



# CURRENT TREATMENTS IN DEVELOPMENT FOR NASH



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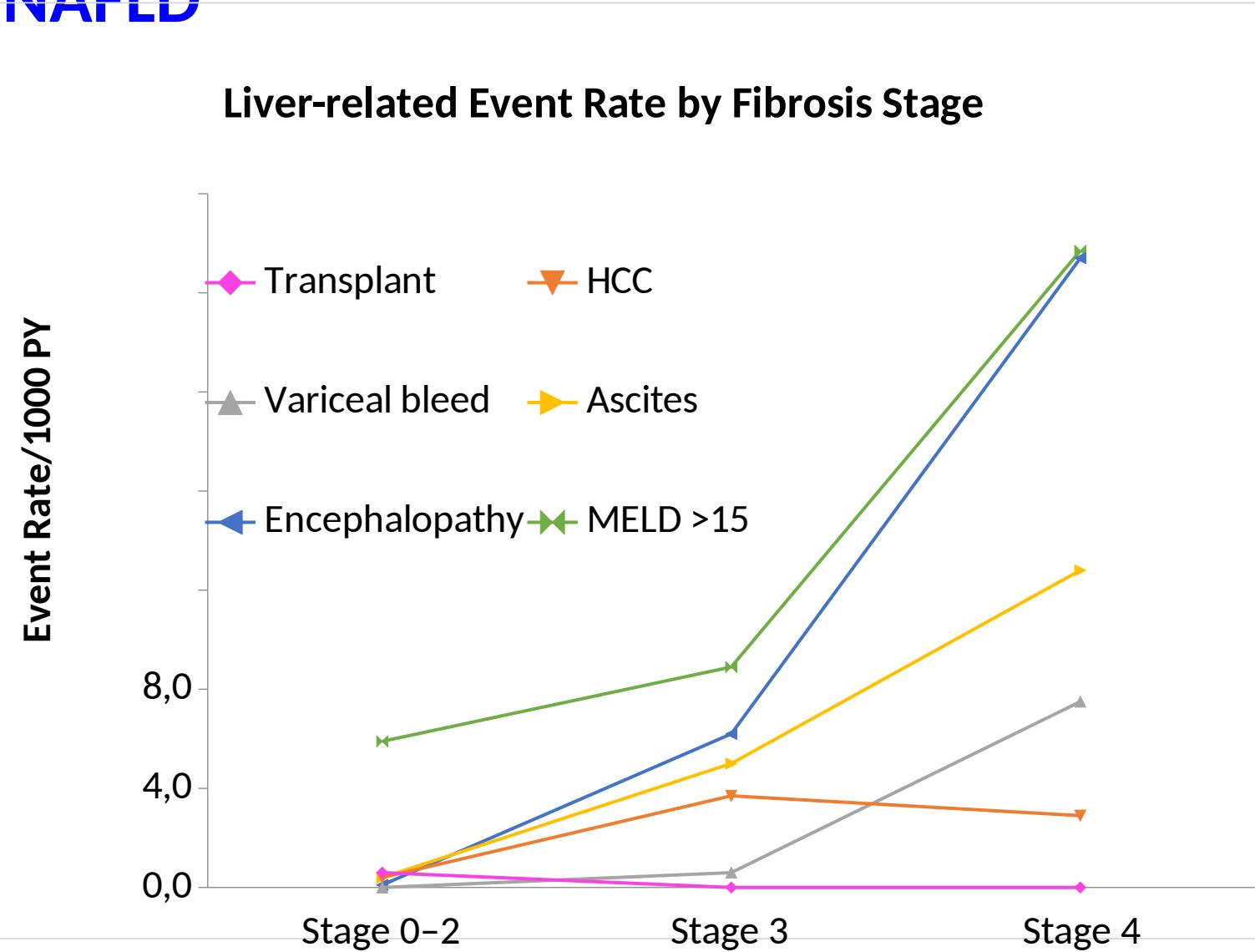
Virginia Commonwealth University School of Medicine

Richmond, VA

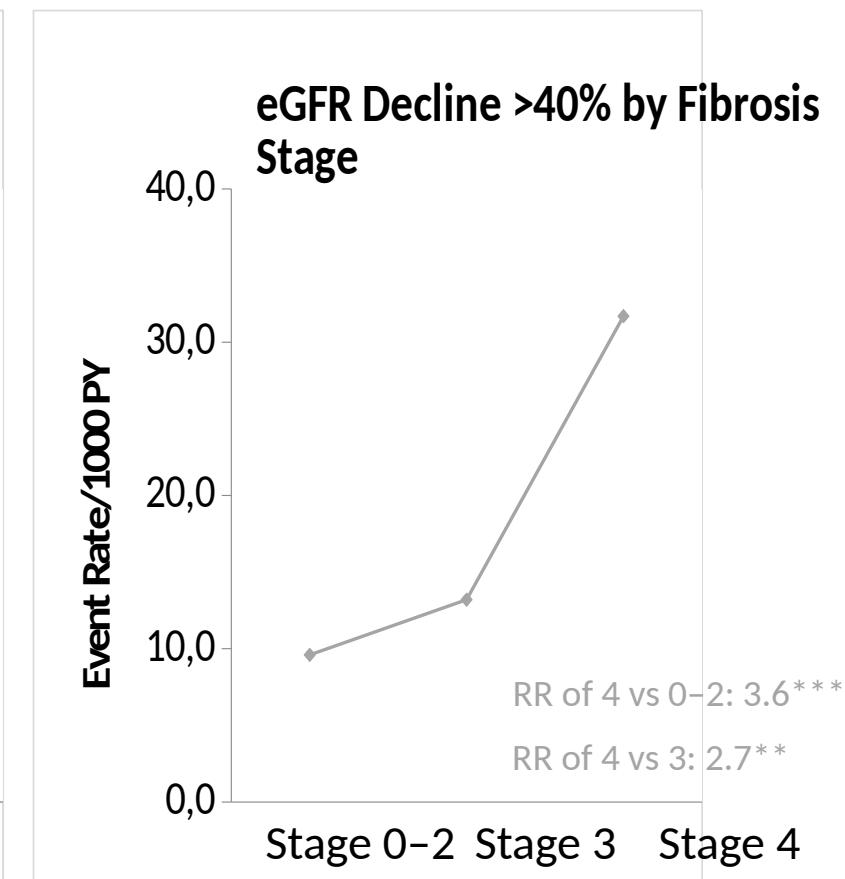
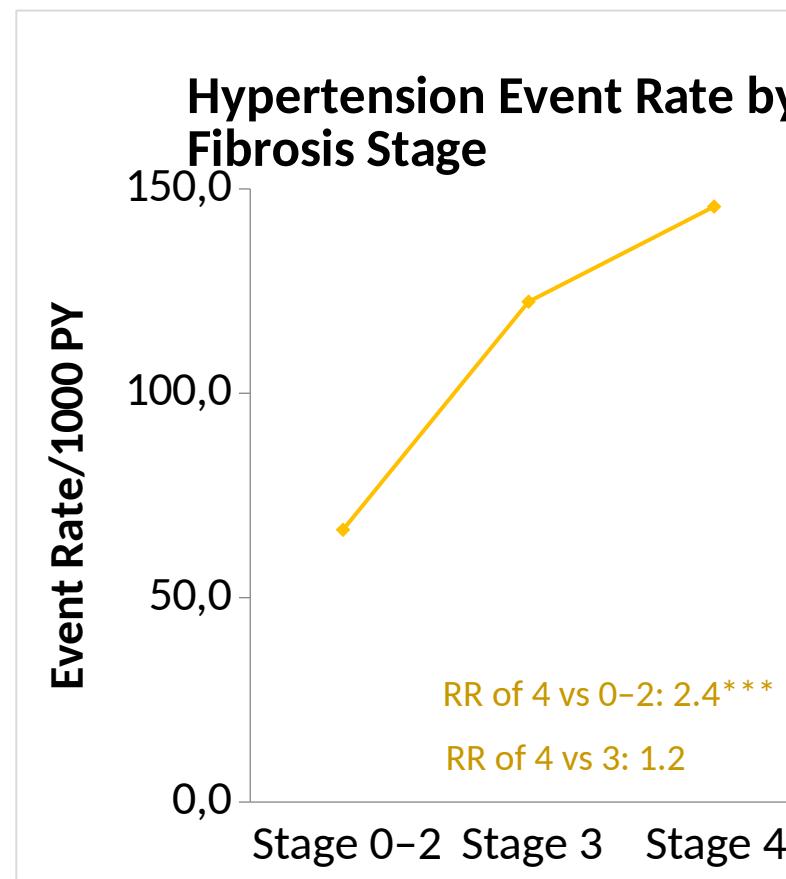
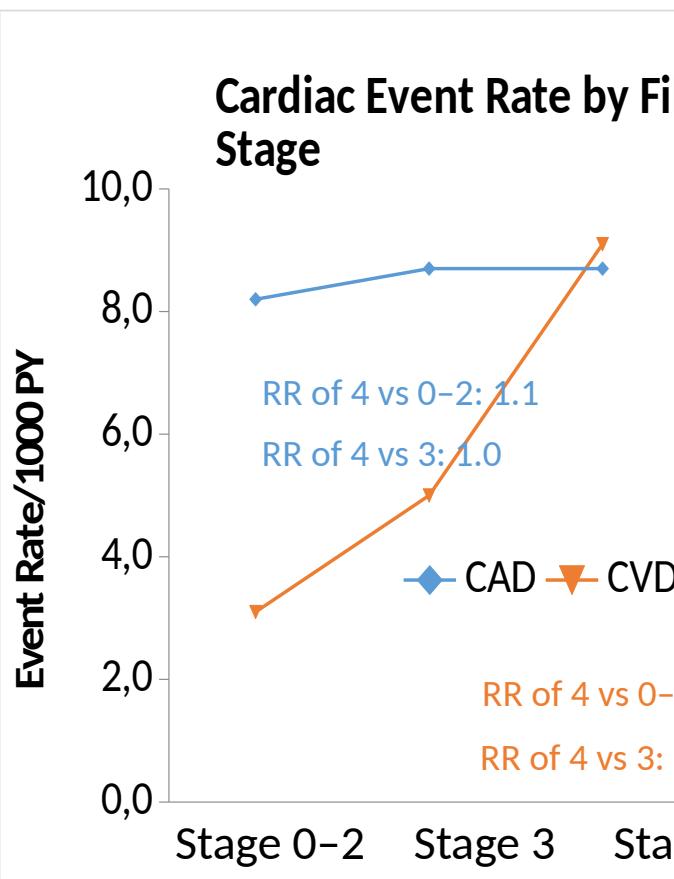
# Conflicts of Interest

- Dr. Sanyal is President of Sanyal Biotechnologies
  - Stock options for Genfit, Tiziana, Indalo, Durect, Exhalenz, Galmed
  - Consultant- Gilead, Intercept\*, Allergan\*, Lilly, Novo Nordisk, Astra Zeneca-Medimmune\*, Novartis, Pfizer, Genentech, Merck, Bristol Myers\*, Boehringer Ingelheim\*, Immuron\*, Echosense, GE, OWL\*, Birdrock, Tern, Sundise, RedX\*, IFMO, Lipocine\*, Innovate\*, Zydus\*, AMRA, Hemoshear,
  - Grant support: Bristol Myers, Intercept, Gilead, Allergan, Merck, Echosense, Novartis, Boehringer Ingelheim
- \* *no financial remuneration in last 24 months*

# A prospective analysis of clinical outcomes across the full spectrum of NAFLD



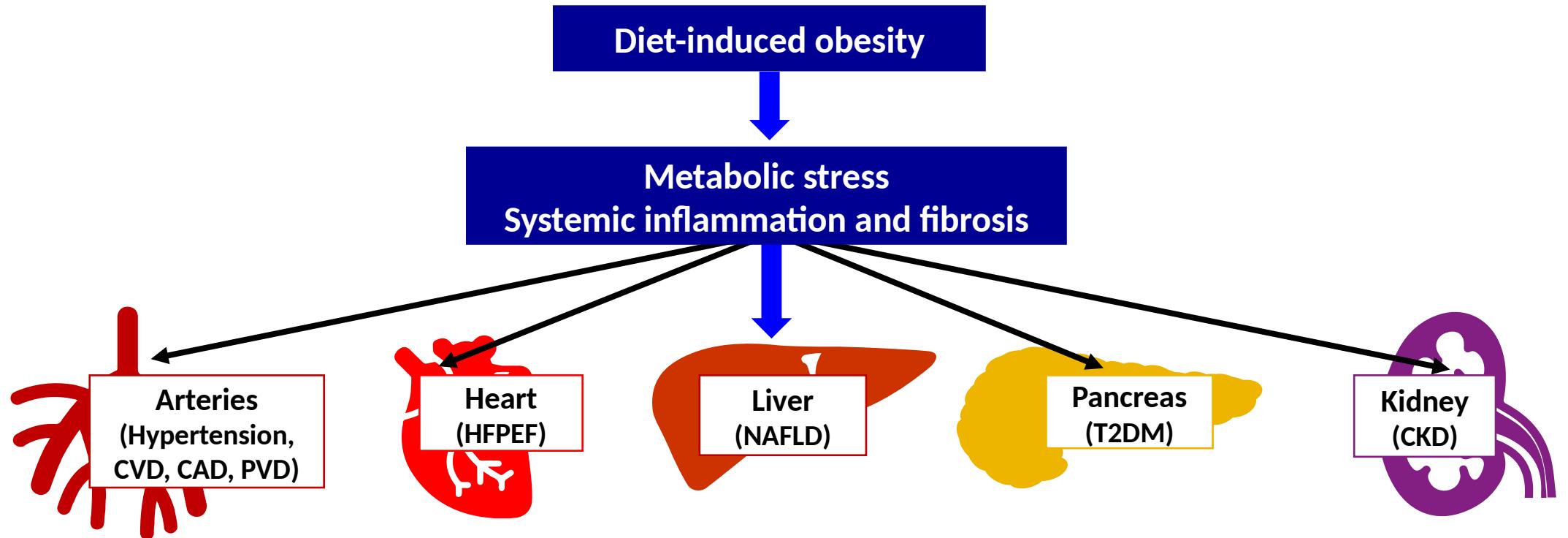
# A prospective longitudinal study of clinical outcomes in adults with nonalcoholic fatty liver disease



\*p<0.05; \*\*p<0.01; \*\*\*p<0.001

- Mortality, HCC & liver-related events in NAFLD largely occur in advanced fibrosis & cirrhosis
- Incidence of extrahepatic outcomes increase with progression from mild/moderate fibrosis to bridging fibrosis to cirrhosis
- In patients with lower fibrosis stages, principal outcomes were extrahepatic

# NASH is part of a multi-system disorder



- Weight loss
- ARBs
- GLP1
- Statins/Fibrates
- Smoking cessation

- Weight loss
- SGLT2i

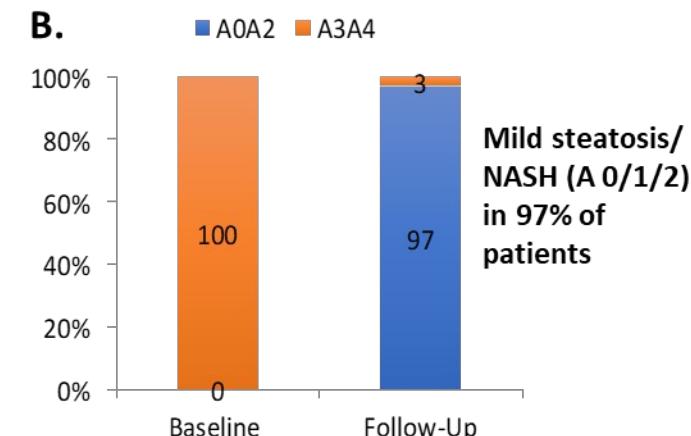
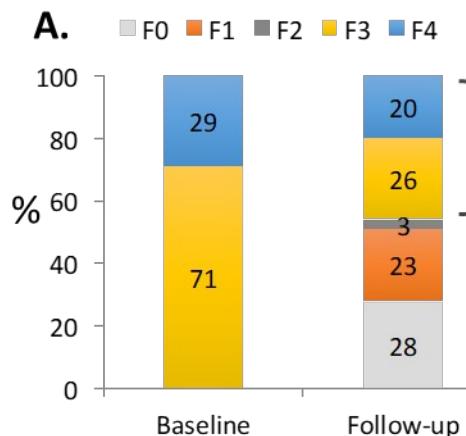
- Weight loss
- GLP1
- ?SGLT2i

- Weight loss
- ARBs
- Metformin
- GLP1
- SGLT2i

- Weight loss
- ARBs
- SGLT2i
- GLP1

# Bariatrics improve disease activity but advanced fibrosis does not regress in all

Histological Changes Post Bariatric Surgery in Patients with Severe Fibrosis  
(A, N=35) and Highly Active Steatohepatitis (B, N=30)



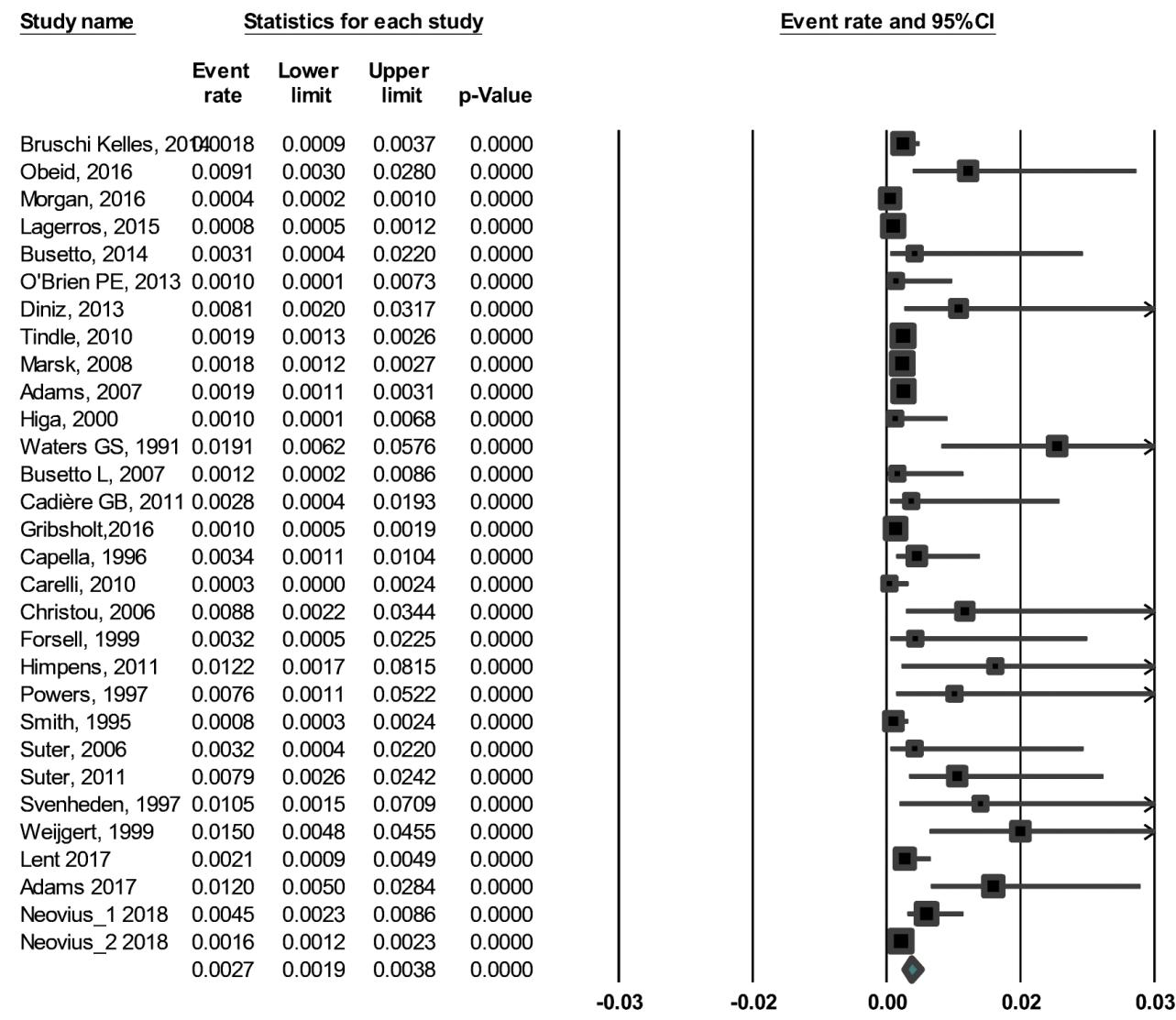
Predictors of persistence of severe fibrosis (F3F4) at f/u

	OR, 95% CI	P
Age	1.083 (0.98 – 1.18)	0.089
Sex	1.12 (0.3 – 4.25)	0.85
Weight loss	1.007 (0.96 – 1.05)	0.76
T2DM regression	0.68 (0.15 – 2.94)	0.60
Gastric by-pass	<b>0.20 (0.053 – 0.782)</b>	<b>0.02</b>

Predictors of normal liver (N=19) at f/u

	OR, 95% CI	P
Age	0.94 (0.88 – 1.006)	0.074
<b>Weight loss</b>	<b>1.05 (1.02 – 1.08)</b>	<b>0.001</b>
<b>ALT changes</b>	<b>1.04 (1.01 – 1.07)</b>	<b>0.009</b>
GGT changes	0.99 (0.98 – 1.01)	0.53
<b>HOMA IR changes</b>	<b>0.80 (0.68 – 0.94)</b>	<b>0.007</b>
<b>Baseline Fibrosis</b>	<b>0.54 (0.30 – 0.97)</b>	<b>0.04</b>
<b>Baseline NAS</b>	<b>2.49 (1.22 – 5.07)</b>	<b>0.012</b>

# Suicide risk is increased after bariatric surgery

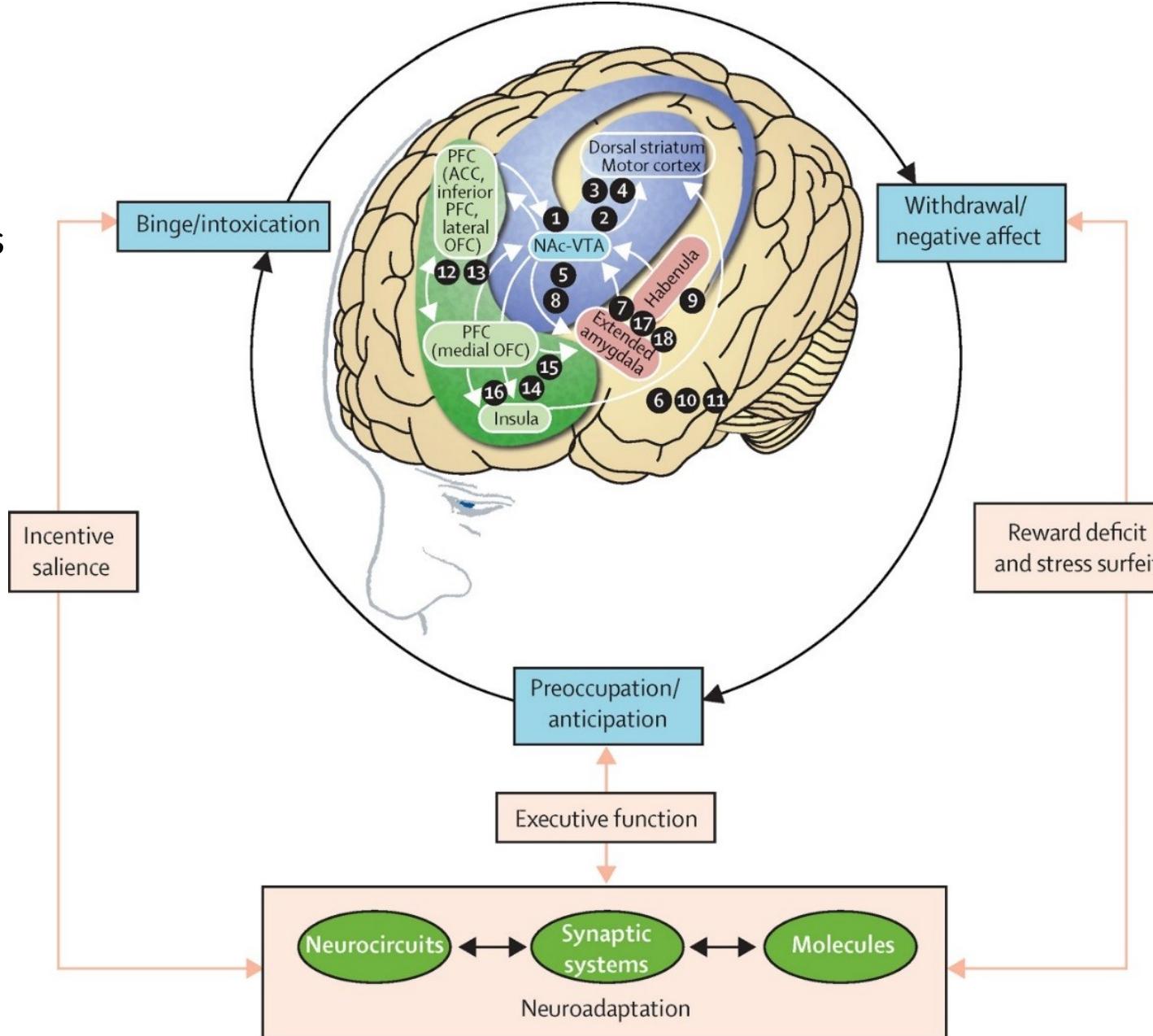


## Binge/Intoxication

- ↑ Dopamine
- ↑ Opioid peptides
- ↑ **Serotonin**
- ↑ GABA
- ↑ Acetylcholine

## Preoccupation/ Anticipation

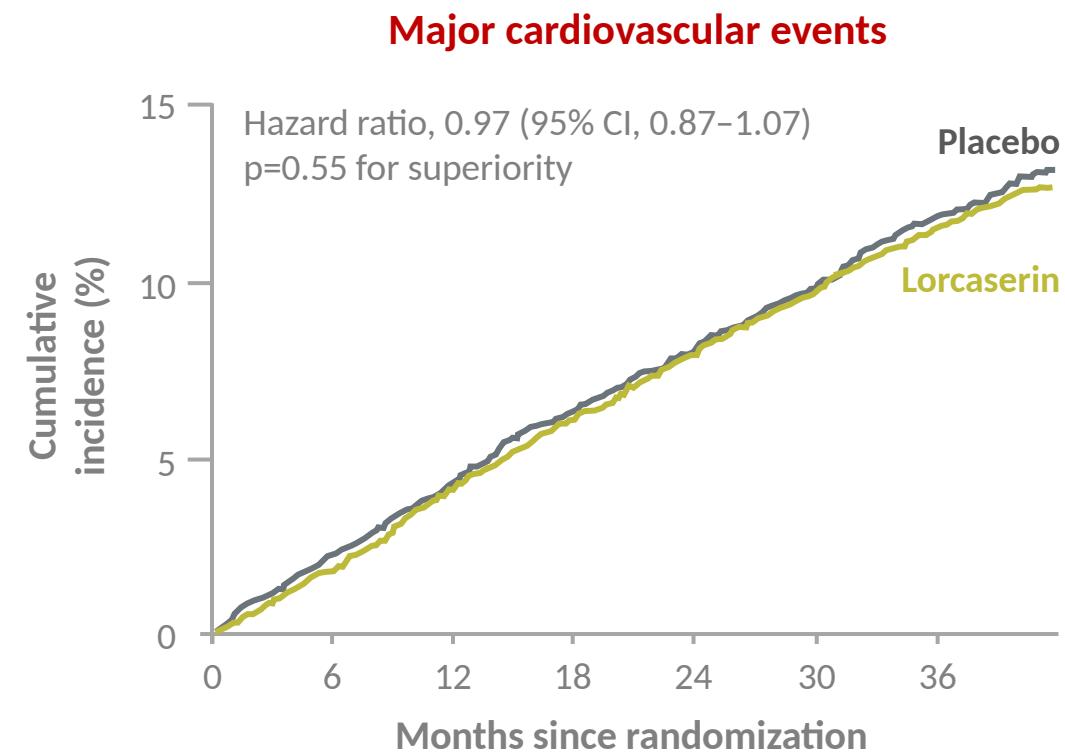
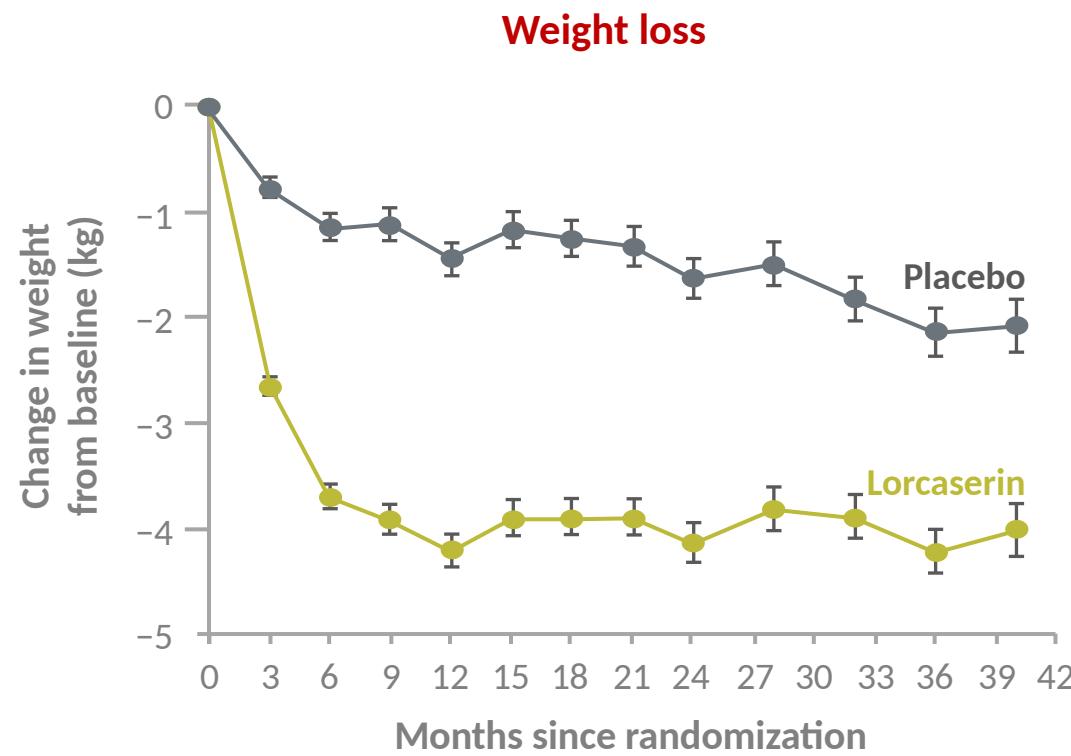
- ↑ Dopamine
- ↑ Glutamate
- ↑ Hypocretin
- ↑ **Serotonin**
- ↑ CRF



## Withdrawal/ Negative Affect

- ↑ CRF
- ↑ Dynorphin
- ↑ Norepinephrine
- ↑ Hypocretin (Orexin)
- ↑ Substance P
- ↓ Dopamine
- ↓ **Serotonin**
- ↓ NPY
- ↓ Nociceptin
- ↓ Endocannabinoids
- ↓ Oxytocin

# Addiction circuitry and weight loss enhancement



Lorcaserin provided sustained weight loss without increasing the risk of major cardiovascular events in a high-risk population of overweight or obese patients

Randomized, double-blind trial comparing lorcaserin and placebo in 12,000 overweight/obese patients and high CV risk. Median follow-up 3.3 years

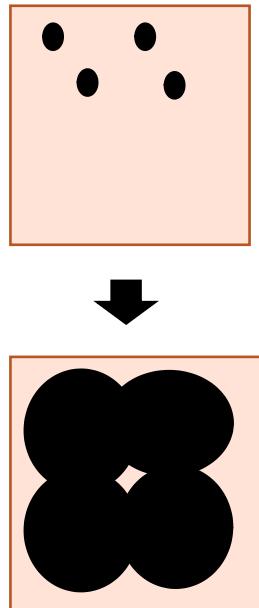
# Simple “non-toxic” and “non-wallet busting” approaches need further assessment

## MINDFULLNESS BASED STRESS REDUCTION

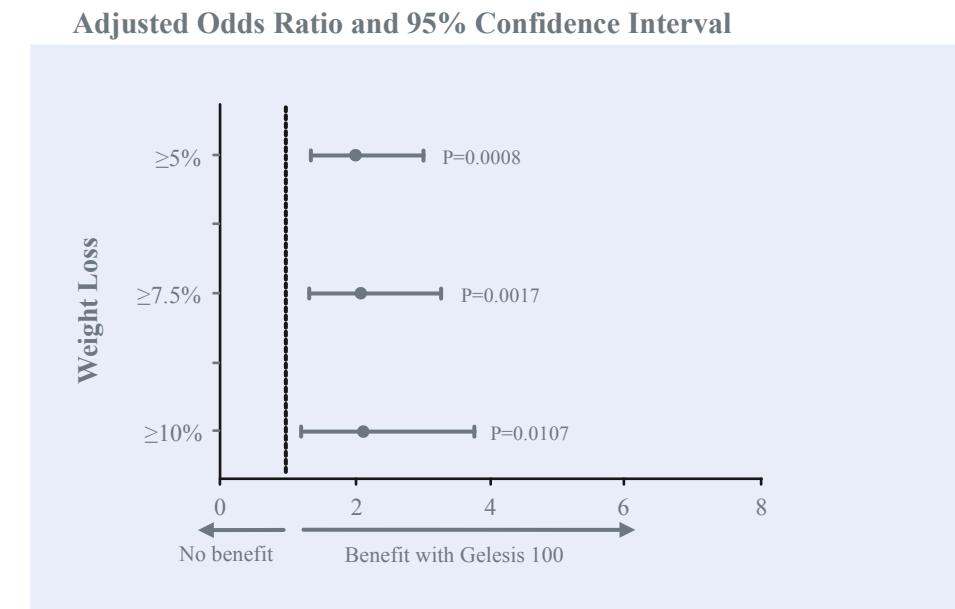
	# studies	# subjects	Effect size	P value
Mental Health	18	894	0.52	P< 0.0001
Physical Health	9	566	0.42	P< 0.0001

Grossman et al, Journal of Psychosomatic Research 57 (2004) 35 – 43

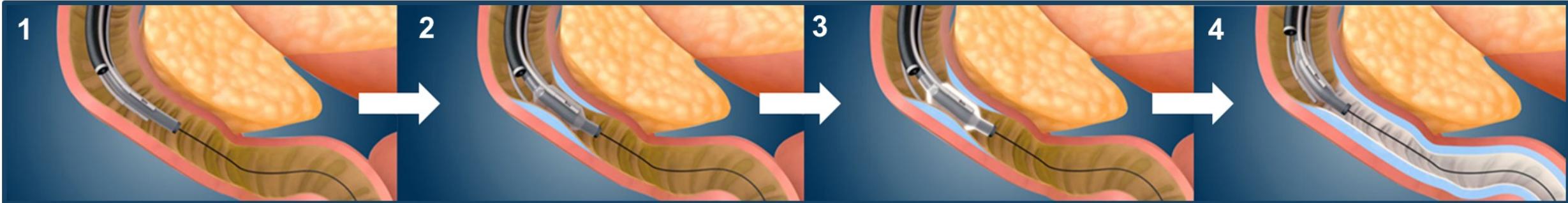
# Gelesis100 doubled odds to achieve clinically meaningful weight loss vs. placebo



\* $P < 0.05$ ; \*\* $P < 0.001$ . All P values are from logistic regression models adjusted for baseline weight and stratification factors.



## DMR: A novel, minimally invasive, outpatient, upper endoscopic procedure



- Revita® DMR catheter is designed to perform submucosal lift and hydrothermal ablation of hyperplastic duodenal mucosa, promote healthy epithelial regrowth within 12 weeks, and reduce insulin resistance and hyperinsulinemia<sup>1,2</sup>
- *Revita II: Phase 2A POC study showed 60% of subjects had 30% or more defatting of liver*
- *A1C decreased by 0.8 vs 0.3 (DMR vs sham)*

1. Hadefi A et al., *Dig Dis.* 2018;36:322-324. 2. Rajagopalan H et al., *Diabetes Care.* 2016. 3. Cherrington A et al., *Gastrointest Endoscopy Clin N Am.* 2017;27:299-311. 4. Van Baar A et al., *Gut.* 2019; pii: gutjnl-2019-318349.

5. Haidry R et al., *GIE.* 2019; 673 - 681.e2. 6. van Baar ACG et al., DTM 2019 poster VAN 19122D. REVITA-2 NCT02879383

DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

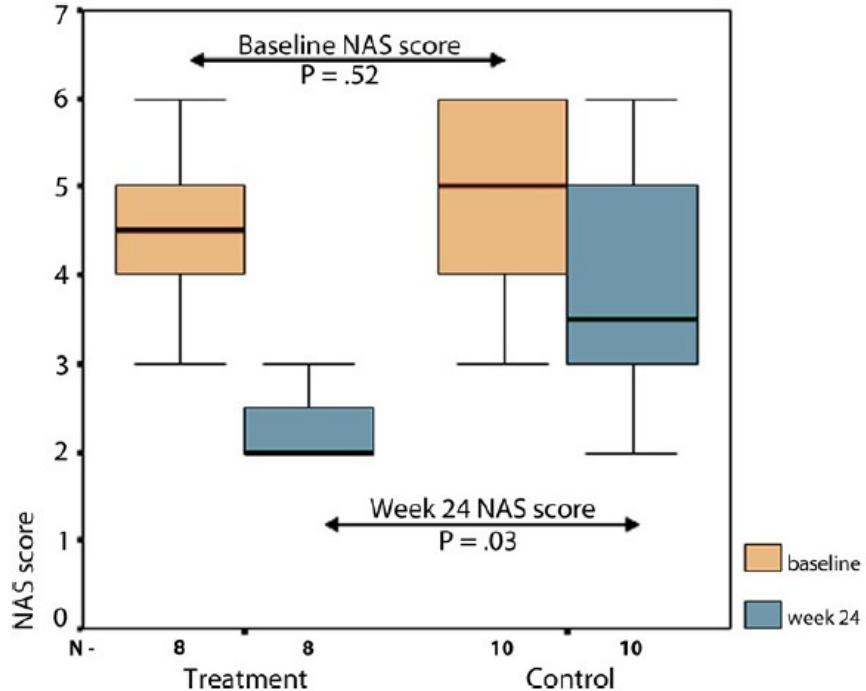
Sanyal et al, LB2, AASLD 2019

# Pilot Study specifically evaluated impact of ORBERA on NAFLD activity score

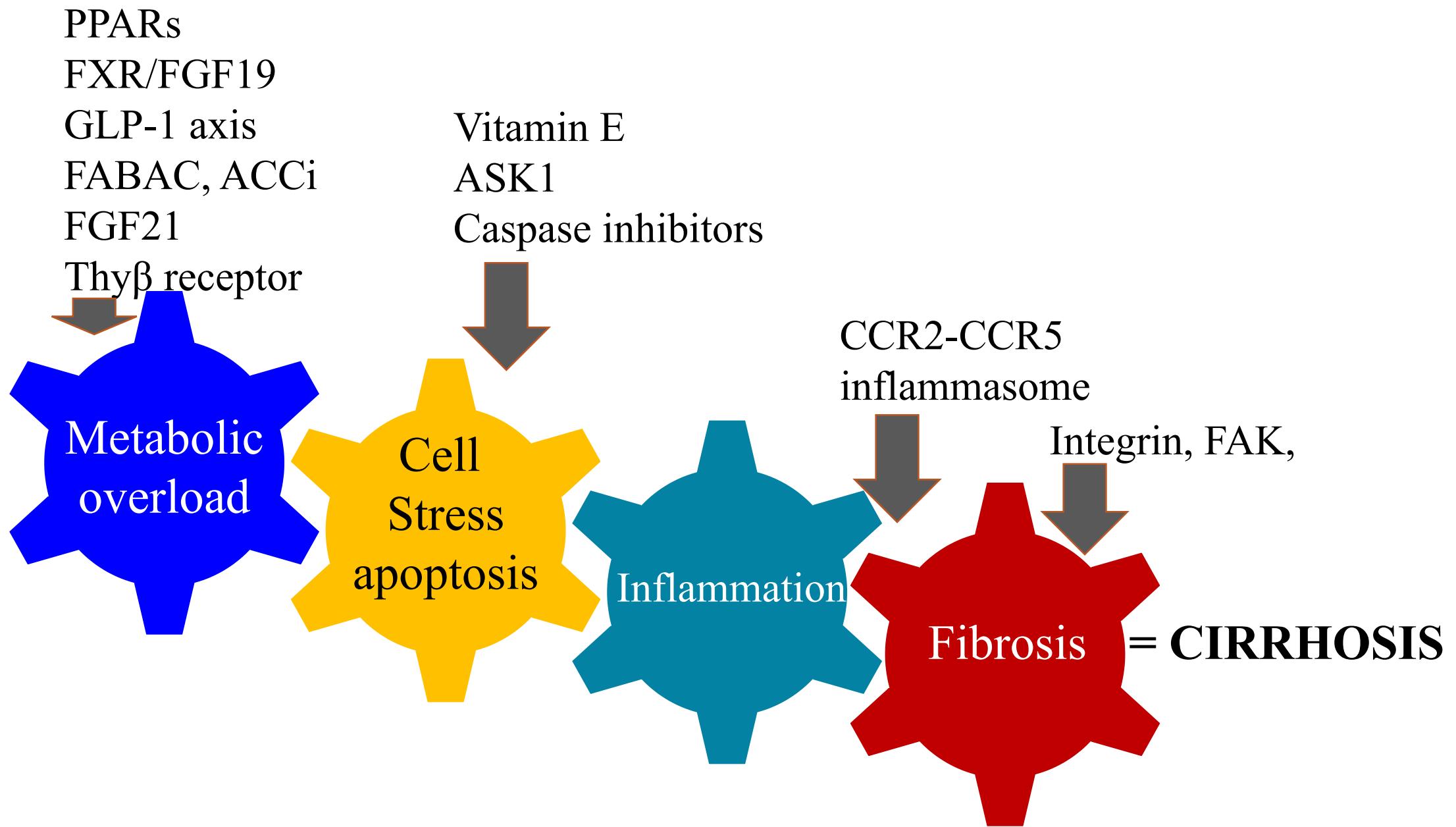
- Randomized sham controlled study that compared ORBERA + Diet / Exercise (n=8) vs. Sham + Diet / Exercise endoscopy (n=10)
- Liver histology assessed before placement and after balloon removal

## NAFLD Activity Score

*lower in ORBERA-treated compared with sham-treated (2 [0.75] vs 4 [2.25]; P=0.03)*

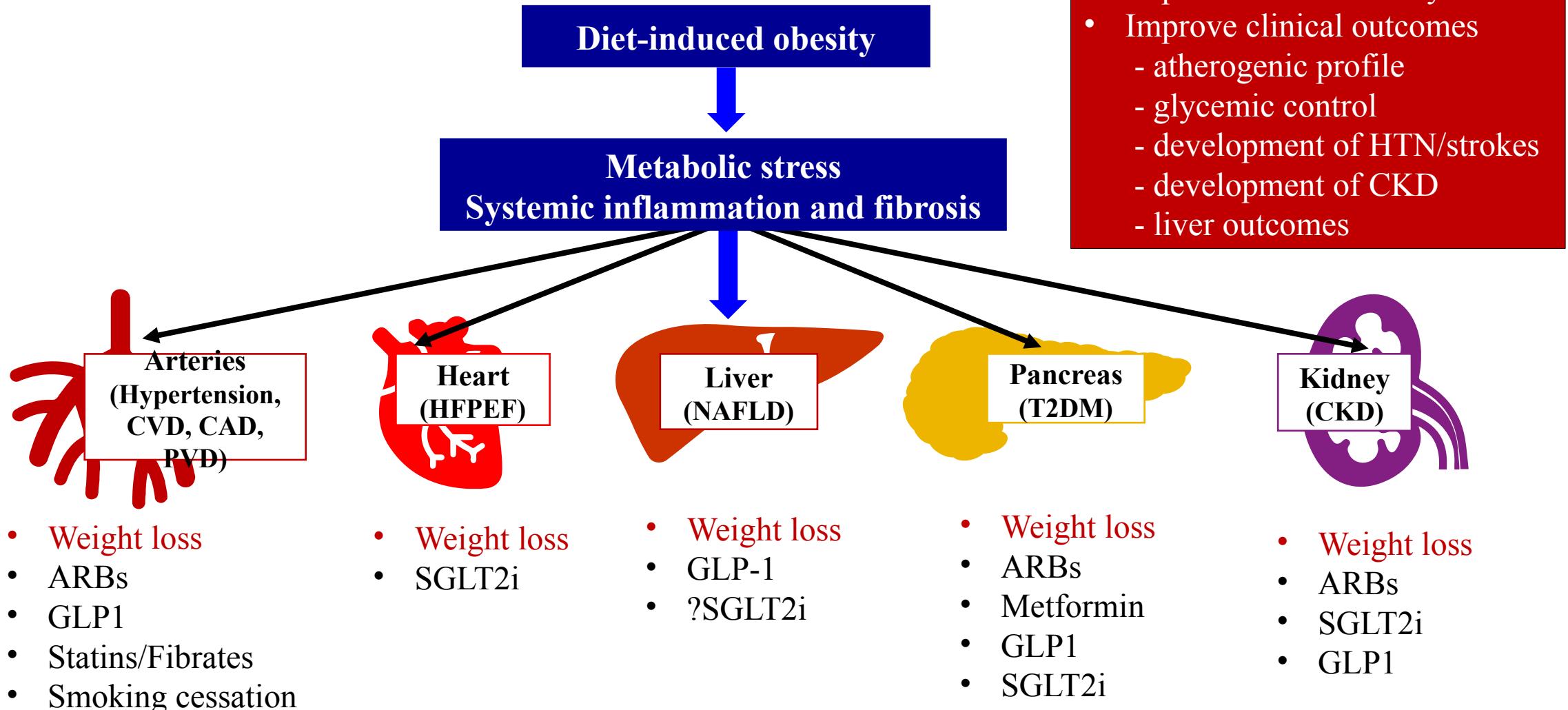


*Significantly lower NAFLD activity score with ORBERA Treatments*



Adapted from Friedman et al, Nature Med 2018

# NASH is part of a multi-system disorder



CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CVS, cardiovascular system; HFPEF, heart failure with preserved ejection fraction; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus.

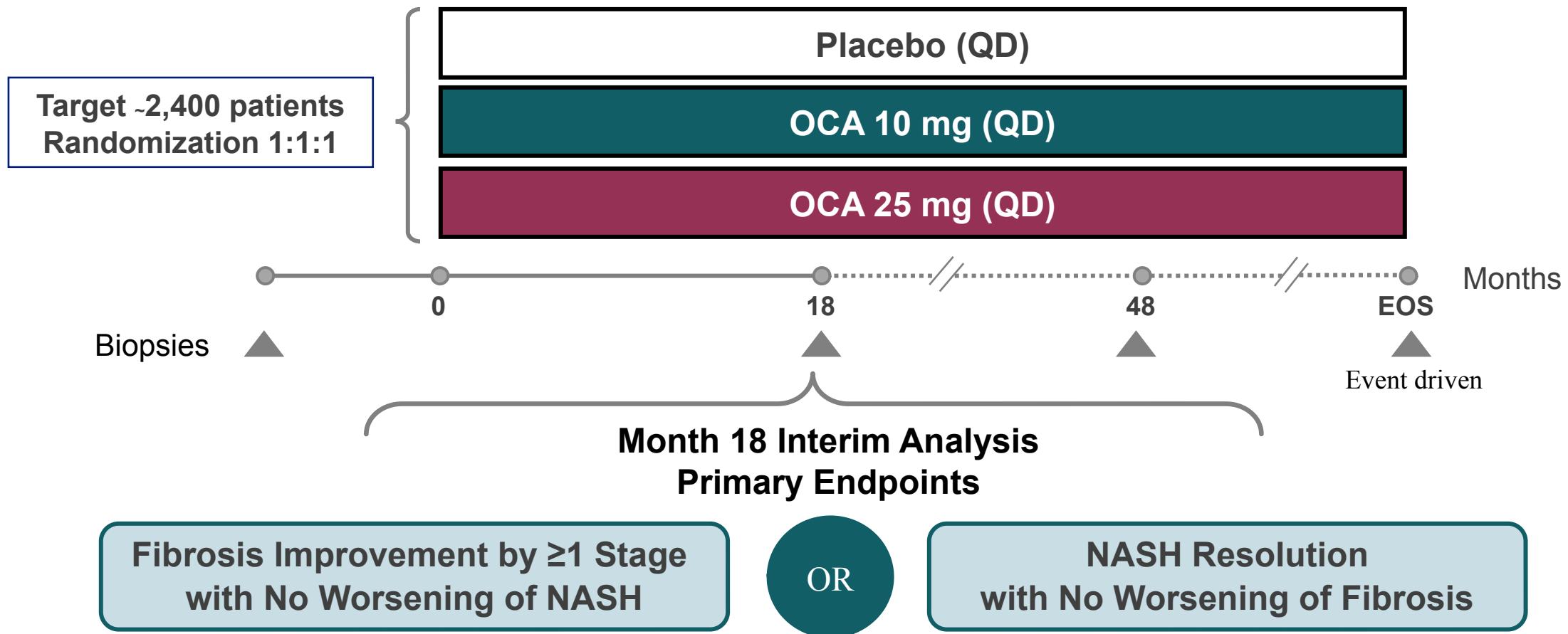
# Profile of frontline therapeutics for pre-cirrhotic NASH

	TZDs	FXR/FGF19	FGF21	Thyroxine B-R	GLP-1
Weight	Gain	Loss/neutral	Loss	?	loss
LDL-C	Increase	Increase	Decrease*	Decrease	neutral
HDL-C	Increase	Decrease	Increase*	Neutral	neutral
TG	Decrease	Decrease	Decrease*	Decrease	neutral
MACE	neutral	?	?	?	Improved
Stabilize GFR	?	?	?	?	Improved
Glycemic control	Improved	neutral	neutral	Neutral**	Improved
Reduce NASH progression	Reduced	Reduced	?	Weak fibrosis improvement	Reduced

# Phase 3 trials

- REGENERATE (OCA)
- RESOLVE-IT (ELAFIBRANOR)
- AURORA (CENICRIVAROC)
- In start up: *Thyroxine Beta receptor (Madrigal, Viking), FABAC (Galmed), FGF19 (NGM)*

# REGENERATE Study Design



**Study success was defined as achievement of one of these two primary endpoints**

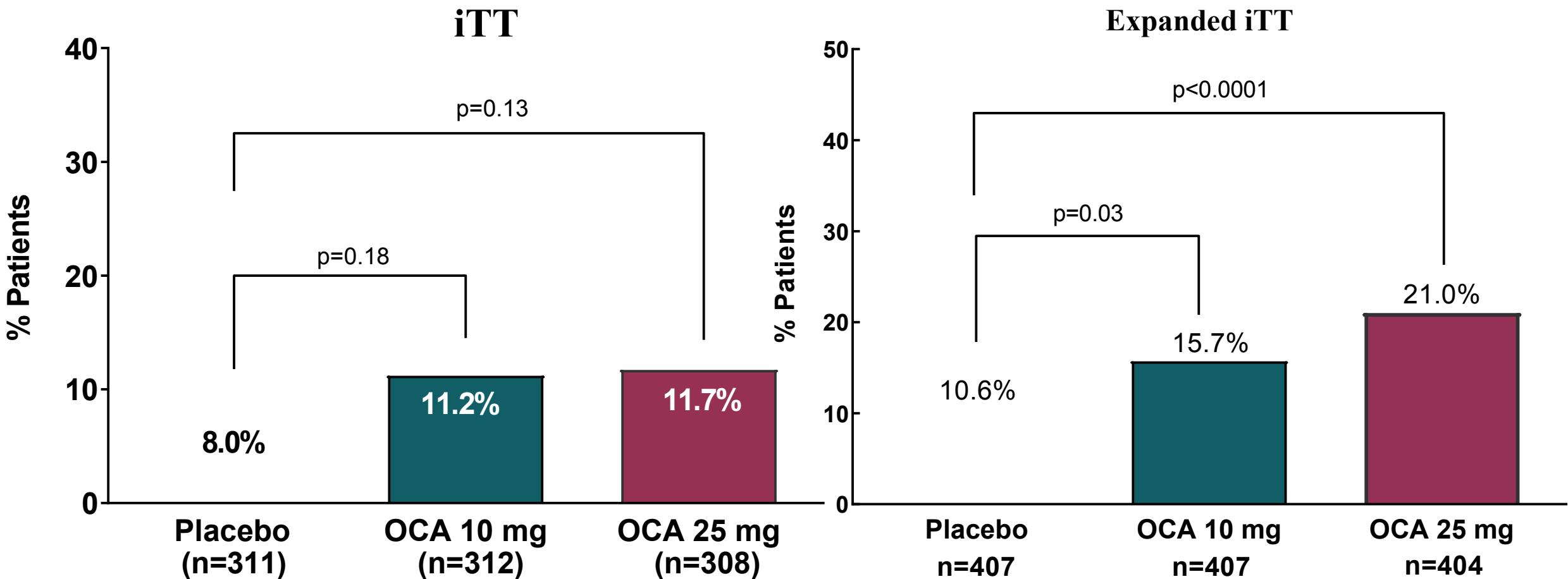
Sanyal et al, Abstract # 34 AASLD 2019

Younossi et al, Lancet 2019

The interim analysis was conducted after 931 randomized patients with fibrosis stage 2 or 3 had or would have reached their actual/planned Month 18 visit (ITT Population). EOS analysis of clinical outcomes to confirm clinical benefit. EOS, end of study; QD, once a day.

# Fibrosis Improvement by $\geq 1$ Stage with No Worsening of NASH

## Primary Endpoint:



Expanded ITT Population, N=1,218.

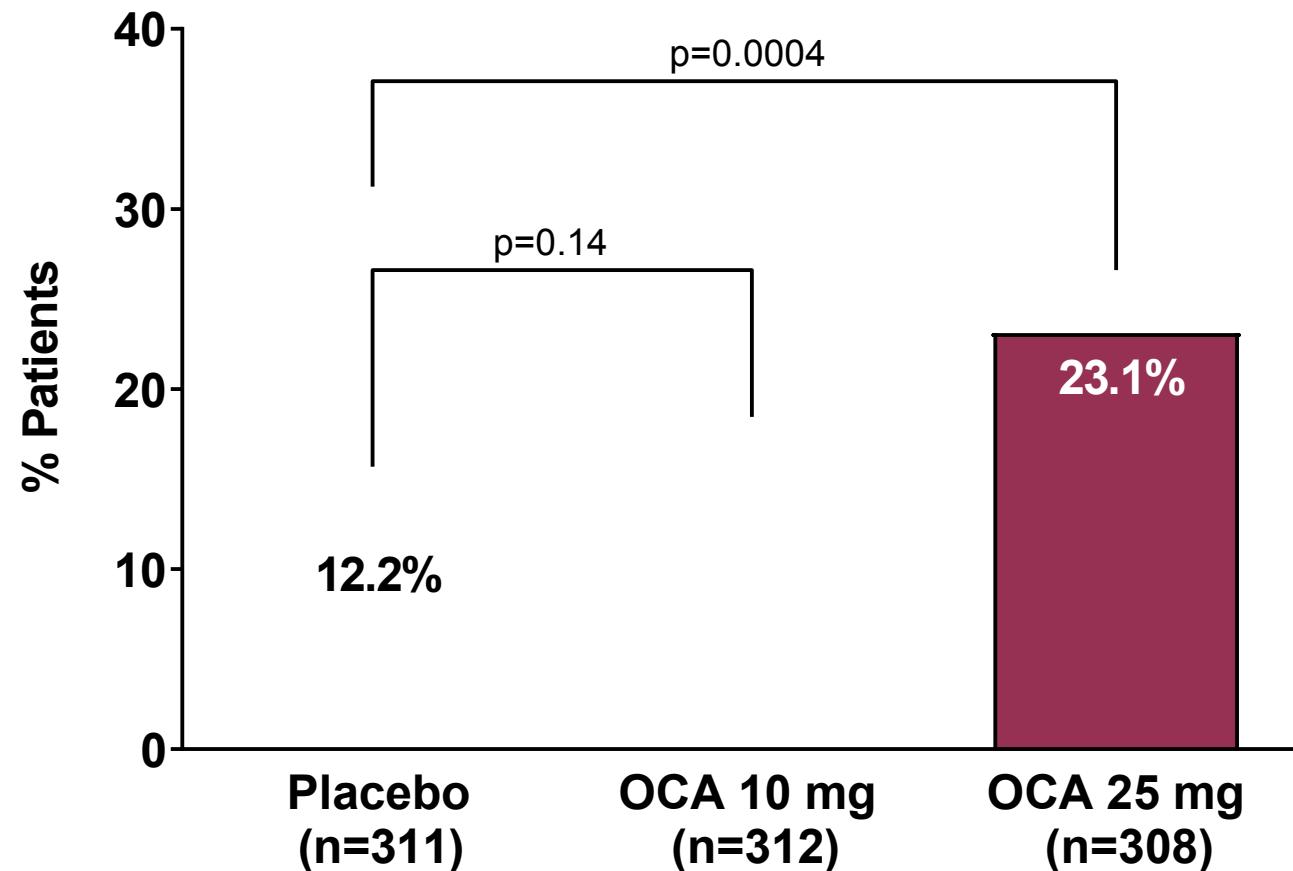
Primary endpoint definition: Fibrosis improvement by  $\geq 1$  stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation, or steatosis).

This primary endpoint was met in the Primary ITT Population.

P values are nominal.

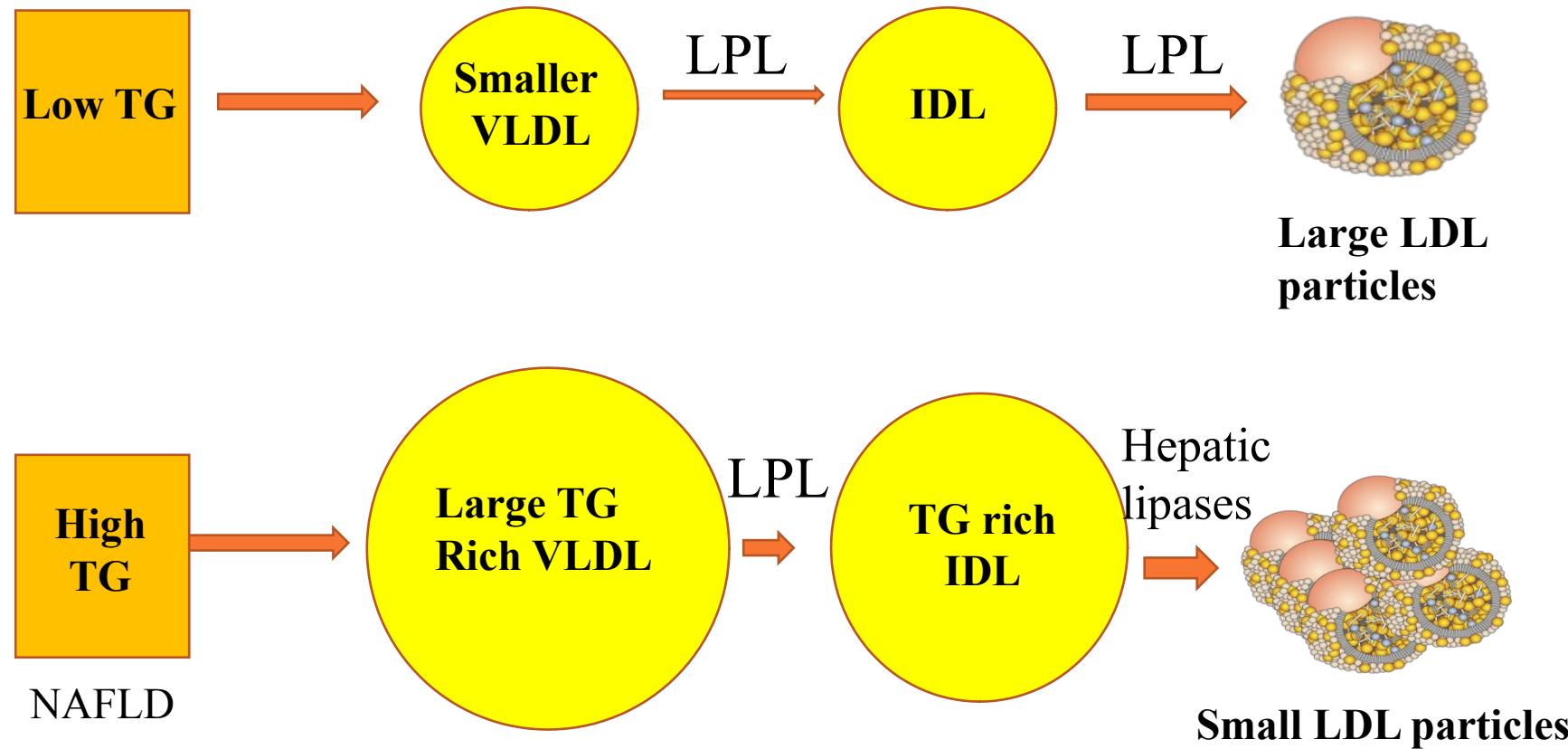
# Resolution of Definite NASH with No Worsening of Fibrosis

*Overall Pathologist Assessment: ITT Population\**

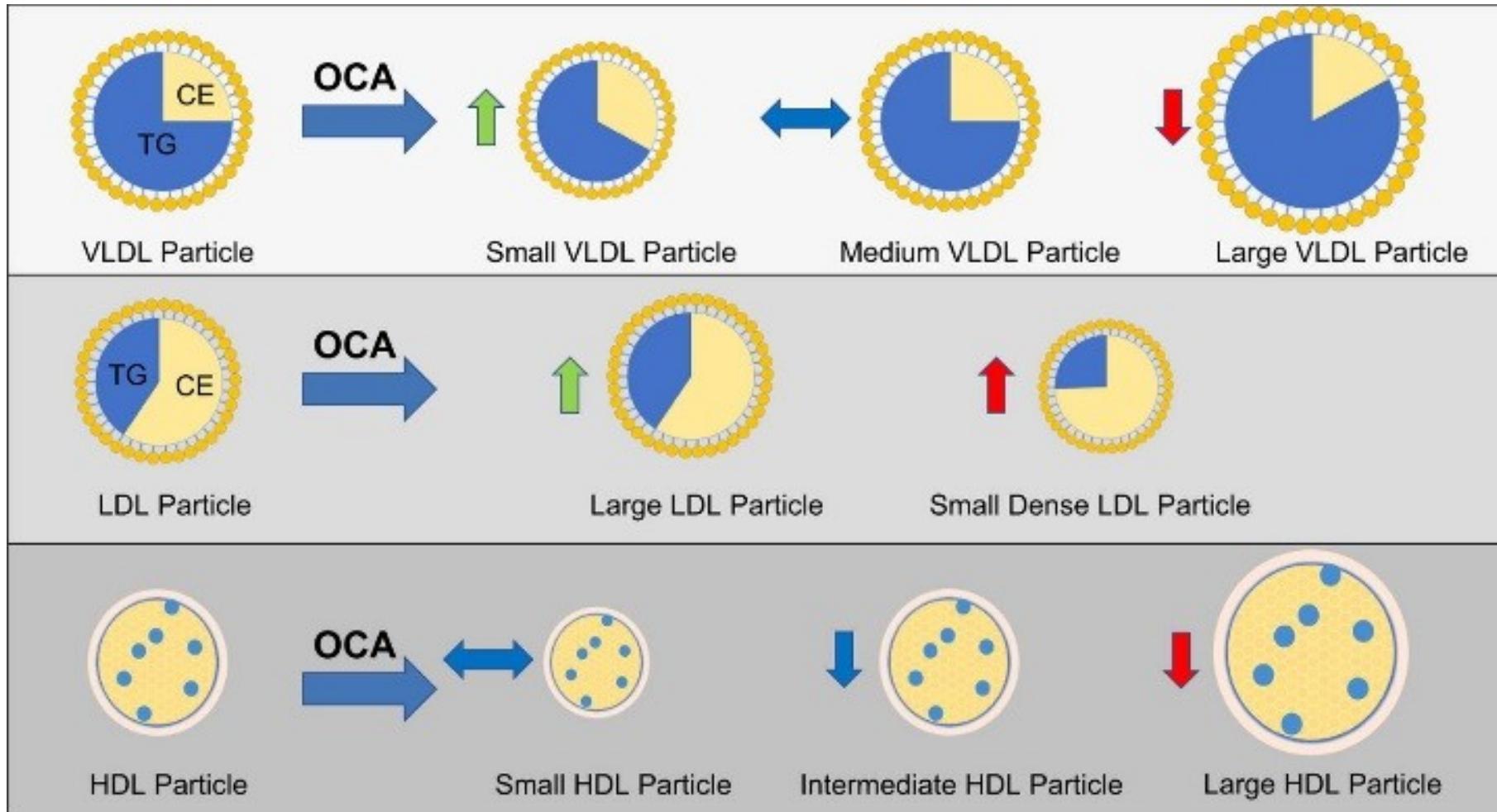


\*Post-hoc analysis with endpoint defined as: (i) overall pathologist assessment of "no steatohepatitis," and (ii) no increase in fibrosis stage from baseline.  
P values are nominal.

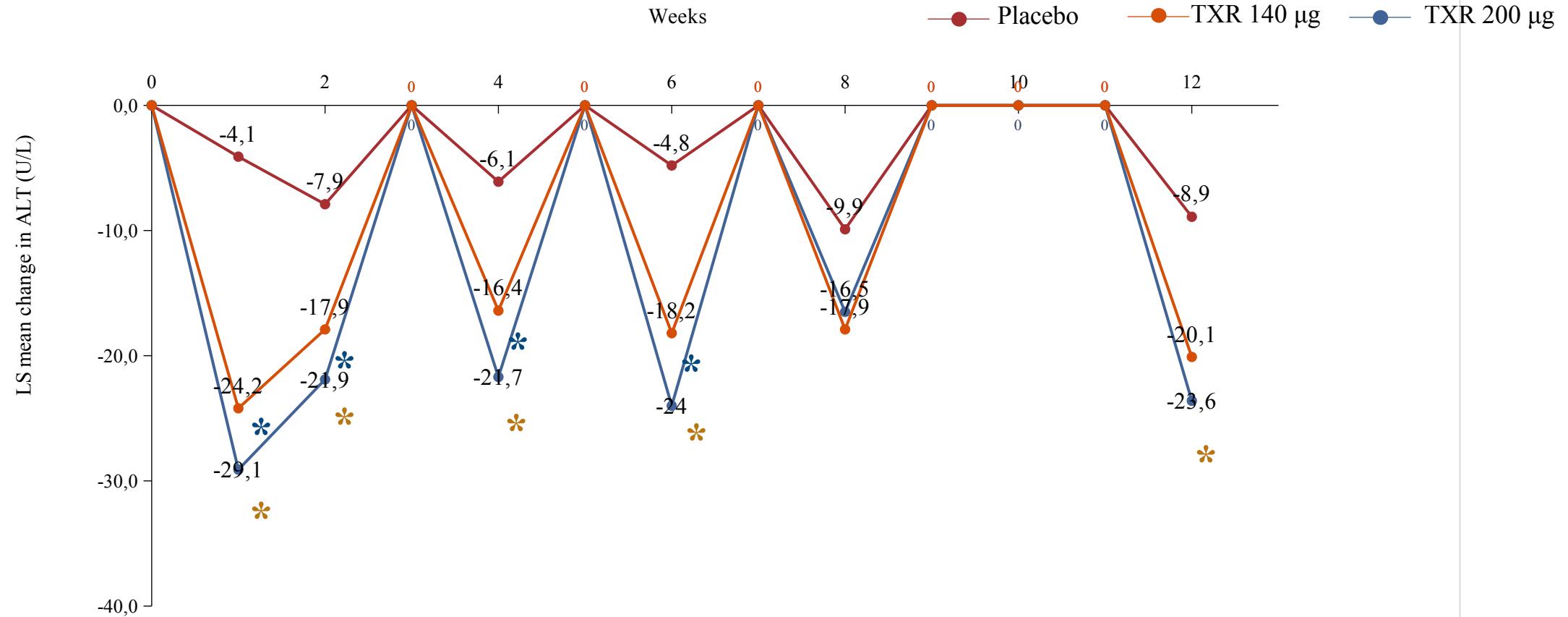
# Steatosis is Central in Development of Atherogenic Lipoproteins



# Impact of OCA on lipoproteins



# Tropifexor- a small molecule FXR agonist also improves ALT



LDL-C INCREASES WITH INCREASING TROPIFEXOR EXPOSURE

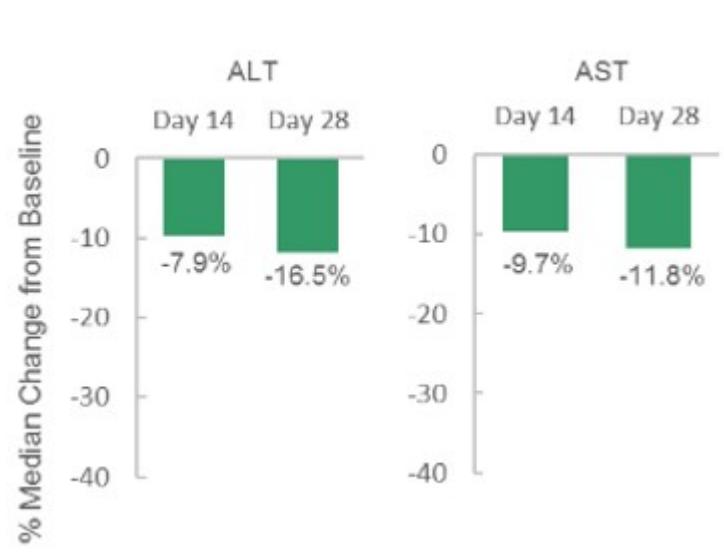
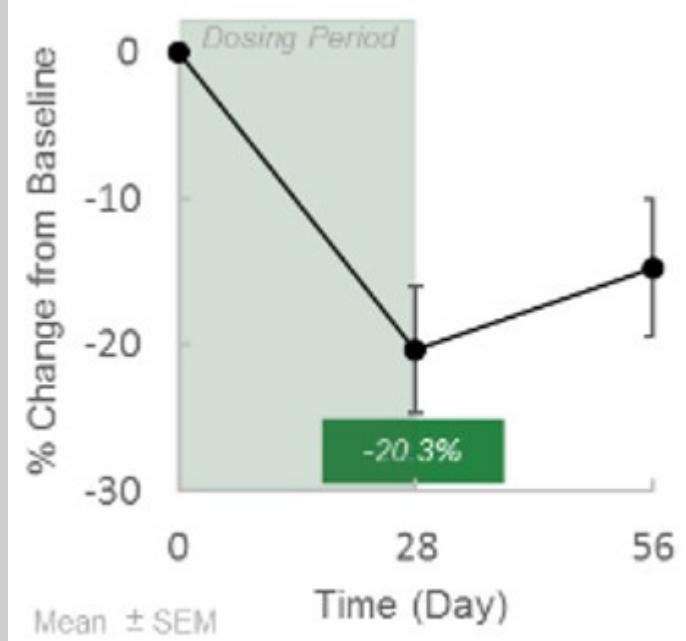
Data are presented as LS mean change (SE) with 2-sided  $P$  values by repeated measures ANCOVA  
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; LS, least square; SE, standard error; TXR, tropifexor; W, week

Sanyal et al, AASLD 2019  
23

# 28 day Phase 1b data for FXR agonist MET409 [Metacrine]

MET409 reduced hepatic fat and improved liver function in an open label study of 10 NASH patients treated with a 50 mg QD dose.

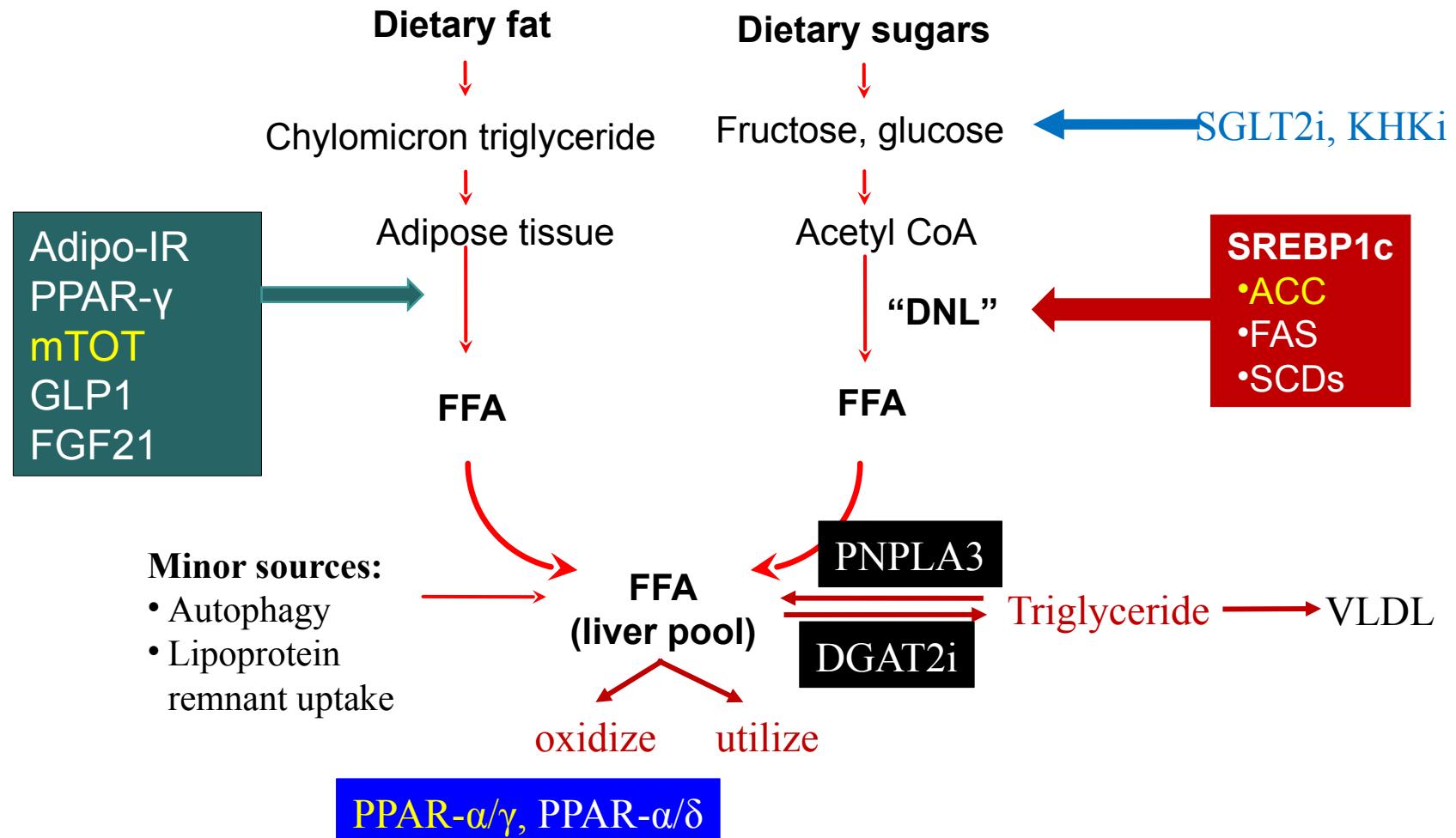
No increase in LDL or pruritus noted.



# Phase II and drugs in early development

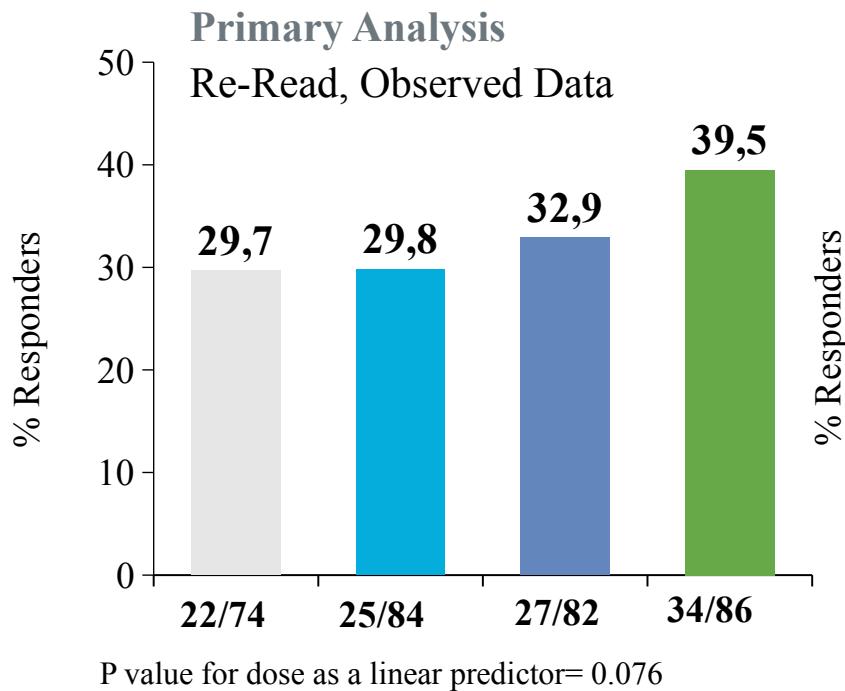
FGF-21 (PEGBELFERMIN) AND SEMAGLUTIDE ARE SCHEDULED TO READ OUT IN 2020

# Metabolic substrate loading promotes energy storage as triglyceride

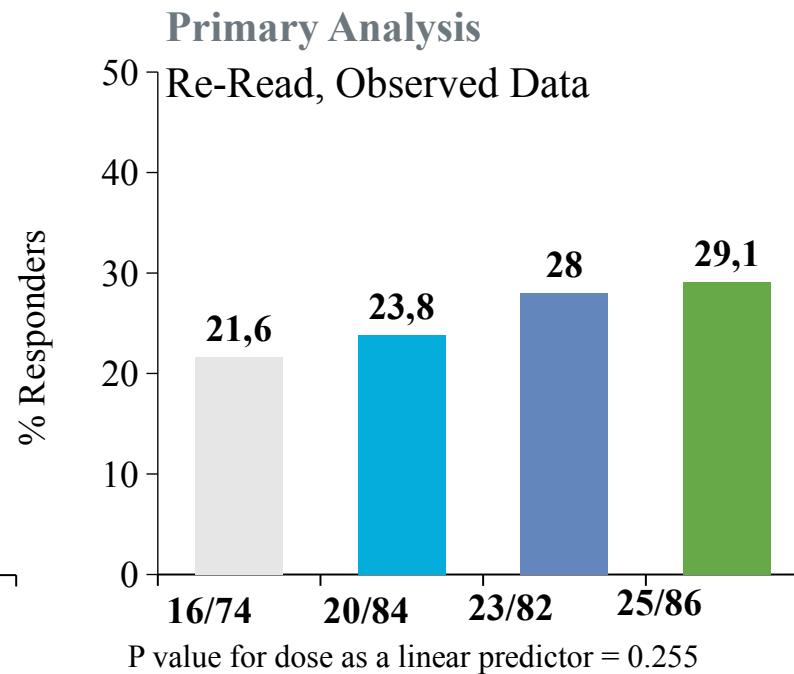


# Results of MSDC-0602K in a large Phase 2b NASH study demonstrate improvement in markers of insulin resistance, glucose metabolism, serum aminotransferases, non invasive markers of NASH and histopathology

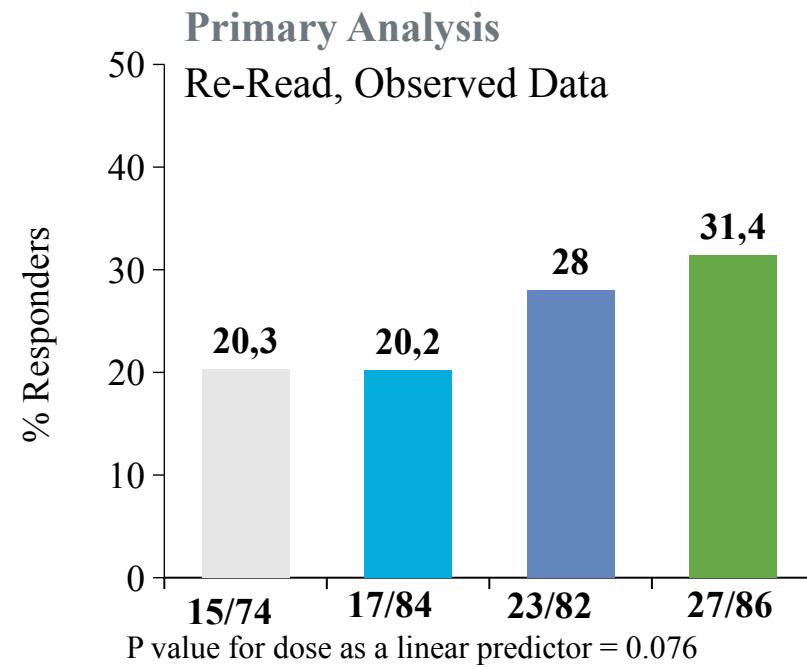
## Histological Improvement (2 point) in NAS with no Worsening of Fibrosis



## Improvement of Fibrosis with no worsening of NASH



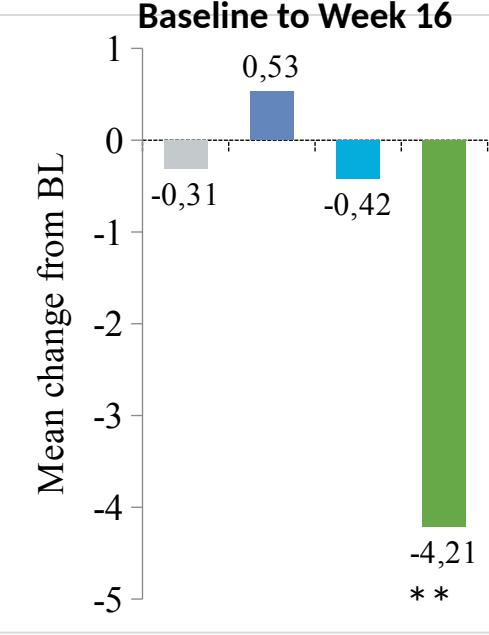
## Resolution of NASH\* no worsening of fibrosis- Old Definition



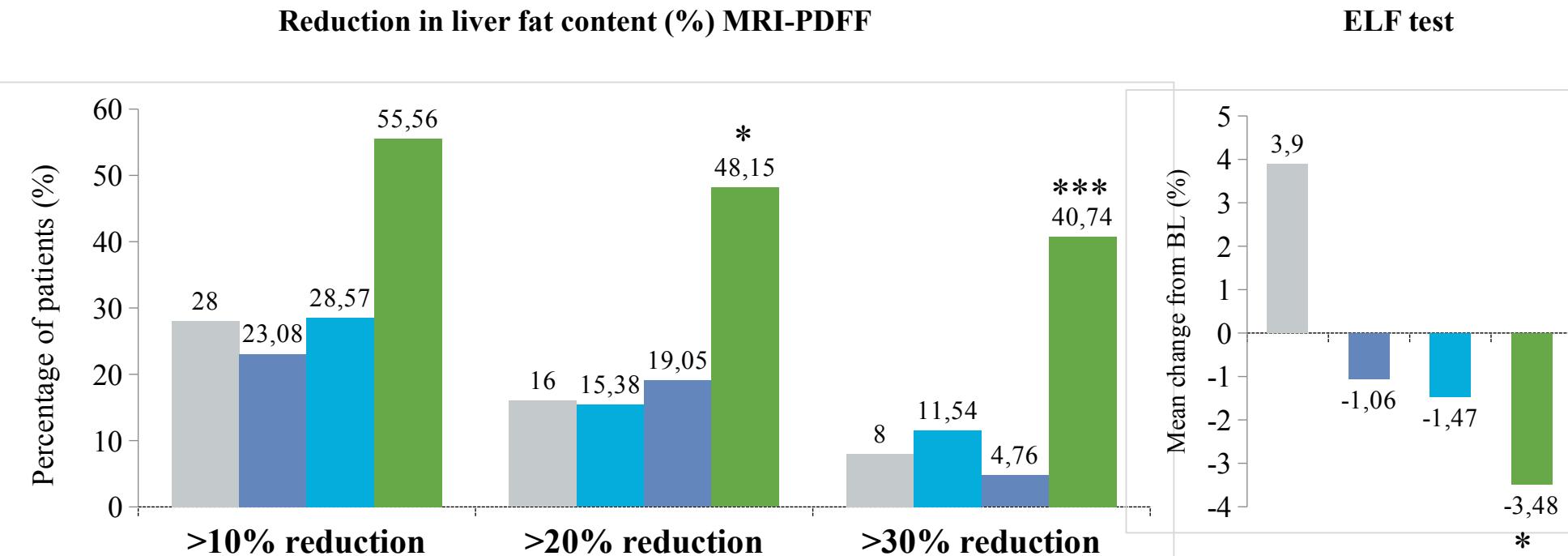
\*Resolution of NASH is defined as a ballooning score of 0 and an inflammation score of 0-1 without worsening of fibrosis.

**A Phase 2, prospective, multicenter, double-blind, randomized study of saroglitazar magnesium 1 mg, 2 mg or 4 mg versus placebo in patients with nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis (evidences iv)**

Absolute change in liver fat content (%) by MR-PDFF from Baseline to Week 16



Reduction in liver fat content (%) MRI-PDFF

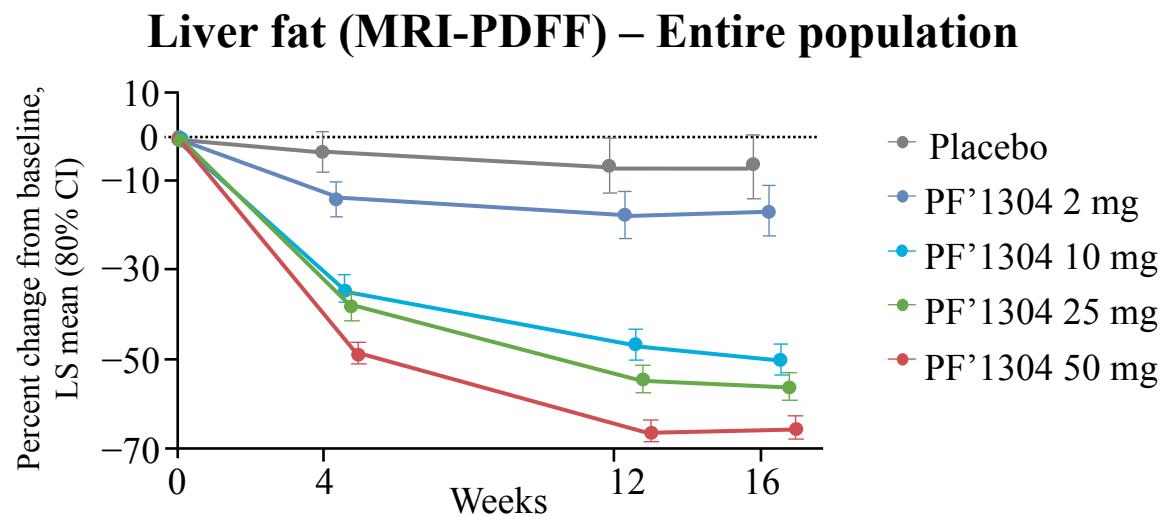


\*p≤0.05, \*\*p≤0.01, \*\*\*p≤0.001.

■ Placebo (n=28) ■ Saro 1 mg (n=26)  
■ Saro 2 mg (n=23) ■ Saro 4 mg (n=27)

**Non-significant trend toward reduced CK-18 and transient elastography**

# PF-05221304 (PF'1304), a liver-targeted acetyl-coa carboxylase inhibitor (ACCI), in adults with NAFLD demonstrates robust reductions in liver fat and ALT – Phase 2a, dose-ranging study

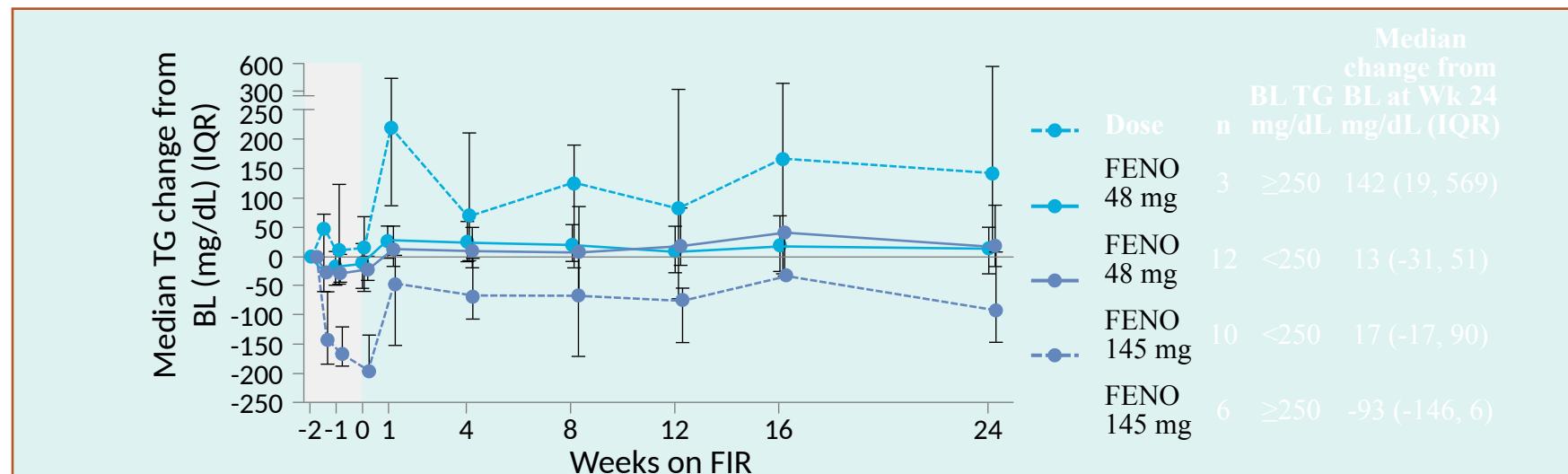
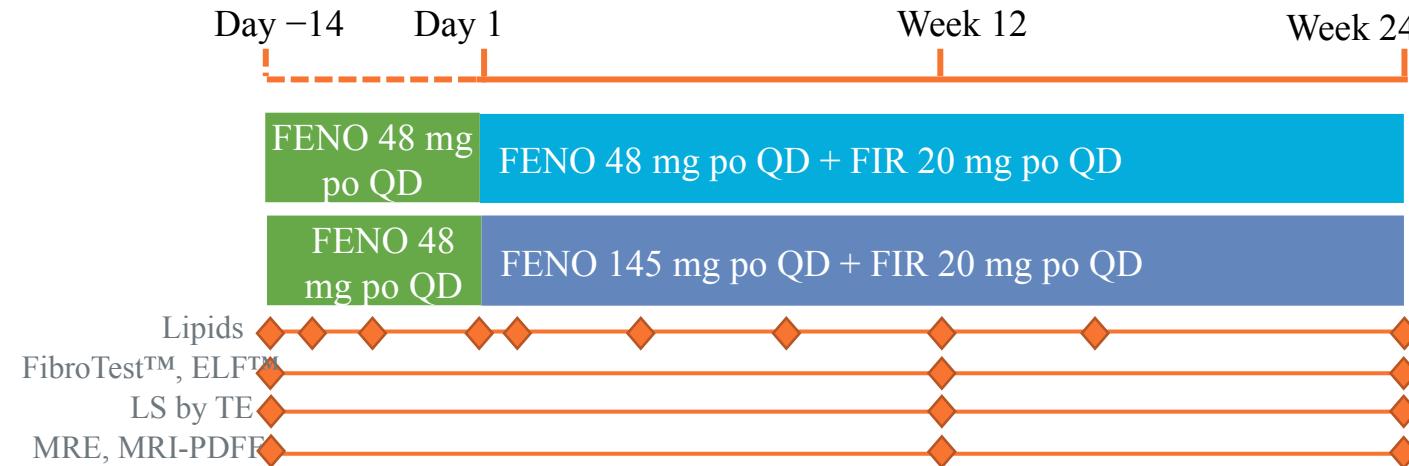


Proportion of patients who achieved relative reduction in MRI-PDFF  $\geq 30\%$  at Week 16

Treatment arm	Percentage
Placebo	6%
PF'1304 2 mg QD	22%
PF'1304 10 mg QD	74%
PF'1304 25 mg QD	87%
PF'1304 50 mg QD	90%

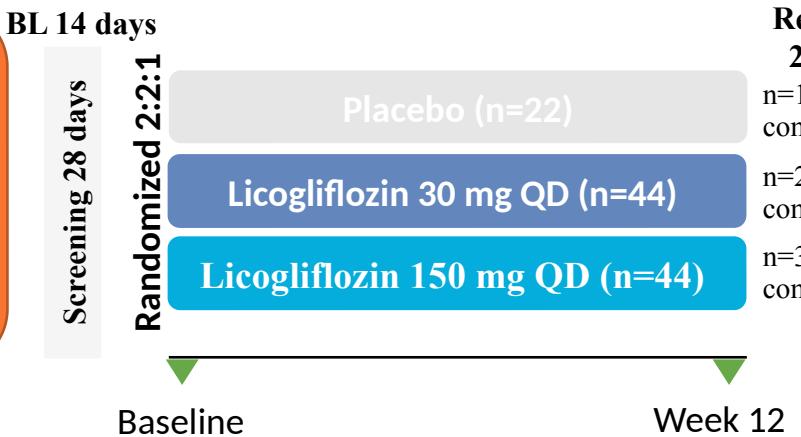
However, triglycerides increased and there was increased alk phos and GGT

# Fenofibrate mitigates increases in serum triglycerides due to the ACC inhibitor firsocostat in patients with advanced fibrosis due to NASH: a Phase 2 randomized trial

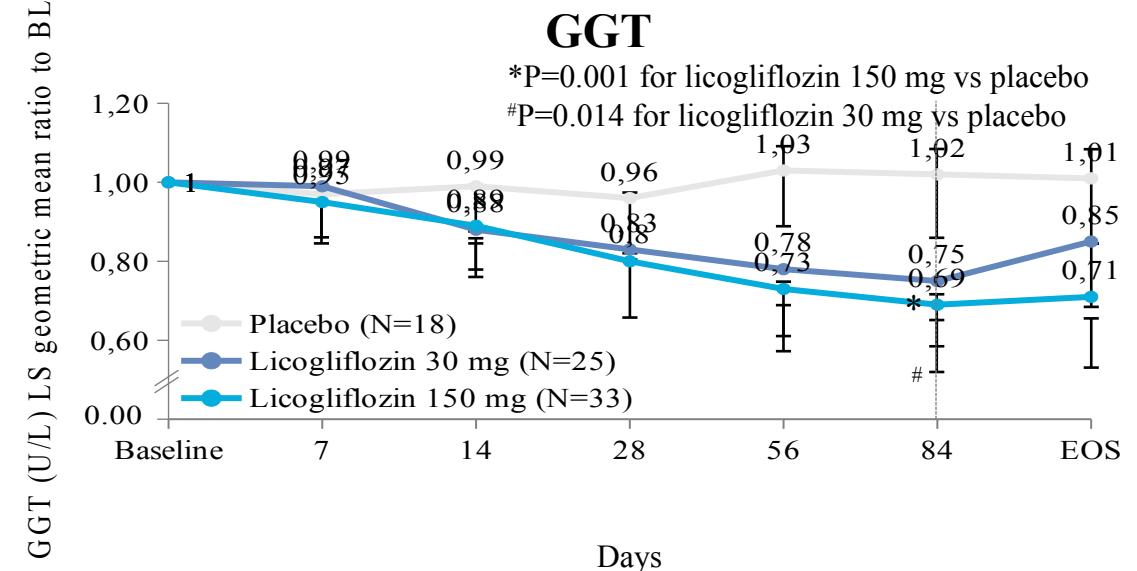
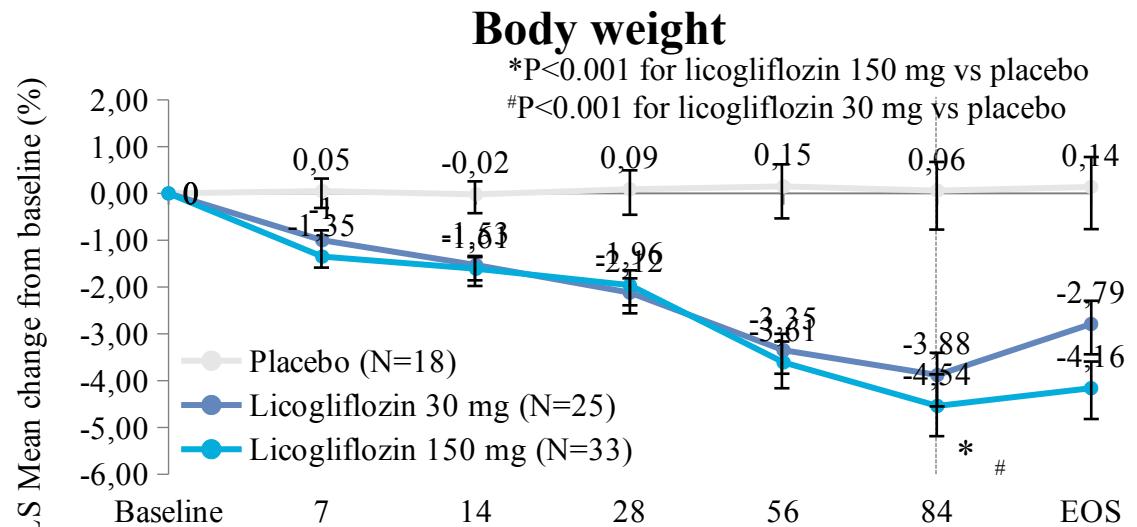
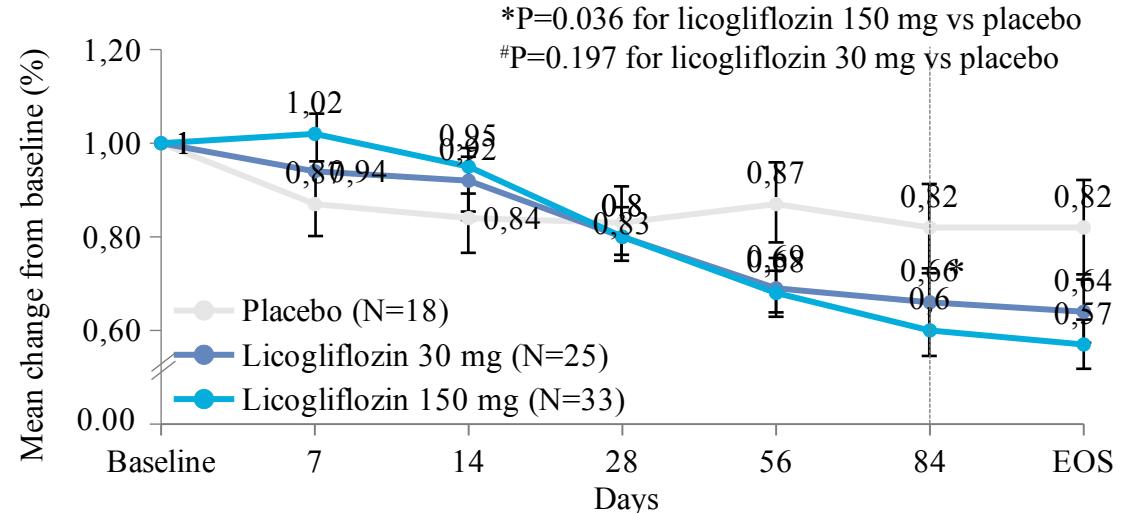


LIK066 (licogliflozin), an SGLT1/2 inhibitor, robustly decreases ALT and improves markers of hepatic and metabolic health in patients with non-alcoholic fatty liver disease: interim analysis of a 12-week, randomized, placebo-controlled, Phase 2a study

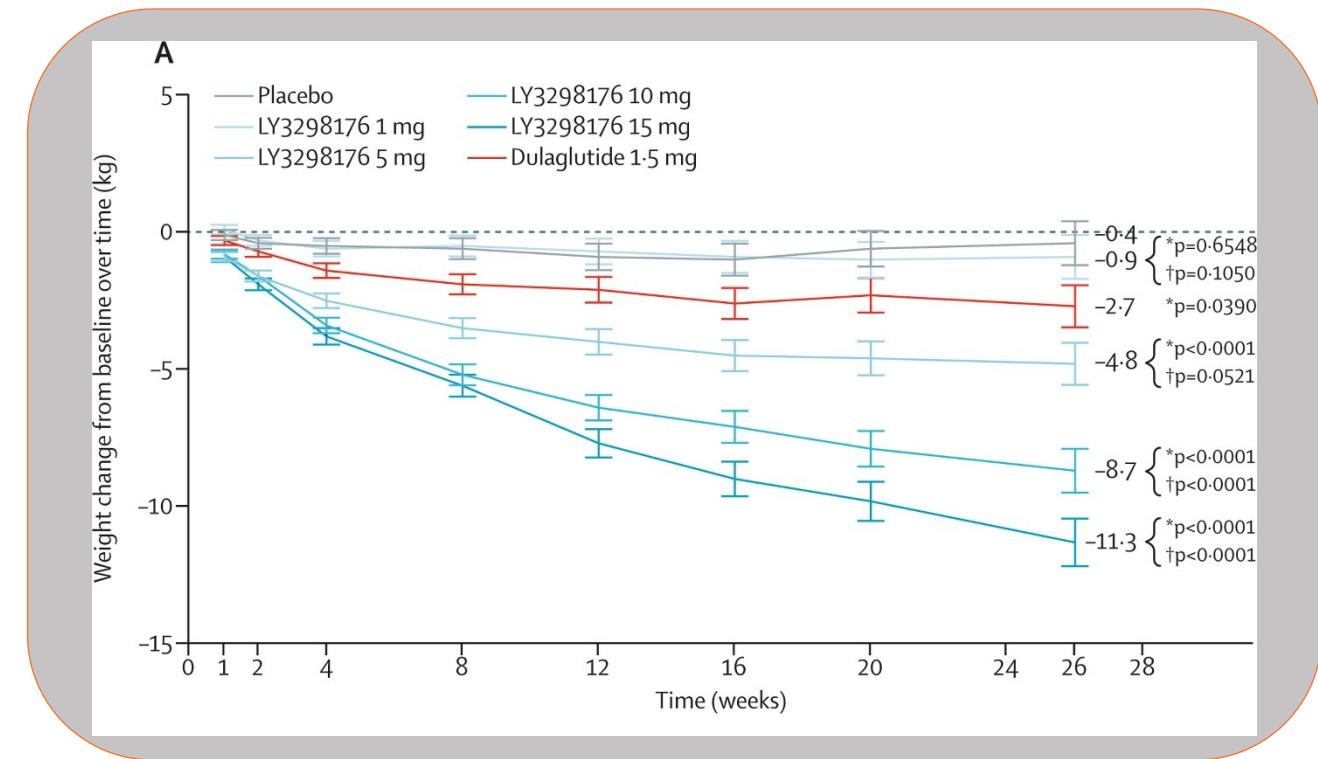
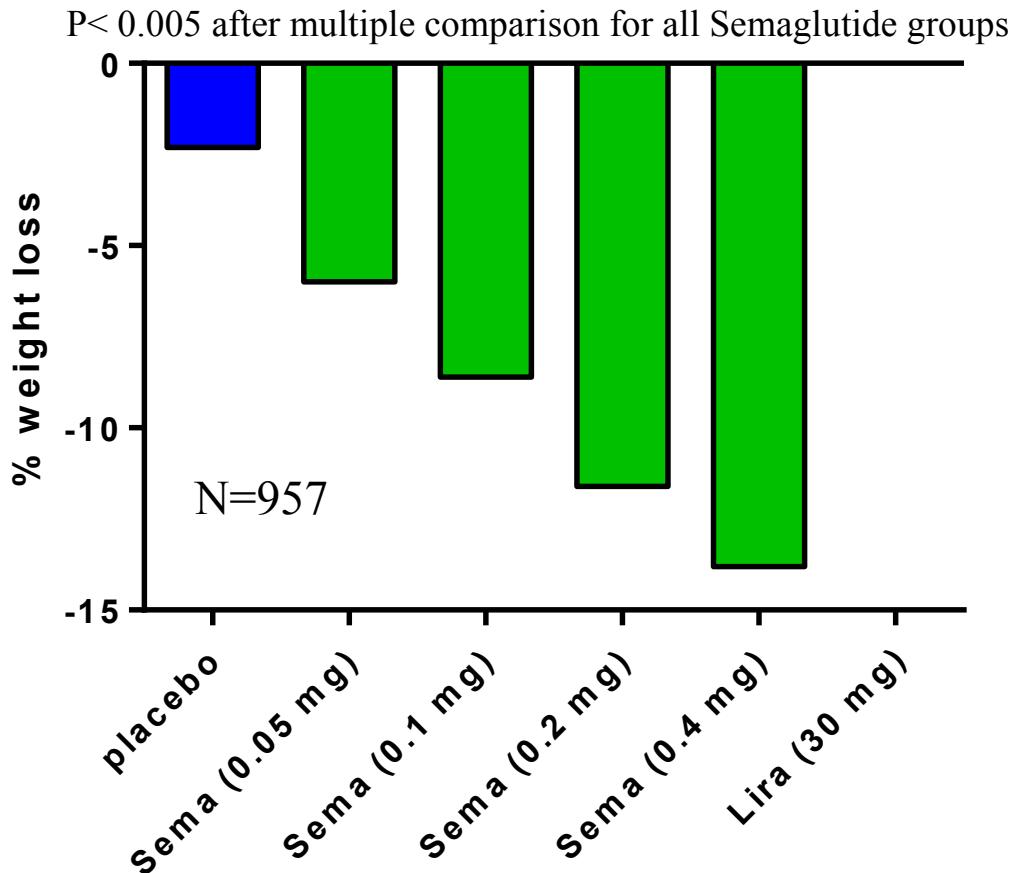
110 enrolled subjects with histologically confirmed or phenotypic NASH (BMI  $\geq 27\text{ kg/m}^2$  in non-Asians or  $\geq 23\text{ kg/m}^2$  in Asians, ALT  $\geq 35$  (females) and T2D)



**Primary endpoint: Change in ALT up to Week 12**



# GLP-based therapeutics are coming- need to see if the evidence lives up to the hype

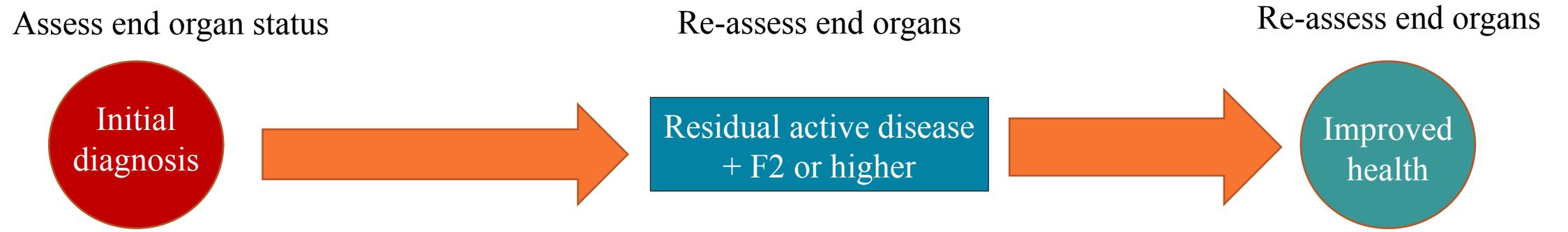


GLP-1/GIP agonist (terzepatide)

O'Neill et al, *Lancet*. 2018 Aug 25;392(10148):637-649.

Frias et al, *Lancet*, in press 2018  
<https://doi.org/10.1016/S0140-6736>

# NASH management paradigm in next decade



## Start:

- Weight loss regimen-drugs are second line
- Statins/fibrates vs Saroglitazar
- SGLT2i + GLP-1 agonist (as indicated)

## Targeted therapy for:

- Active NASH
- F3/F4
- Enhance healthy living/stop weight loss meds

## Improved:

- mortality
- health care cost
- function
- QOL

# THANK YOU FOR YOUR ATTENTION



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