110 mg/dL
- US Phase I showed that there was no significant drug-drug interactions between ASC41/ASC41-A and the most frequently used drugs of NASH patients such as antidepressants and statins
- Based on above studies, doses have been selected for Phase II trials in patients with NASH



# THRβ Differentiations: Gannex vs Viking and Madrigal

	Gannex ASC41 <sup>1</sup>	Viking VK2809 <sup>2</sup>	Madrigal MGL3196 <sup>3</sup>
Oral formulation	Tablet, room temp storage, commercially ready	Capsule, refrigerated	Tablet, room temp storage, commercially ready
Dosing frequency	Once a day	Once every two days	Once a day
DDI	-	+	-
Human dose needed for > 30% TG reduction	1 mg	2.5 mg	50 mg

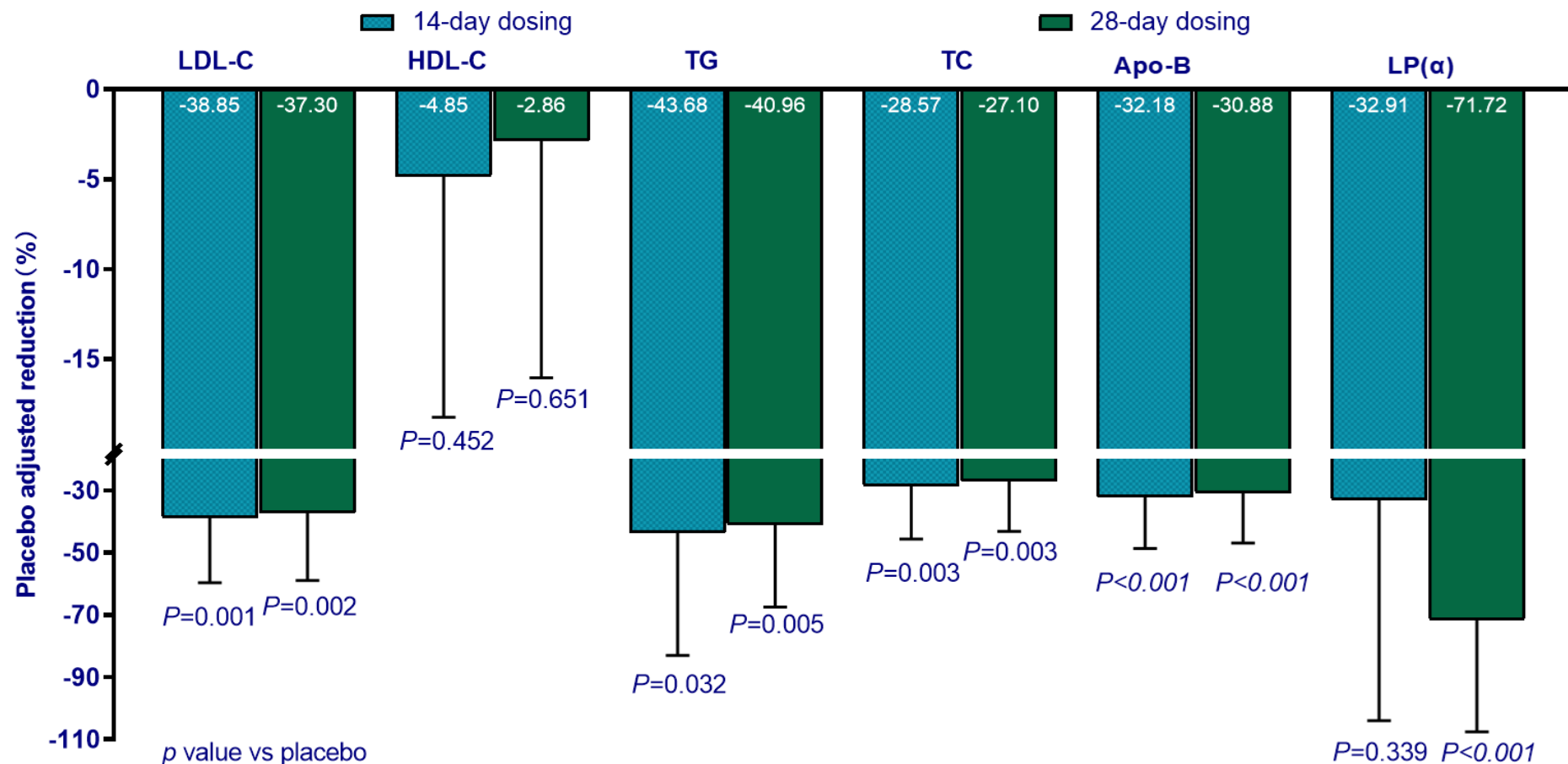
## Placebo adjusted triglyceride reduction from baseline after 14 day dosing



1.EASL 2021 Abstract No. PO-1851 2.EASL2020 Abstract No. AS073. 3.Stephen A Harrison et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. [www.thelancet.com](https://doi.org/10.1016/S0140-6736(19)32517-6) Published online November 11, 2019 [https://doi.org/10.1016/S0140-6736\(19\)32517-6](https://doi.org/10.1016/S0140-6736(19)32517-6) 4 [VK2809 data presented at the 2016 Meeting of the American College of Cardiology](#) 5 Taub et al. Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor- $\beta$  agonist. *Atherosclerosis* 230 (2013) 373e380

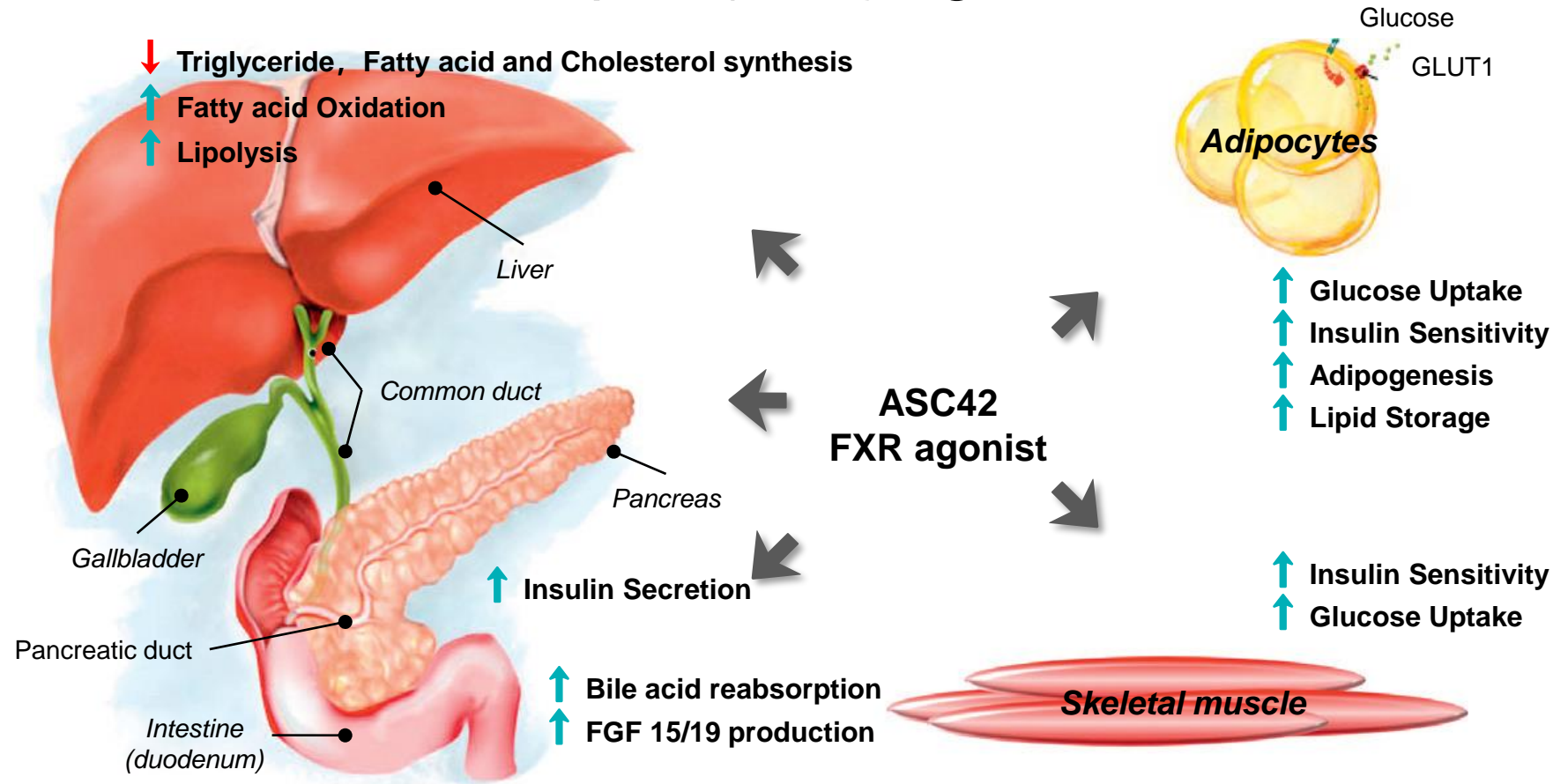
# Positive Clinical Results in Overweight and Obese Subjects

Placebo-adjusted relative change (mean) from baseline after 14 or 28 days of once daily oral dosing of 10 mg ASC41 tablets in overweight and obese subjects



Source: A Phase Ib Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ASC41, a THR- $\beta$  Agonist, for 28-days in Overweight and Obese Subjects with Elevated LDL-C, a Population with Characteristics Of NAFLD. 72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting®, November 12-15, 2021. Virtual Conference.

# ASC42: A Farnesoid X Receptor (FXR) Agonist



- Increased insulin sensitivity of adipocytes and skeletal muscle cells increases glucose uptake in peripheral tissues and increases energy consumption
- Reduced the synthesis of triglycerides, fatty acids and cholesterol in the liver, promoted liver fat decomposition and fatty acid oxidation

# ASC42: A Novel Non-steroidal, Selective, Potent FXR Agonist

- Potentially best-in-class, no pruritus at human therapeutic doses
- U.S. FDA IND approval in Oct 2020
- U.S. FDA Fast Track Designation in Dec 2020
- U.S. Phase I trials completed
  - Single ascending doses and multiple ascending doses
  - Food effect
- Phase II/III clinical trials for PBC approved in Nov 2021 by China NMPA
- Oral tablet formulation developed with in-house proprietary technology and stable at room temperature

# ASC42: Topline Results of the U.S. Phase I Trial

Dose (QD)	5mg	15mg
Incidence rate of pruritus during 14 days treatment (%)	0	0
LDL-C change from baseline on Day 14 (% , Median)	-6.6	2.43
FGF19 on Day 14 versus baseline (%)	471	1780
C4 reduction on Day 14 (%)	53	91
ALT change from baseline on Day 14 (U/L, Median)	-1.0	-2.5

Source: ASC42, a Novel Non-steroidal FXR Agonist, Demonstrates a Normal Cholesterol Profile and Lack of Pruritus at Therapeutic Doses in a 14-day Phase I Randomized, Double-blind, Placebo Controlled Study in Healthy Volunteers. 72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting®, November 12-15, 2021. Virtual Conference.

# FDC: Complementary among ASC40, ASC41 and ASC42

Treatment Goals	Monotherapy			FDC One-Pill, Once-a-Day		
	ASC40 FASN	ASC41 THRβ	ASC42 FXR	ASC43F THRβ + FXR	ASC44F FASN + FXR	ASC45F FASN + THRβ
Liver fat reduction	★ ★ ★	★ ★ ★	★ ★	★ ★ ★	★ ★ ★	★ ★ ★
Anti-inflammation	★ ★	★ ★	★ ★	★ ★	★ ★	★ ★
Anti-fibrosis	★ ★	★ ★	★ ★ ★	★ ★ ★	★ ★ ★	★ ★
Lowering LDL-C and TG		★ ★ ★		★ ★ ★		★ ★ ★

THANKS

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