GANNEX

*A Member of the Ascletis 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, THRβ 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.

**Middle-aged population (U.S.)**

**The prevalence of NAFLD is approximately 38%**

**The prevalence of NASH is approximately 14%**

**Significant liver fibrosis 5.9%**

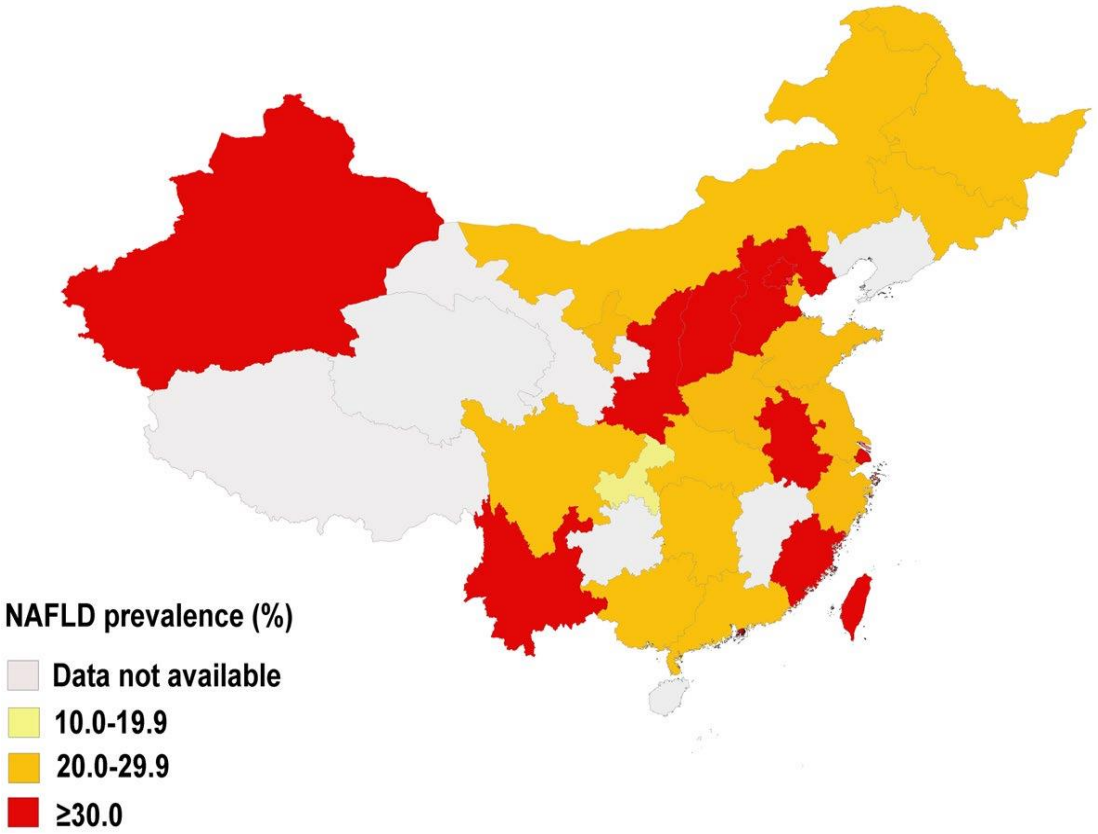
**Bridging liver fibrosis 1.6%**

**Obesity and Diabetes are risk factors for progression to NASH**

Source: Harrison S A, Gawrieh S, Roberts K, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort [J]. Journal of hepatology 2021, DOI: 10.1016/j.jhep.2021.02.034..

# 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%)

Source: Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis [J]. Hepatology 2019, 70(4): 1119-33. DOI: 10.1002/hep.30702.

# NASH Pipeline: Single Agents and Fixed-Dose Combinations[1]

| Target | Drug Candidates | Commercial Rights | Pre-IND | IND | Phase I | Phase IIa | Phase IIb/III | Anticipated Key Milestone(s) in next 12 months |
|---|---|---|---|---|---|---|---|---|
| FASN | ASC40 | Greater China[2] | ***U.S. FDA Fast Track*** | | | | | • **US:** Interim results from 52-week liver-biopsy Phase IIb study[3] |
| THRβ | ASC41 | Global | | | | | | • **US:** First patient dosed in 52-week liver-biopsy adaptive Phase IIa/IIb study[3] |
| FXR | ASC42 | Global | ***U.S. FDA Fast Track*** | | | | | • **US:** Submission for approval of 52-week liver-biopsy adaptive Phase IIa/IIb study[3] |
| THRβ + FXR | ASC43F One-Pill, Once-a-Day FDC | Global | | | | | | • **US:** Completion of human PK |
| FASN + FXR | ASC44F One-Pill, Once-a-Day FDC | Global[2] | | | | | | • Completion of FDC development |
| FASN + THRβ | ASC45F One-Pill, Once-a-Day FDC | Global[2] | | | | | | • Completion of FDC development |

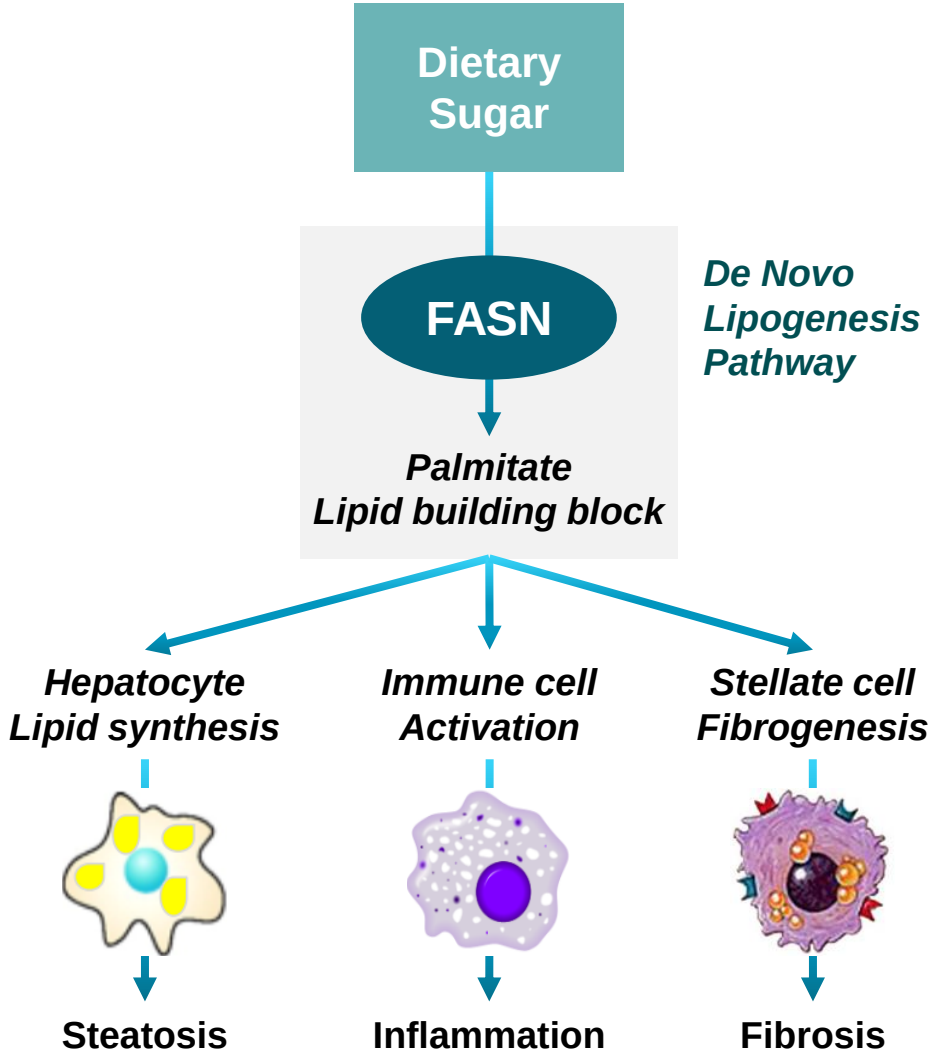
1. NASH pipeline is owned by Gannex Pharma Co., Ltd., an independent biotech which is currently wholly-owned by Ascletis Pharma Inc.(1672.HK).
2. ASC40 is licensed from Sagimet Biosciences Inc. for the exclusive rights in the Greater China.
3. The Company plans to initiate global phase III clinical trials in US, China and other countries after the completion of Phase IIb studies of ASC40, ASC41 and ASC42.

Disclaimer: The above milestones are only anticipations and the Company makes no guarantees for the achievement of the milestones.

# 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

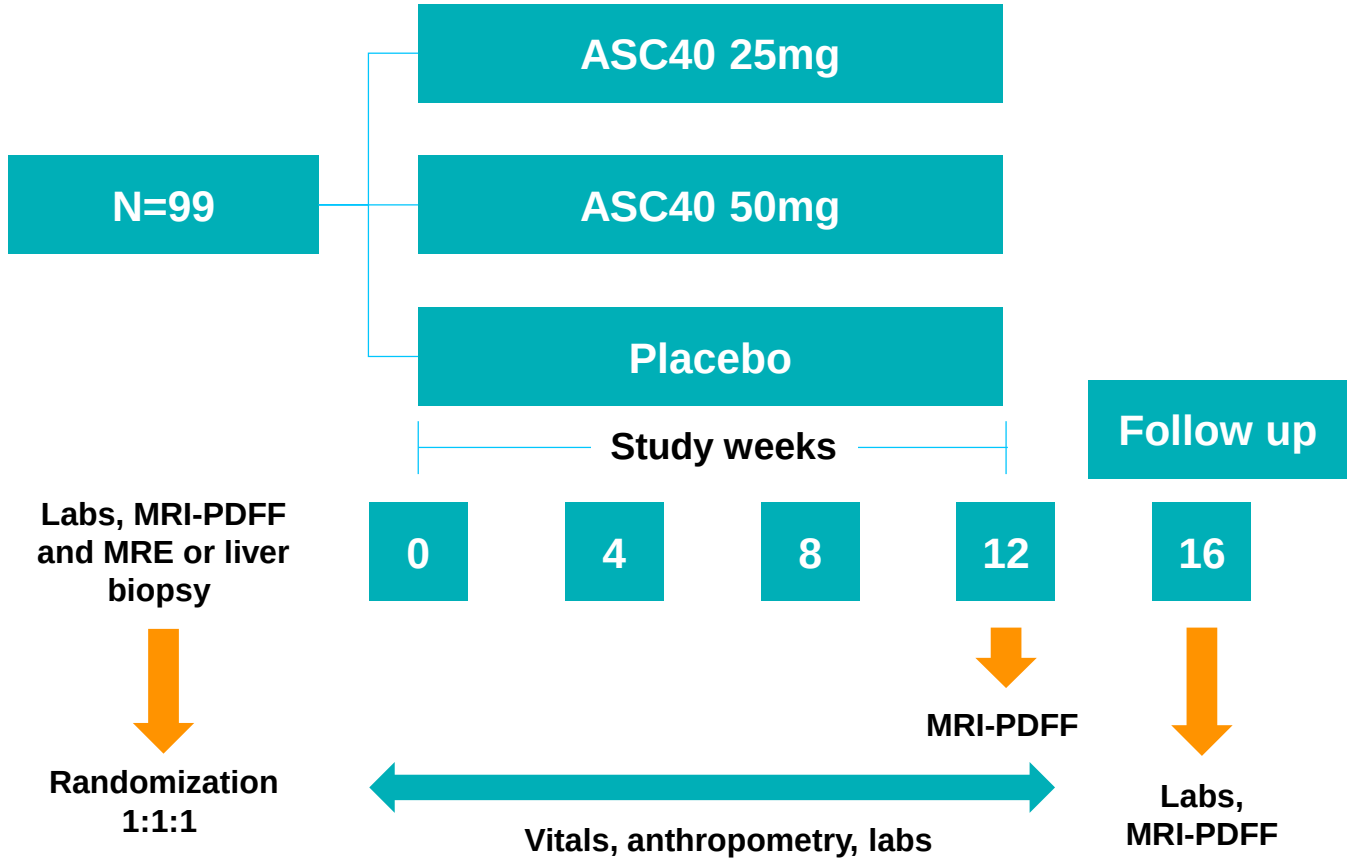
■ Multicenter, randomized, placebo-controlled trial 1:1:1 25mg:50mg:placebo (N=99)

**Criteria**

- Inclusion
  - ≥ 8% liver fat
  - MRE ≥ 2.5kPa or recent biopsy
- Exclusion
  - Evidence of cirrhosis
  - Other chronic liver disease

**Endpoints**

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

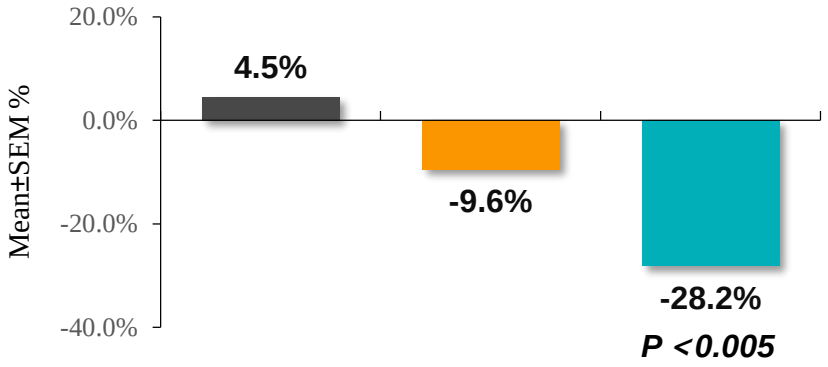



Source: Rohit Loomba et al. 2020,Hepatology 72;103.EASL 2020 Oral Presentation

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

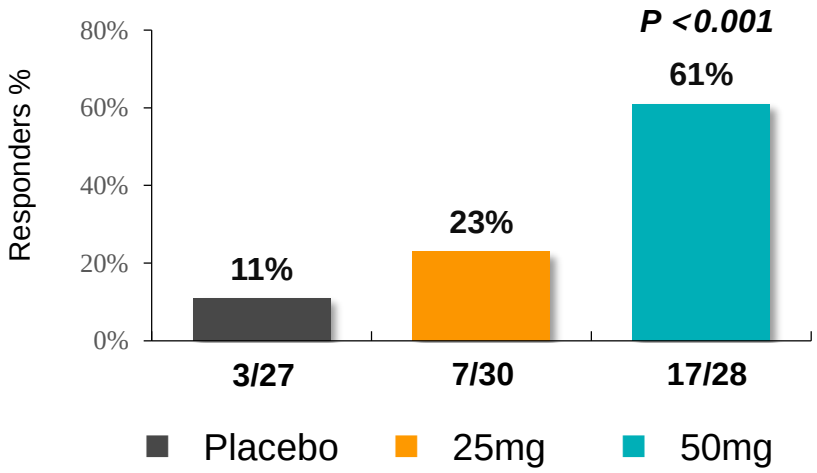
**Mean relative liver fat reduction**

MRI-PDFF at week 12

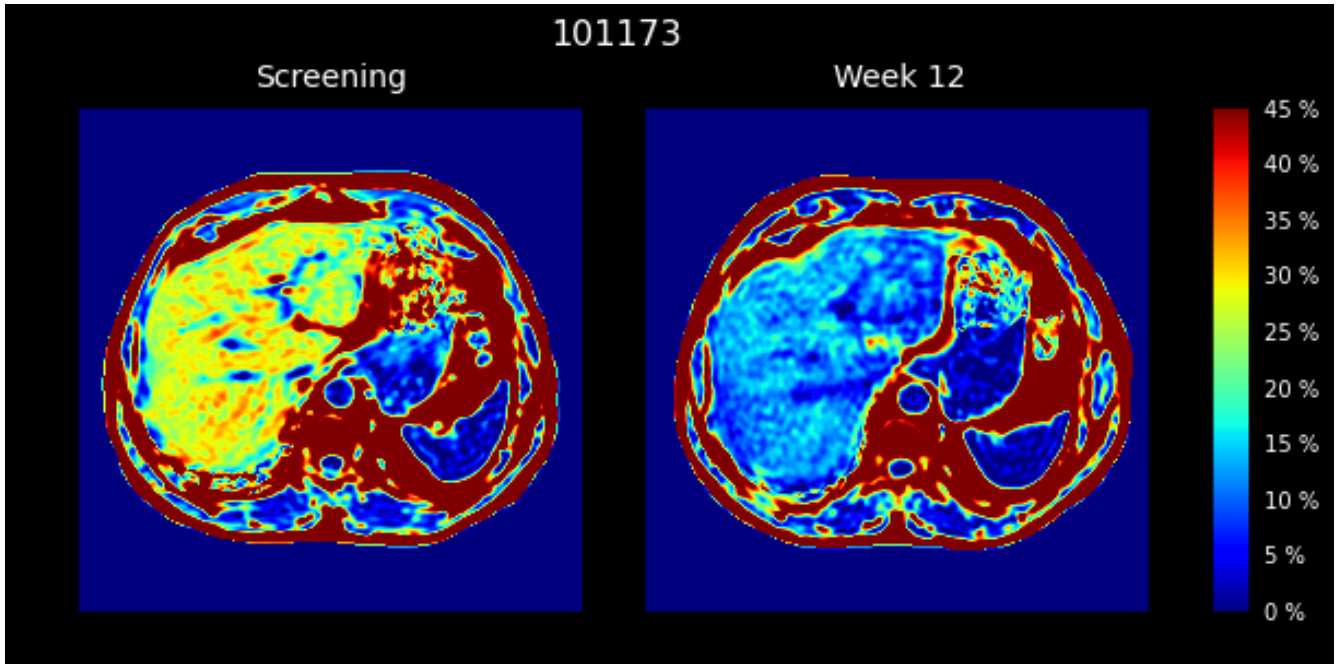



**Responder frequency**

Patients with ≥30% relative reduction




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

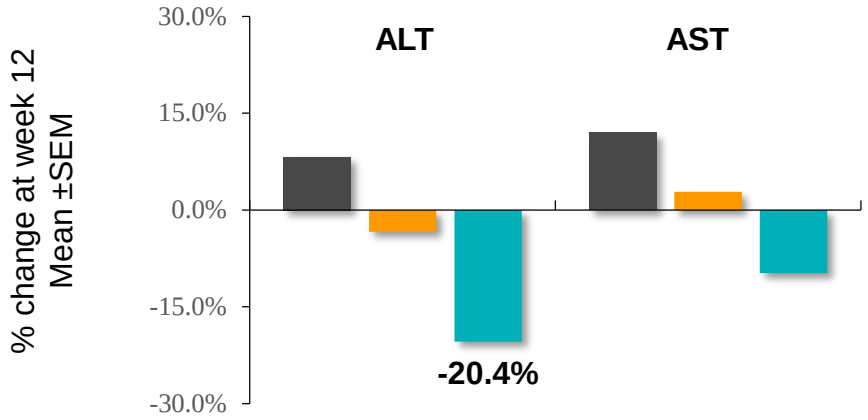



MRI-PDFF responders were defined as those with ≥ 30% MRI-PDFF decline relative to baseline

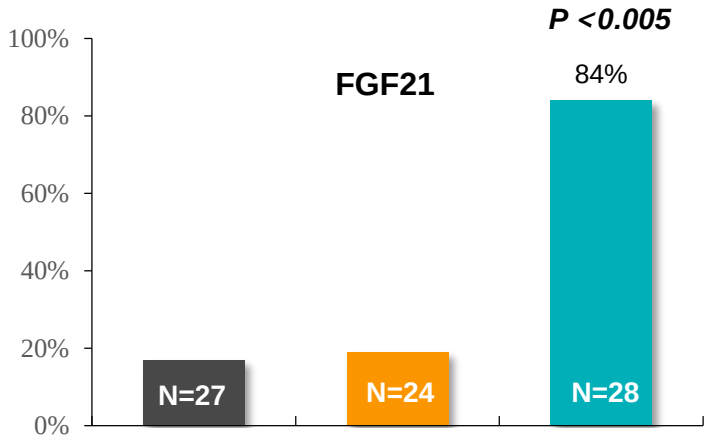
Source: Rohit Loomba et al. 2020, Gastroenterology & Hepatology 72;103AASLD 2020 Oral Presentation

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

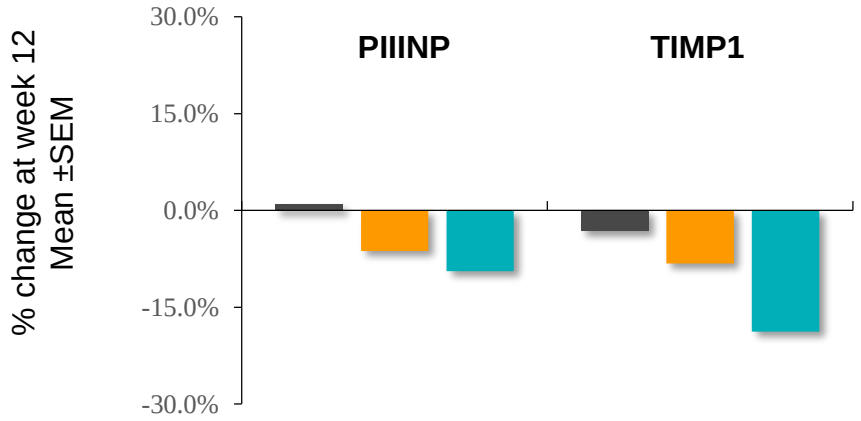
**Dose-dependent response in reducing ALT/AST**



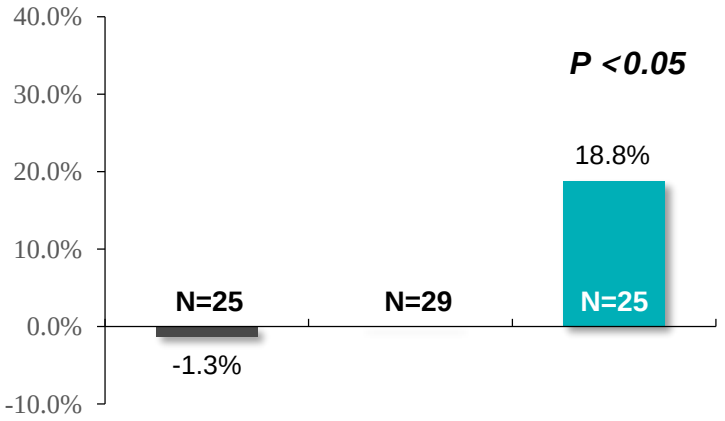

**Improves markers of hepatic insunlin sensitivity**




**Decreases fibrosis markers**




**Adiponectin**




Placebo 25mg 50mg

Source: Rohit Loomba et al. 2020, Gastroenterology & Hepatology 72;103 AASLD 2020 Oral Presentation

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

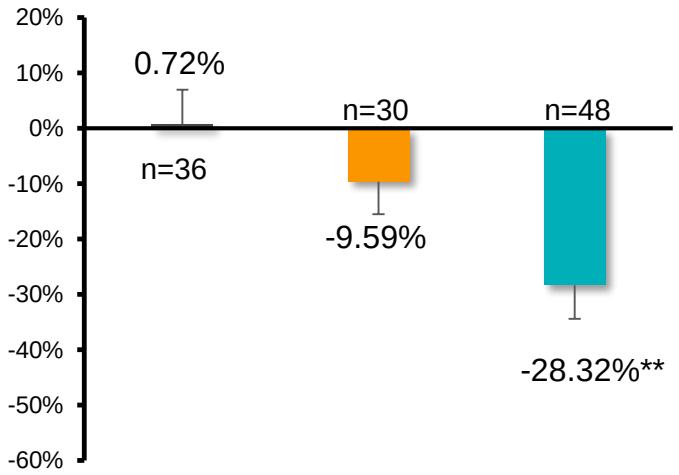
| Drug Candidate | Company | Target | Dose | Weeks | ≥ 30% liver fat reduction responder rate, % | | Placebo adjusted ≥ 30% liver fat reduction responder rate, % | Safety |
|---|---|---|---|---|---|---|---|---|
| | | | | | Drug | Placebo | | |
| ASC40[1] | Gannex /Sagimet | FASN | 50 mg | 12 | 60.7 |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

Non-head to head research

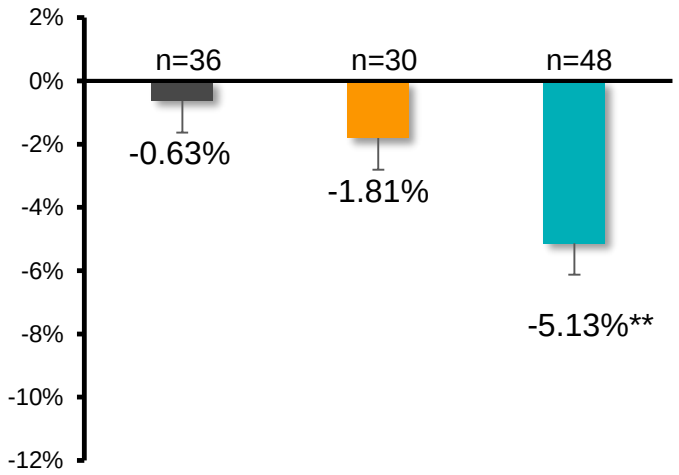

1、Rohit Loomba et al. 2020,Hepatology 72;103.EASL 2020 Oral Presentation
2、Eric J Lawitz et al. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1983-1991
3、 Marcos Pedrosa et al. Contemp Clin Trials. 2020 Jan;88:105889.
4、Stephen A Harrison et al. Lancet. 2019 Nov 30;394(10213):2012-2024

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

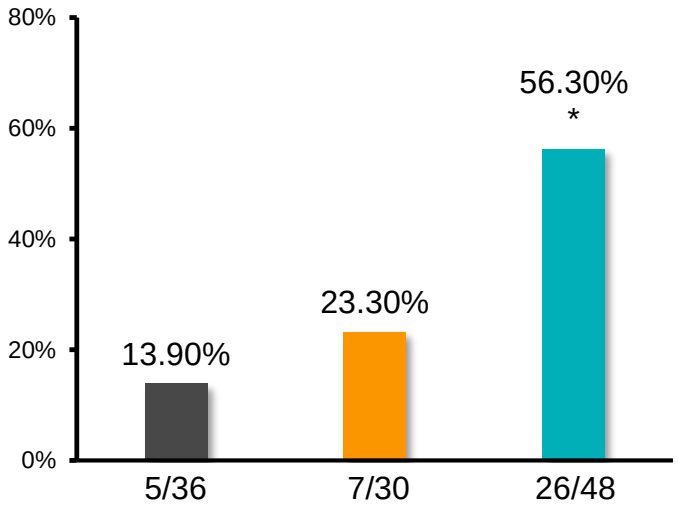
**Mean relative liver fat reduction**
MRI-PDFF at week 12




**Mean absolute liver fat reduction**
MRI-PDFF at week 12



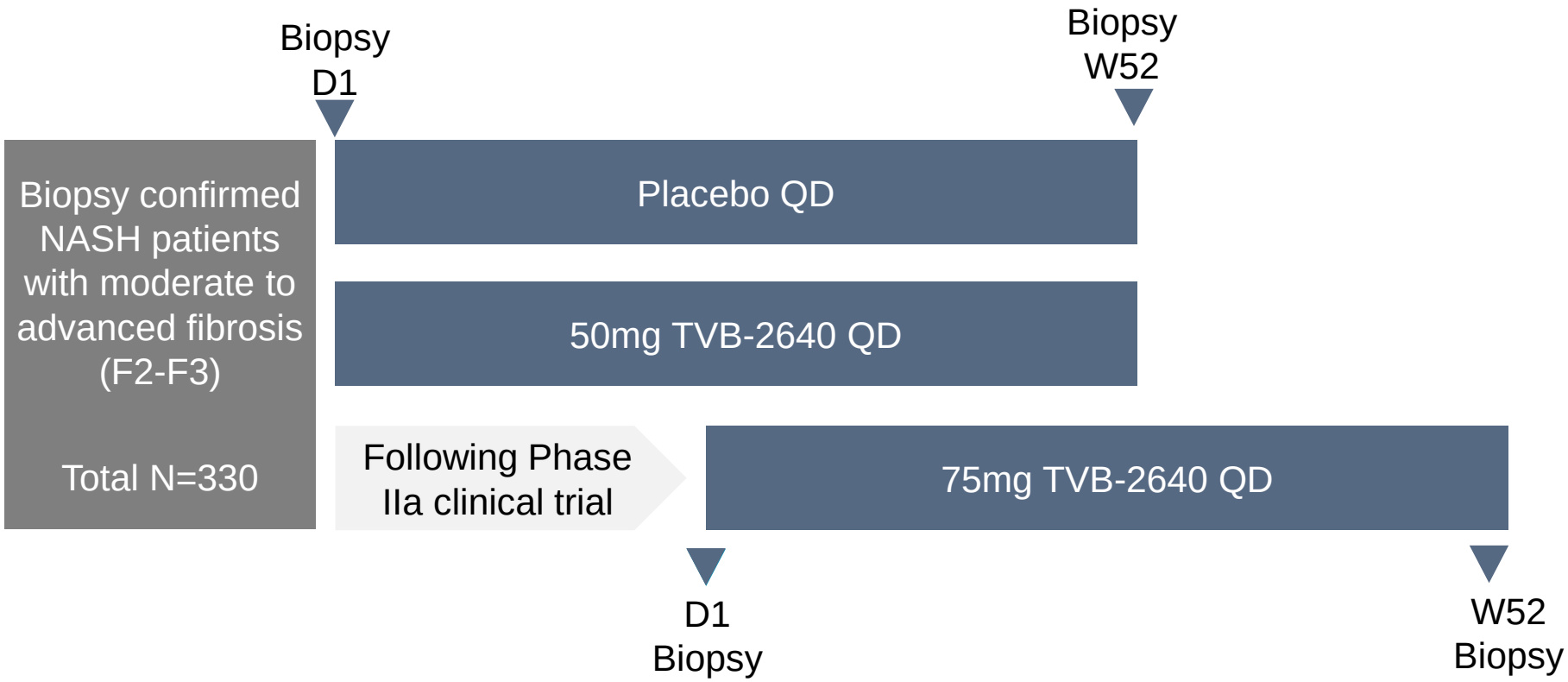

**Responder frequency**
Patienct with ≥30% relative reduction




**Placebo** **25mg** **50mg**

Source: Gannex data
***p<0.001 Mean ± SEM LSM difference versus placebo for liver fat.Common risk difference for responder frequence*
**p=0.0002*

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

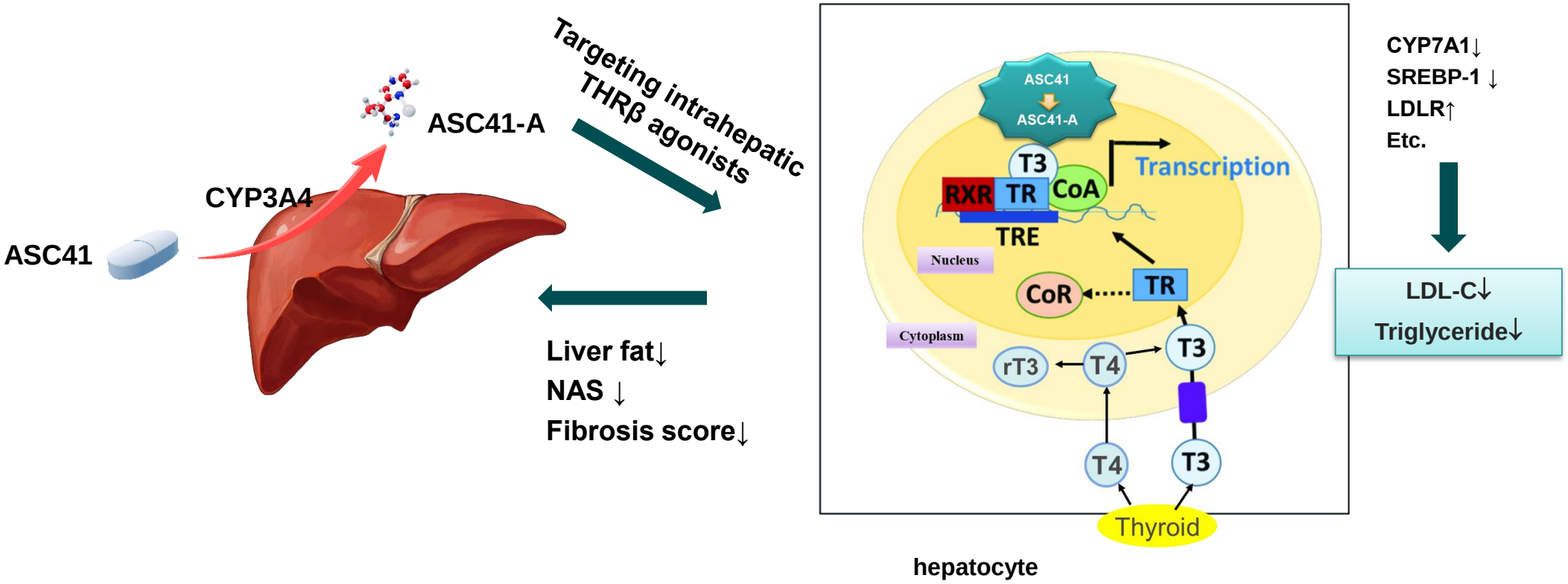



*Primary efficacy endpoints:*

1. *≥ 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 (THRβ) Agonist

- ASC41 is a liver targeted small molecule which is converted to its active metabolite ASC41-A - a potent and selective THRβ agonist




Source: Gannex data

# ASC41: Third-in-class THRβ Agonist in USA
# First-in-class THRβ Agonist in China

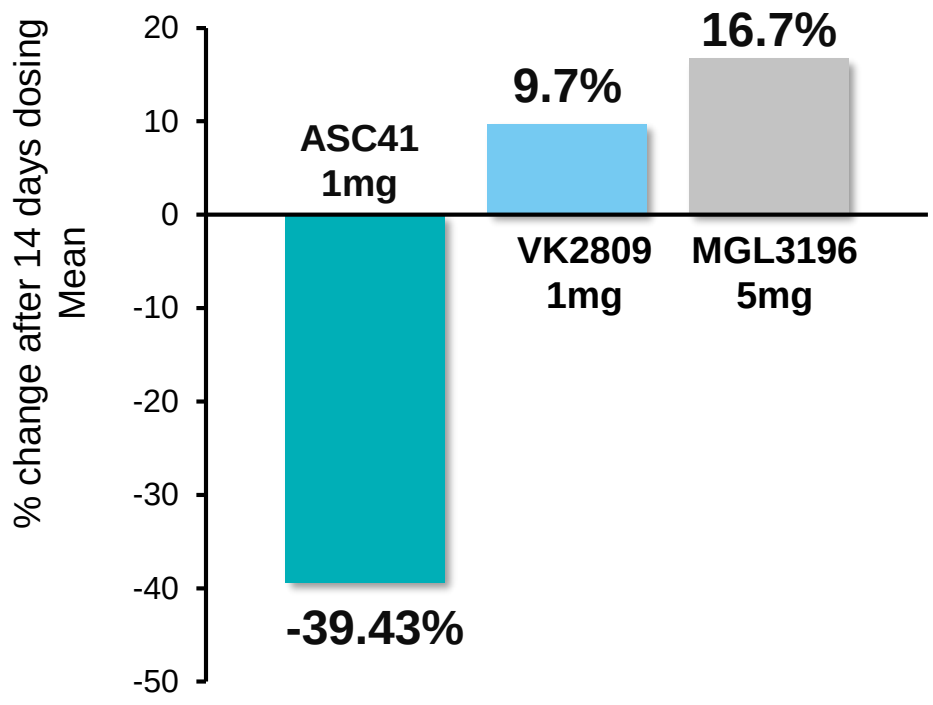
- In two NASH animal models, at 1/10th dose of MGL-3196, ASC41 demonstrated the same improvement in liver steatosis, inflammation and fibrosis.
- Commercially ready oral tablet formulation developed with in-house proprietary technology
- 2 Phase I studies completed
  - Single doses (1, 2, 5, 10, 20 mg) 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
- U.S. IND approved Feb 2021
- 1 Phase Ib study completed
  - 28 day, 10 mg in 20 overweight and obese subjects with elevated LDL-C > 110 mg/dL
- Based on above studies, doses have been selected for Phase II trials in patients with NASH

Source: 1. PO1908. Significant Improvement of NAFLD Activity Scores and Liver Fibrosis by ASC41, a Selective THRβ Agonist, in HIgh Fat Diet Induced NASH SD Rats. Journal of Hepatology 2021 vol. 75(2) | S294–S803
2. PO1851. Significant lipid lowering by ASC41oral tablet, a liver targeted THRβ agonist, in a phase I randomized, double-blind, placebo controlled single- and multiple-ascending dose study. Journal of Hepatology 2021 vol. 75(2) | S294–S803

# THRβ Differentiations: Gannex vs Viking and Madrigal

| | Gannex ASC41[1] | Viking VK2809[2] | Madrigal MGL3196[3] |
|---|---|---|---|
| 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 |
| Human dose needed for > 30% TG reduction | 1 mg | 2.5 mg | 50 mg |

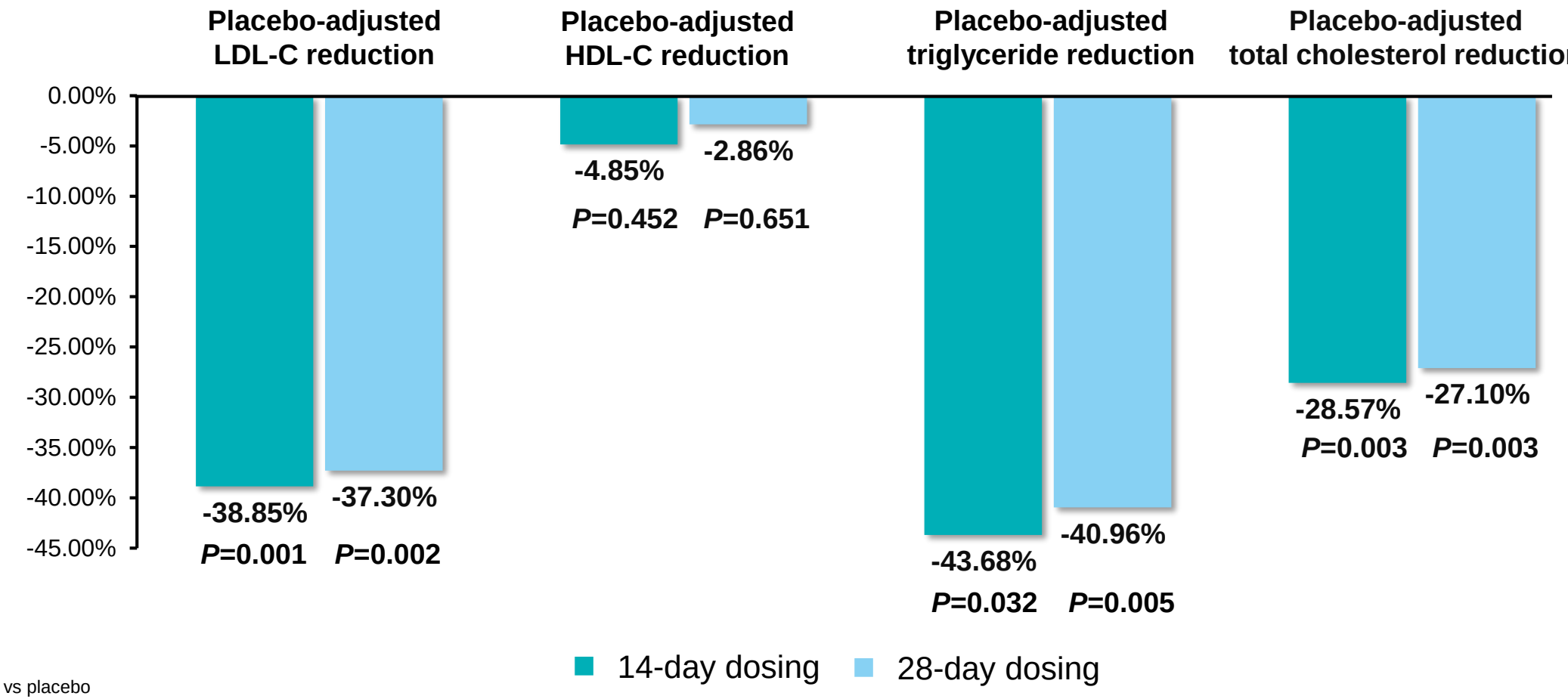
**Placebo adjusted triglyceride reduction from baseline after 14 day dosing**




Source: 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 Published online November 11, 2019 https://doi.org/10.1016/S0140-6736(19)32517-6

# Positive Clinical Results in Overweight and Obese Subjects

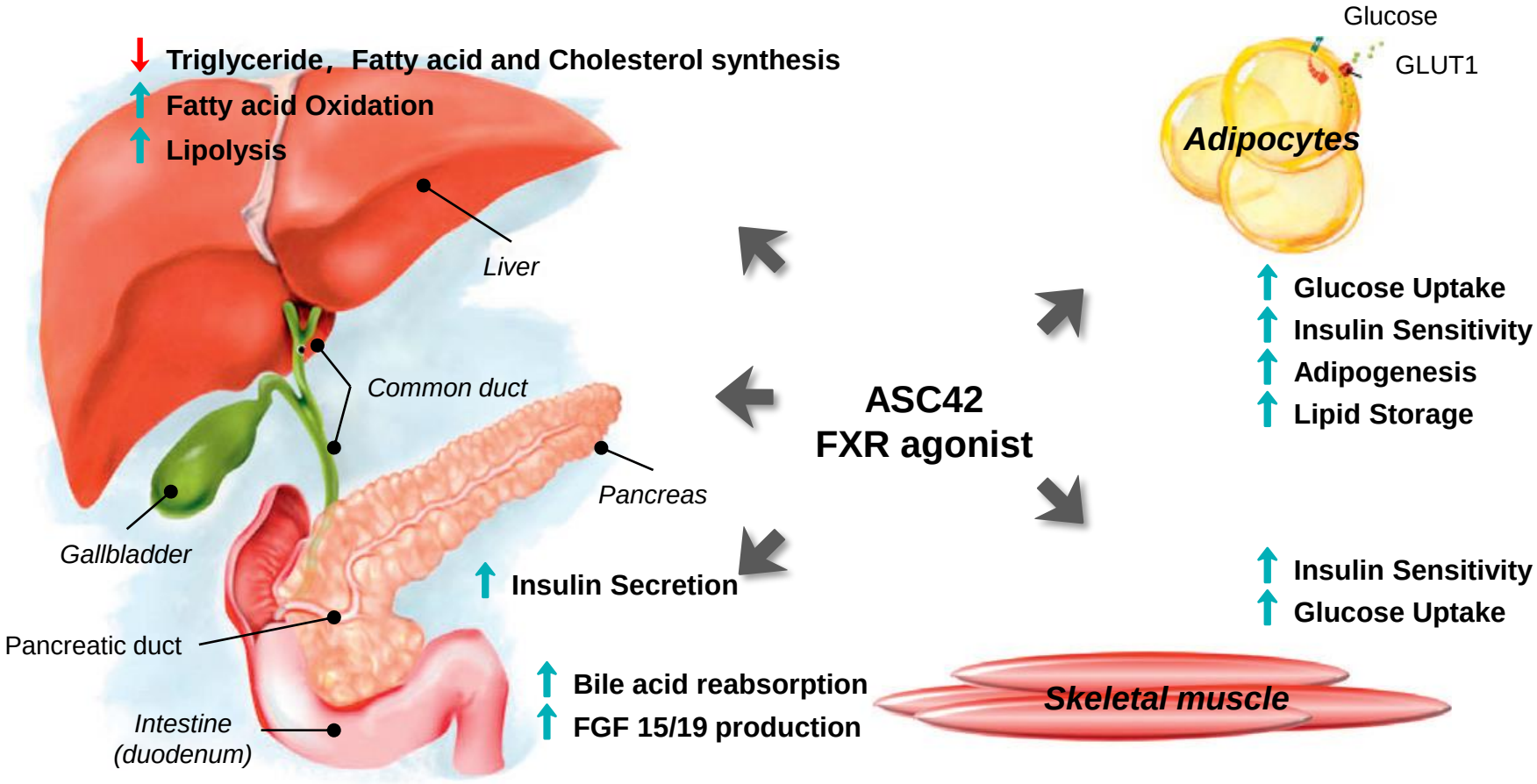
**Placebo-adjusted relative change (mean) from baseline after 14 or 28 days of once daily oral dosing of 10 mg ASC41 tablets in overweight and obese subjects**




*P*-value vs placebo

Source: Gannex data

# 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

Source: Luciano Adorini et al. Farnesoid X receptor targeting to treat nonalcoholic steatohepatitis. Drug Discovery Today Volume 17, Numbers 17/18 September 2012

# 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
- Oral tablet formulation developed with in-house proprietary technology and stable at room temperature

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

- No pruritus observed during 14-day treatment of the once-daily human therapeutic dose of 15 mg.
- FXR target engagement biomarker FGF19 increased 1632% on Day 14 of treatment with 15 mg, once-daily
- FXR target engagement biomarker C4 decreased 93% on Day 14 of treatment with 15 mg, once-daily
- Mean LDL-C values remained within the normal range during 14-day, once daily treatment with 15 mg
- There were no treatment-emergent ALT and AST elevations during 14-day, once daily treatment with 15 mg
- Doses selected for Phase II trial in patients with NASH, which will be initiated by the end of 2021

Source: Press Release on June 16, 2021

# FDC: Synergies 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

GANNEX