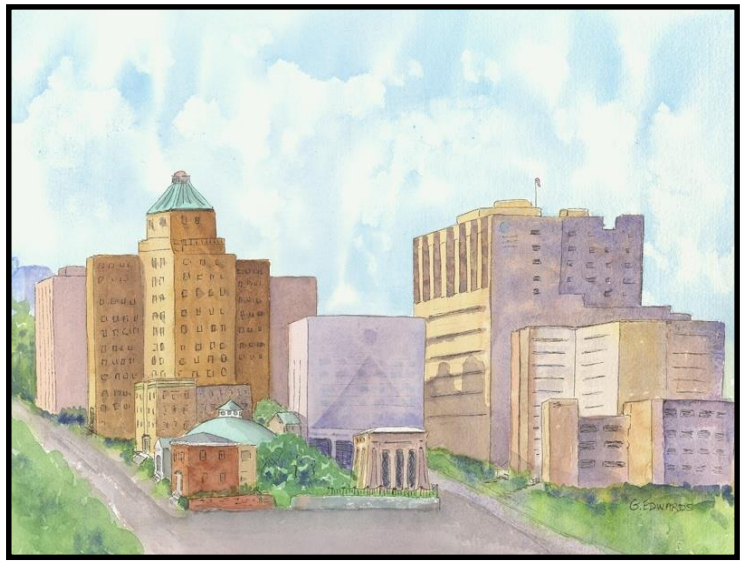
CURRENT TREATMENTS IN DEVELOPMENT FOR NASH



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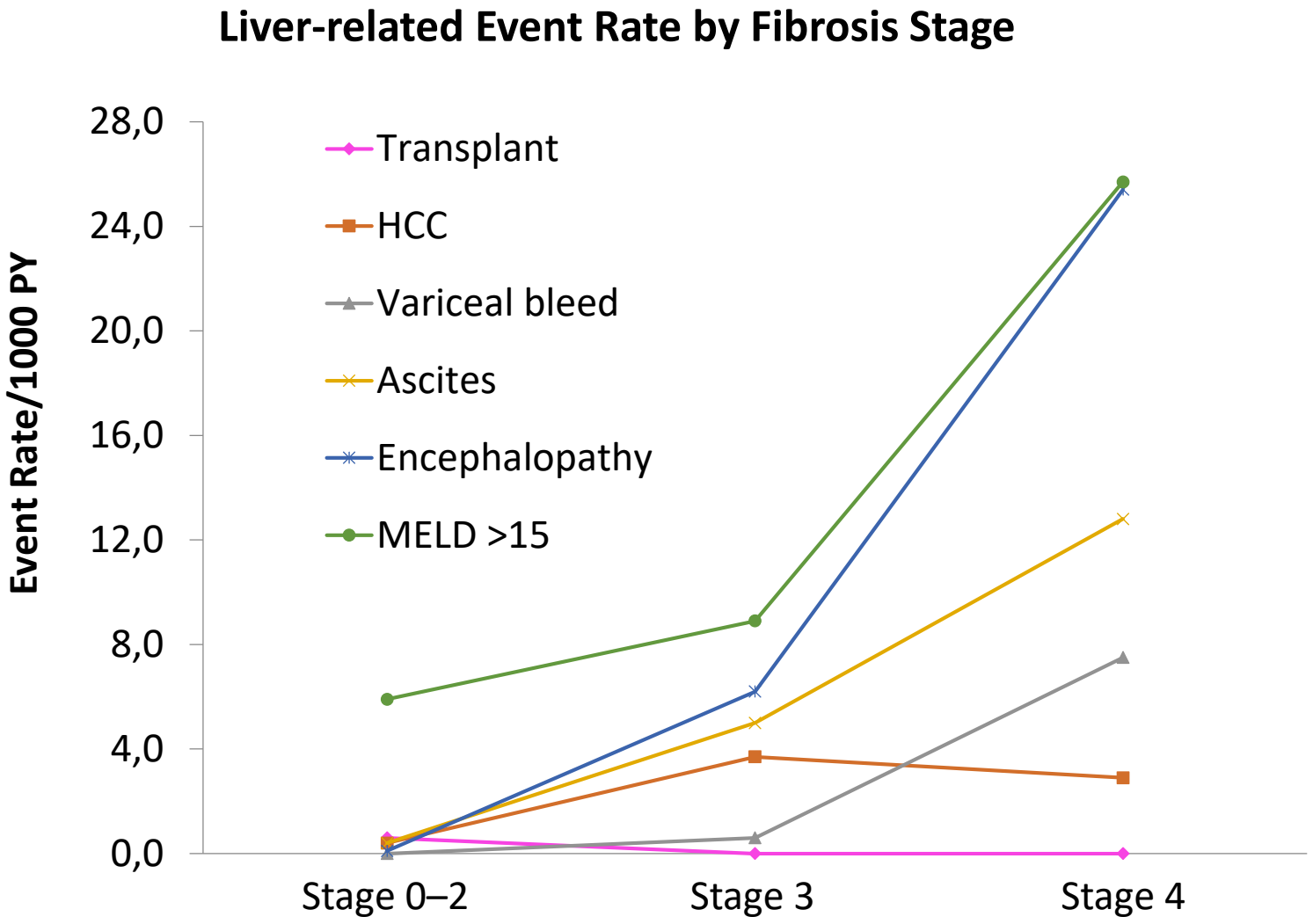
Conflicts of Interest

- 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 Ingelhiem*, 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 Ingelhiem

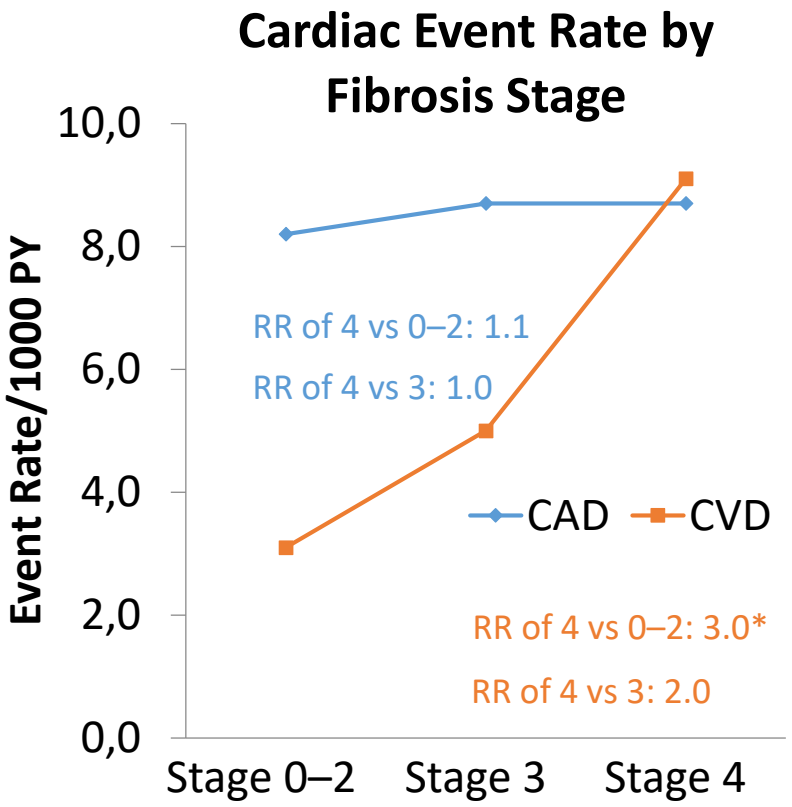
* *no financial remuneration in last 24 months*

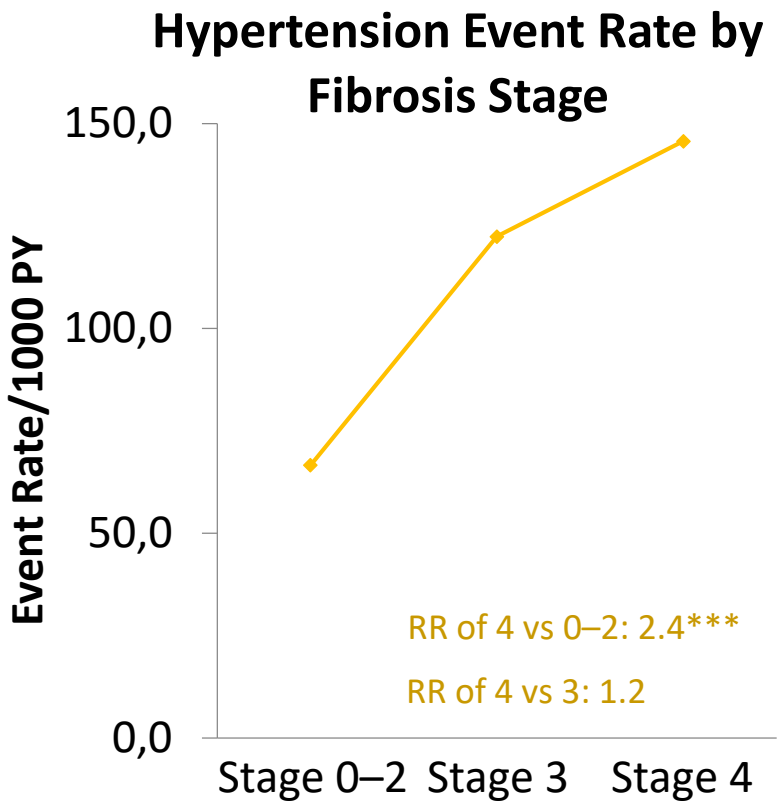
A prospective analysis of clinical outcomes across the full spectrum of NAFLD

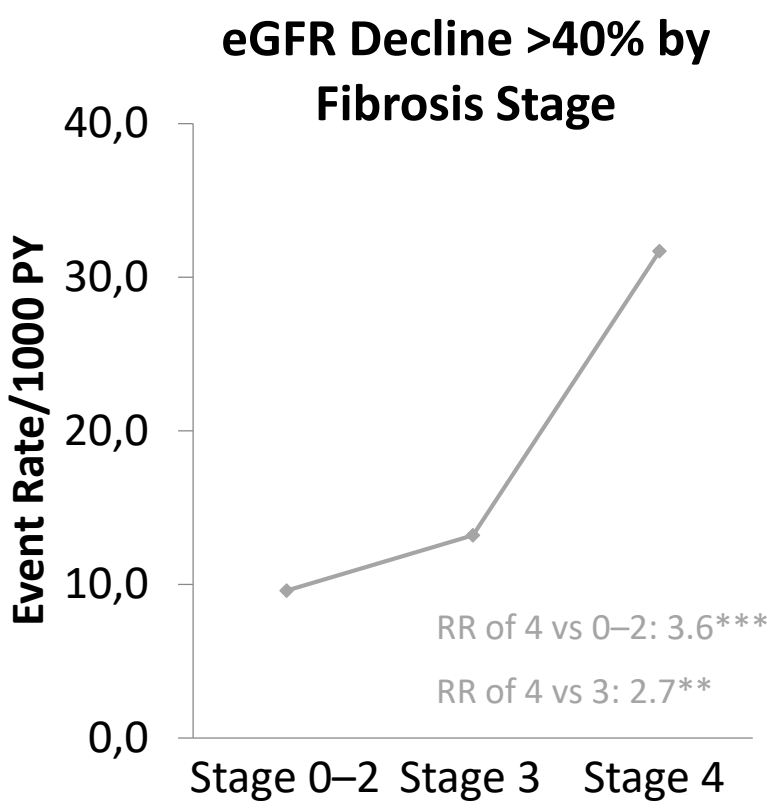


Sanyal A, et al. AASLD 2019, Boston, USA. #1190

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





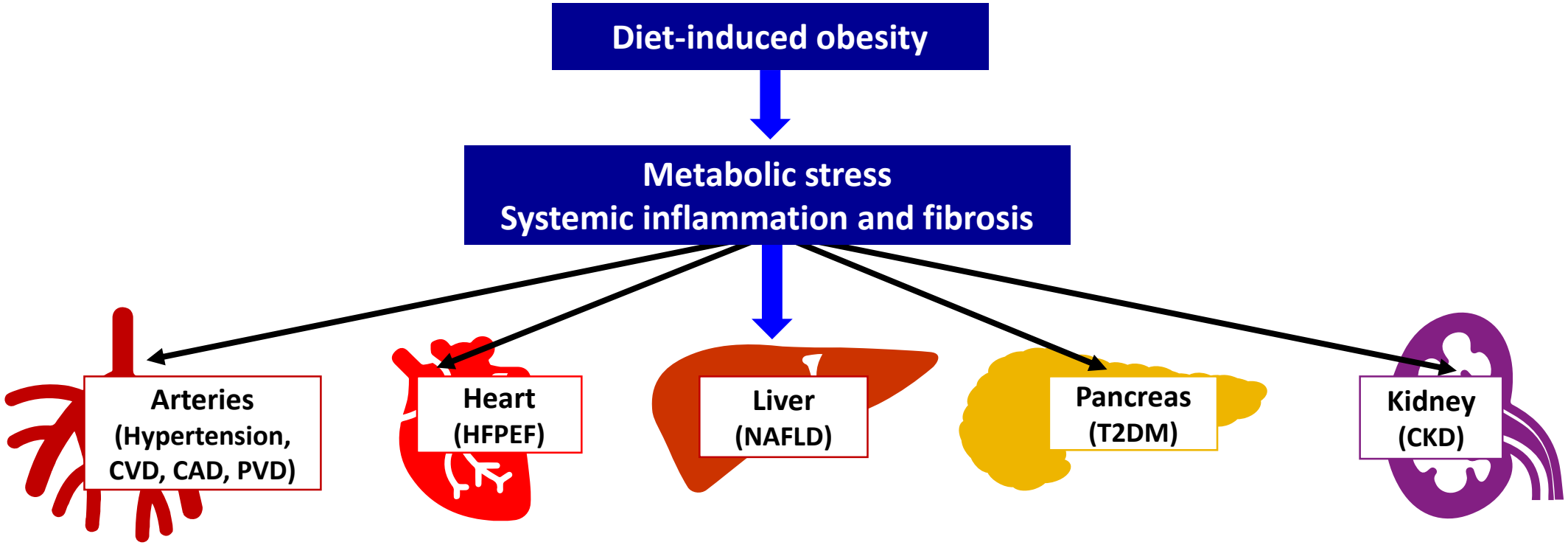


*p<0.05; **p<0.01; ***p<0.001

- 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

Sanyal A, et al. AASLD 2019, Boston, USA. #1190

NASH is part of a multi-system disorder



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

- Weight loss
- SGLT2i

- Weight loss
- GLP-1
- ?SGLT2i

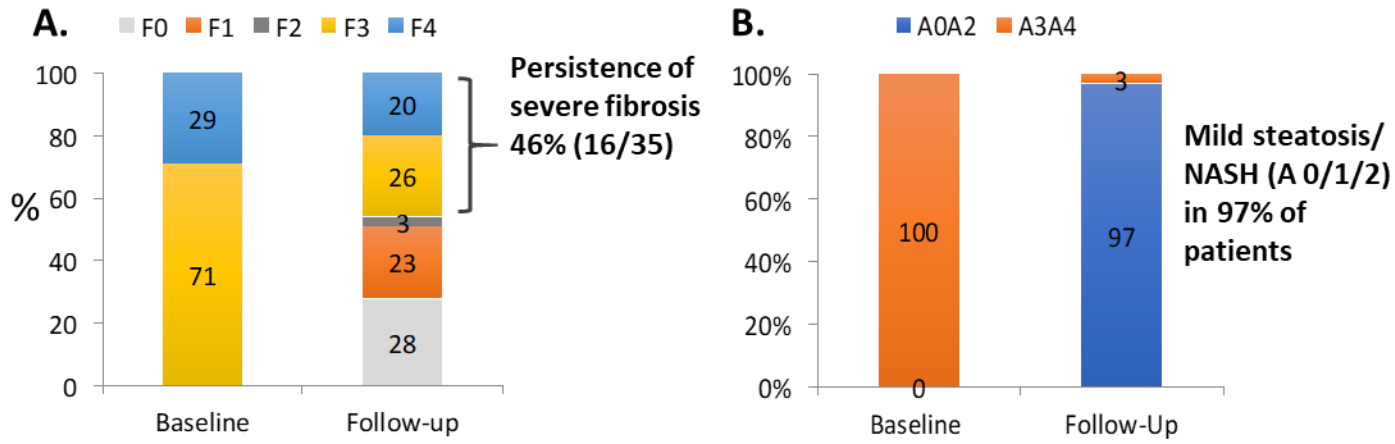
- Weight loss
- ARBs
- Metformin
- GLP1
- SGLT2i

- Weight loss
- ARBs
- SGLT2i
- GLP1

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.

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

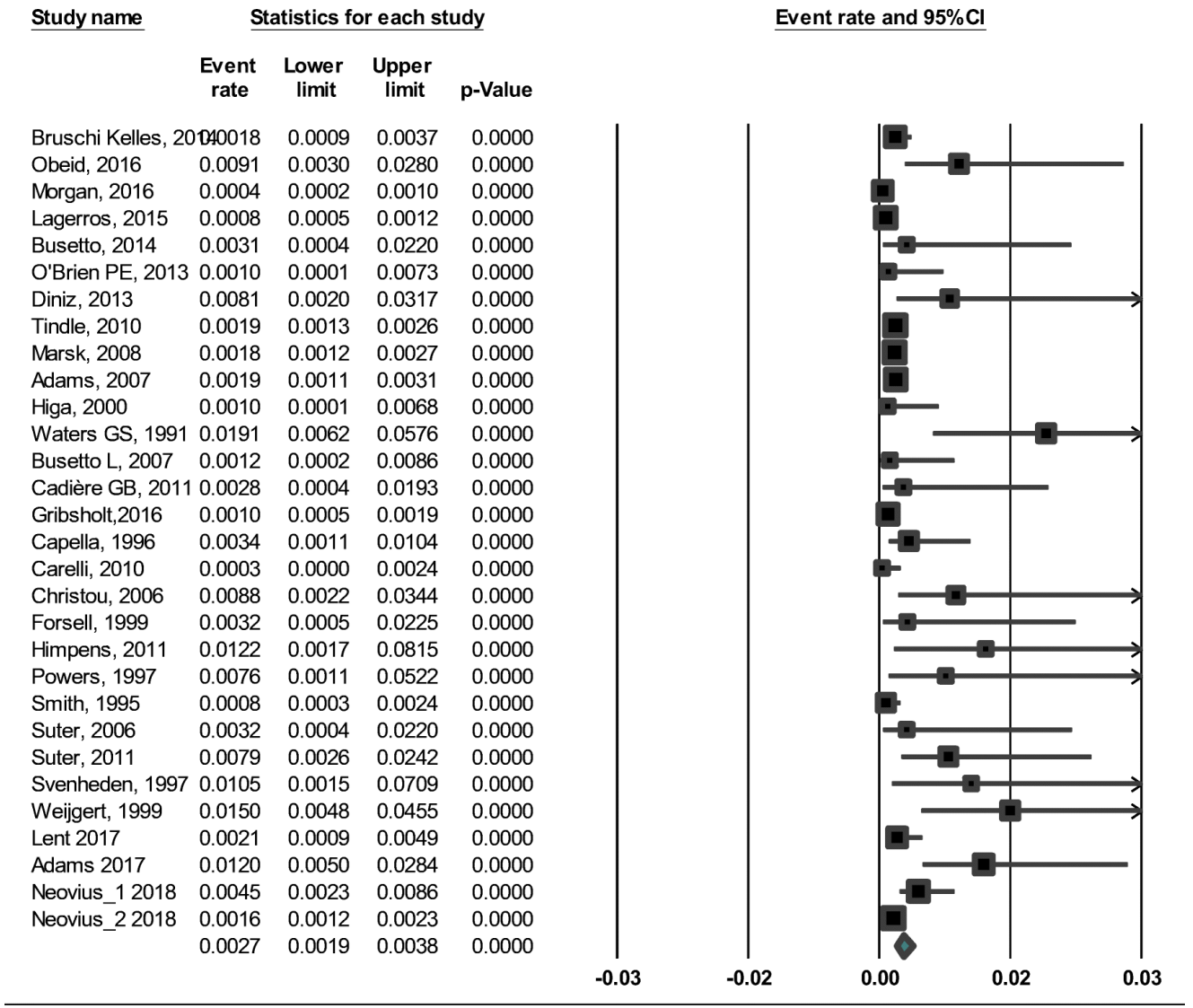
	OR, 95% CI	P
Age	1.083 (0.98 – 1.18)	0.089
Sex	1.12 (0.3 – 4.25)	0.85
Weight loss	1.007 (0.96 – 1.05)	0.76
T2DM regression	0.68 (0.15 – 2.94)	0.60
Gastric by-pass	**0.20 (0.053 – 0.782)**	**0.02**

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

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

Pais et al, Abstract # 42, AASLD 2019

Suicide risk is increased after bariatric surgery



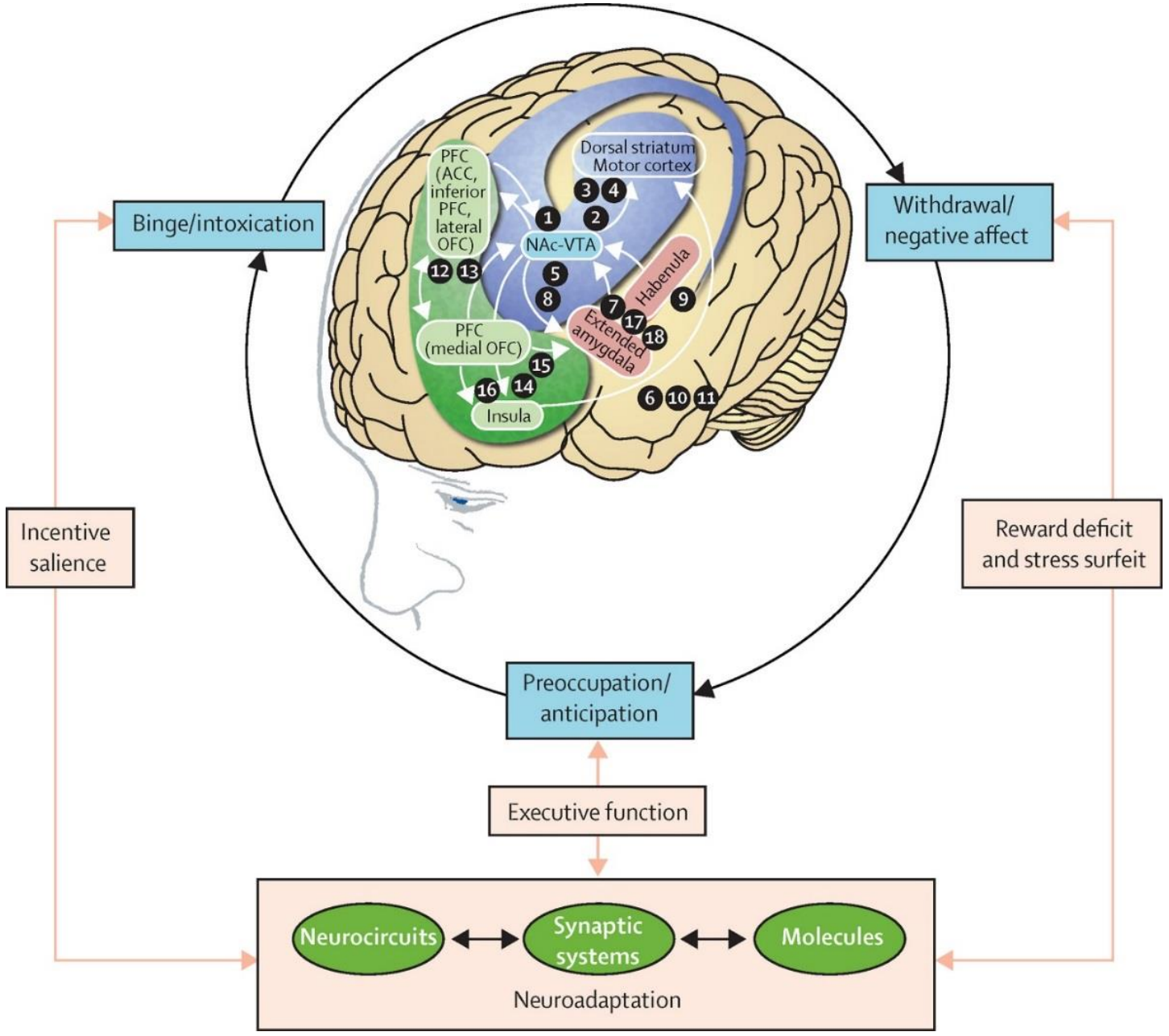
Obes Surg. 2019 Jan;29(1):322-333. doi: 10.1007/s11695-018-3493-4.

Binge/Intoxication

↑ Dopamine
↑ Opioid peptides
↑ Serotonin
↑ GABA
↑ Acetylcholine

Preoccupation/ Anticipation

↑ Dopamine
↑ Glutamate
↑ Hypocretin
↑ Serotonin
↑ CRF



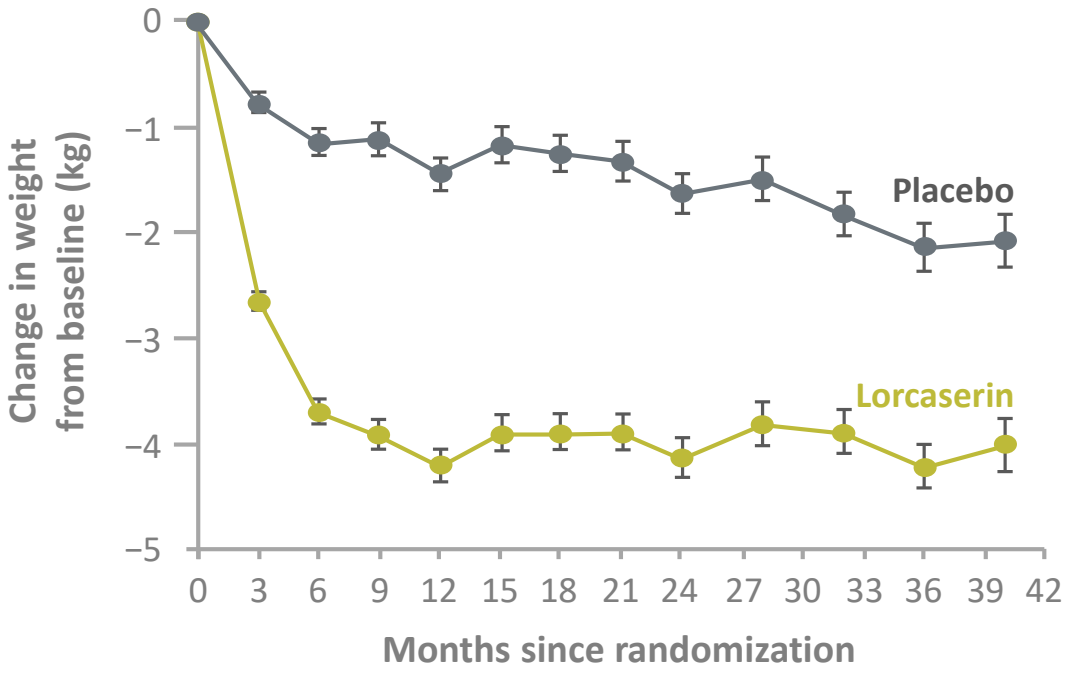
Withdrawal/ Negative Affect

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

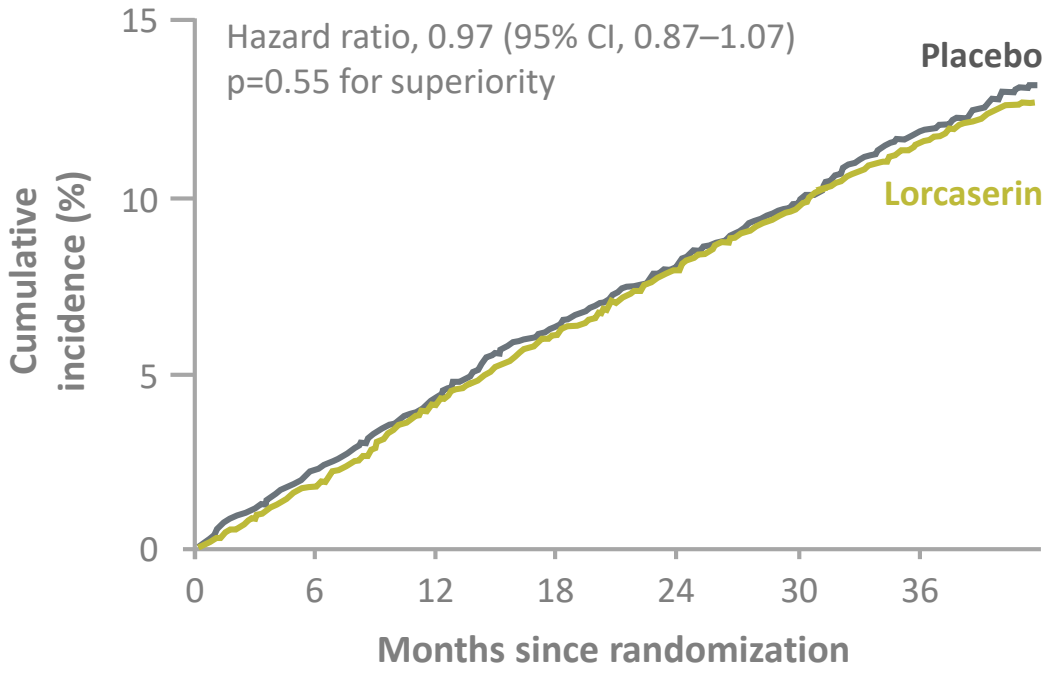
Koob, Volkow, 2017

Addiction circuitry and weight loss enhancement

Weight loss



Major cardiovascular events



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

Bohula EA, et al. *N Engl J Med* 2018;379:1107−17.

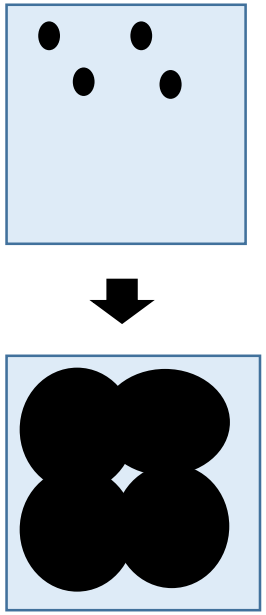
Simple “non-toxic” and “non-wallet busting” approaches need further assessment

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

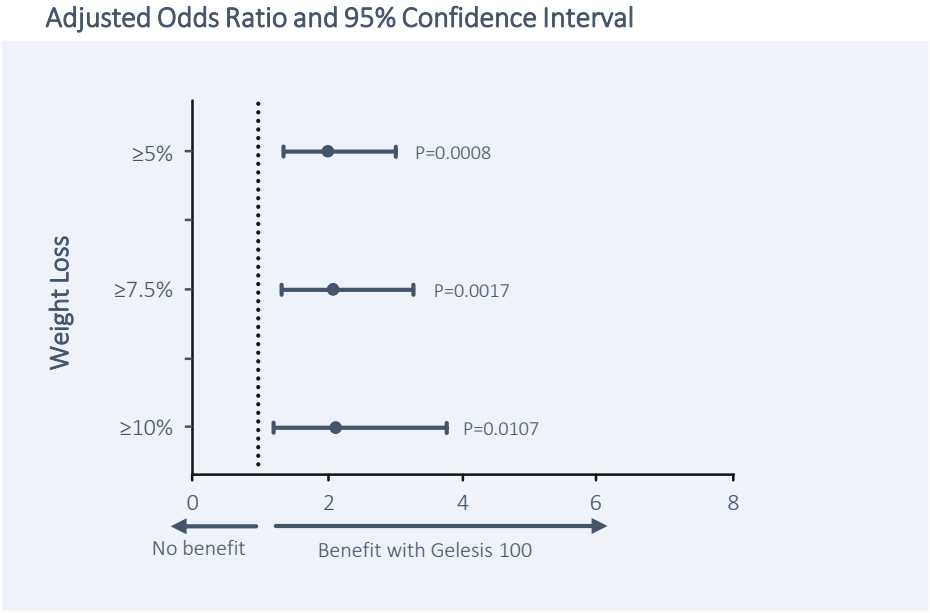
Grossman et al, Journal of Psychosomatic Research 57 (2004) 35 – 43

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



Percent responders with ≥ 5% (P = 0.0008), ≥ 7.5% (P = 0.0017), or ≥ 10% (P =0.0107) weight loss in all patients.

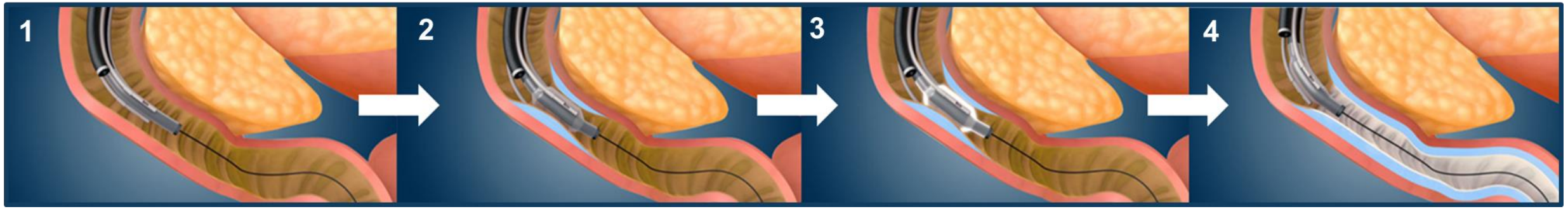
*P < 0.05; **P < 0.001. All P values are from logistic regression models adjusted for baseline weight and stratification factors.



Adjusted odds ratio for achieving ≥ 5% (2.0 [1.3-3.0]), ≥ 7.5% (2.1 [1.3-3.3]), and ≥ 10% (2.1 [1.2-3.8]) weight loss.

Greenway FL, Aronne LJ, Raben A, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Gelesis100: A Novel Nonsystemic Oral Hydrogel for Weight Loss. *Obesity*. 2019;27(2):205-16.

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[1,2]
- *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.

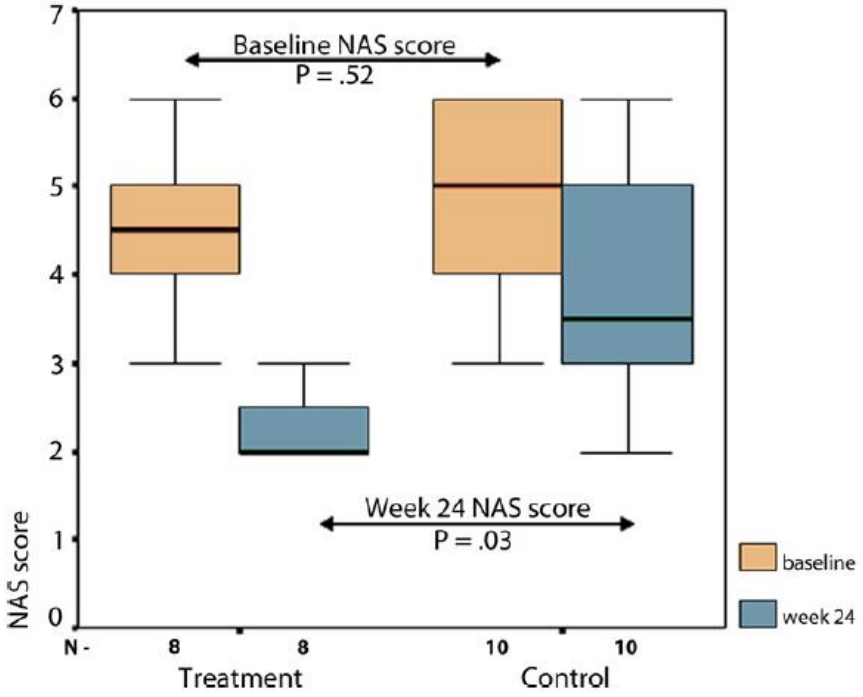
Sanyal et al, LB2, AASLD 2019

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

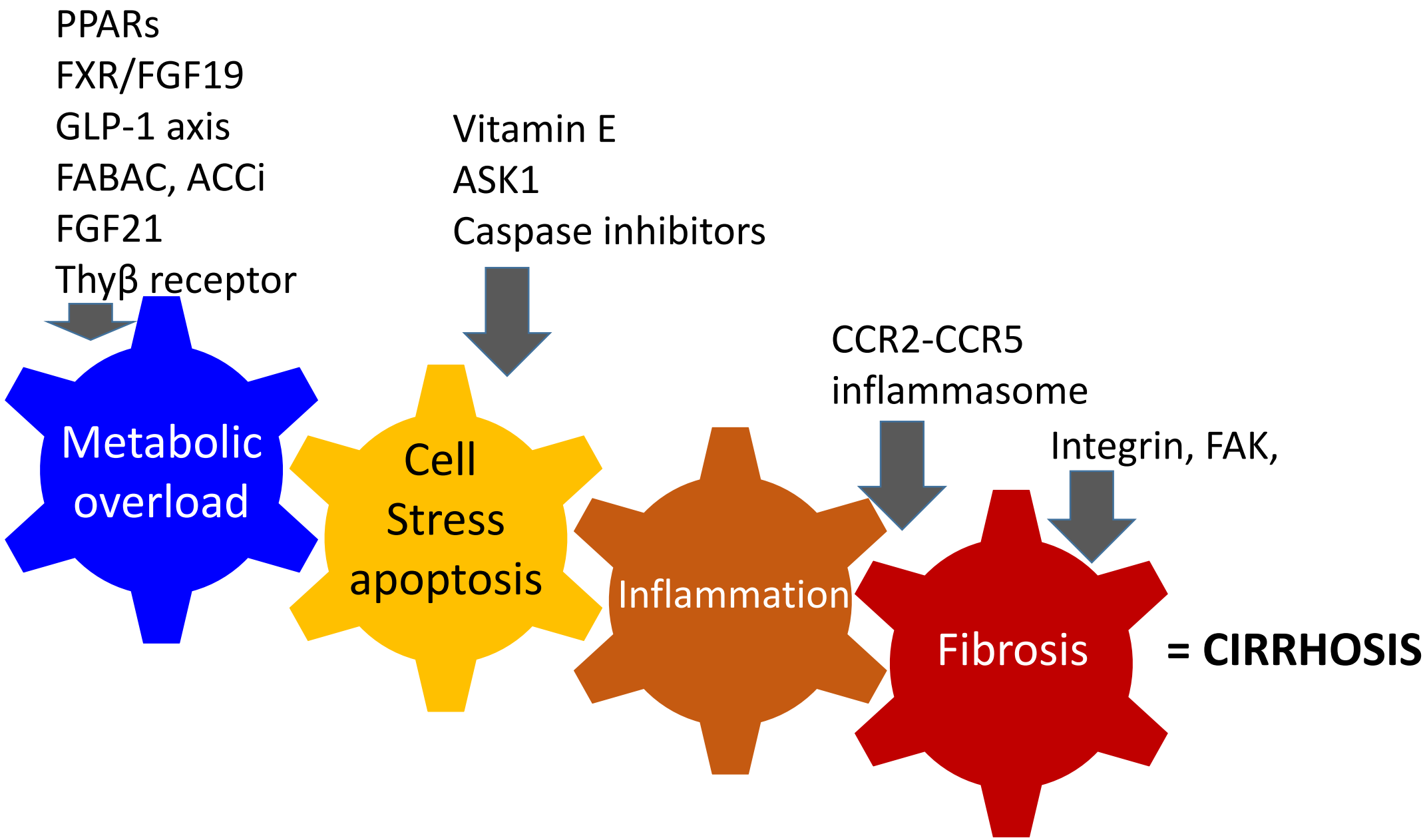
NAFLD Activity Score

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

Mayo Clinic study presented at DDW 2018



Adapted from Friedman et al, Nature Med 2018

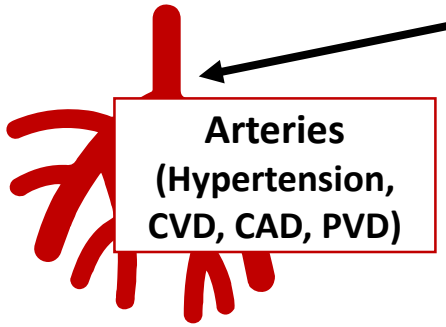
NASH is part of a multi-system disorder

- Improve NASH activity/fibrosis
- Improve clinical outcomes
  - atherogenic profile
  - glycemic control
  - development of HTN/strokes
  - development of CKD
  - liver outcomes

Diet-induced obesity

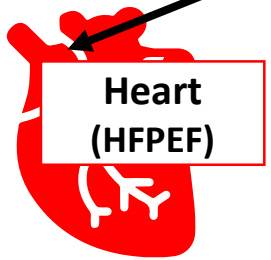
↓

Metabolic stress
Systemic inflammation and fibrosis



Arteries (Hypertension, CVD, CAD, PVD)

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



Heart (HFPEF)

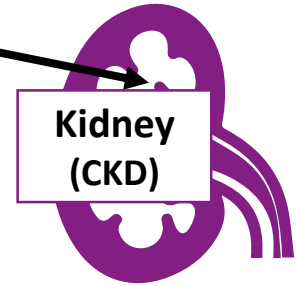
- Weight loss
- SGLT2i

Liver (NAFLD)

- Weight loss
- GLP-1
- ?SGLT2i

Pancreas (T2DM)

- Weight loss
- ARBs
- Metformin
- GLP1
- SGLT2i



Kidney (CKD)

- Weight loss
- ARBs
- SGLT2i
- GLP1

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

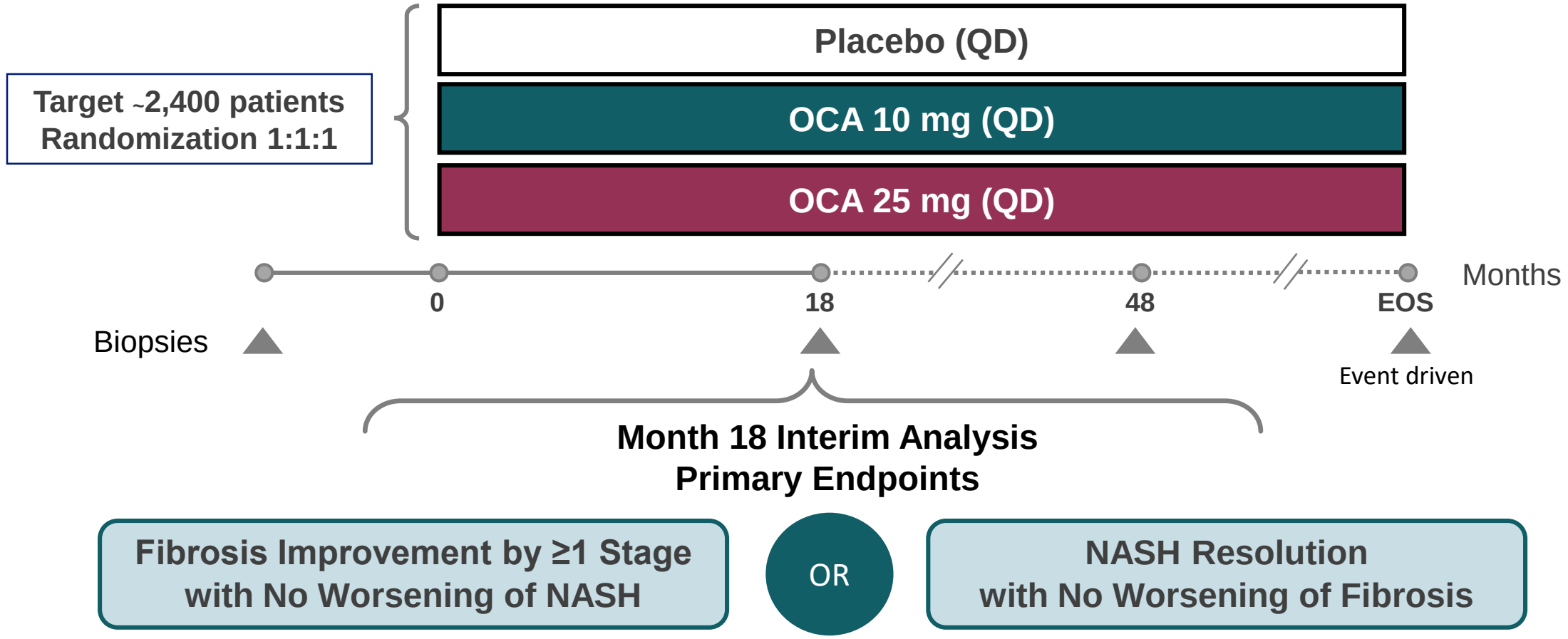
	TZDs	FXR/FGF19	FGF21	Thyroxine B-R	GLP-1
Weight	Gain	Loss/neutral	Loss	?	loss
LDL-C HDL-C TG	Increase Increase Decrease	Increase Decrease Decrease	Decrease* Increase* Decrease*	Decrease Neutral Decrease	neutral neutral neutral
MACE	neutral	?	?	?	Improved
Stabilize GFR	?	?	?	?	Improved
Glycemic control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

Sanyal et al, NEJM 2010, Neuschwander-Tetri et al, Lancet 2014, Sanyal et al Lancet 2018, Harrison et al Lancet 2018, Harrison et al AASLD 2018, Newsome et al Lancet 2016

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

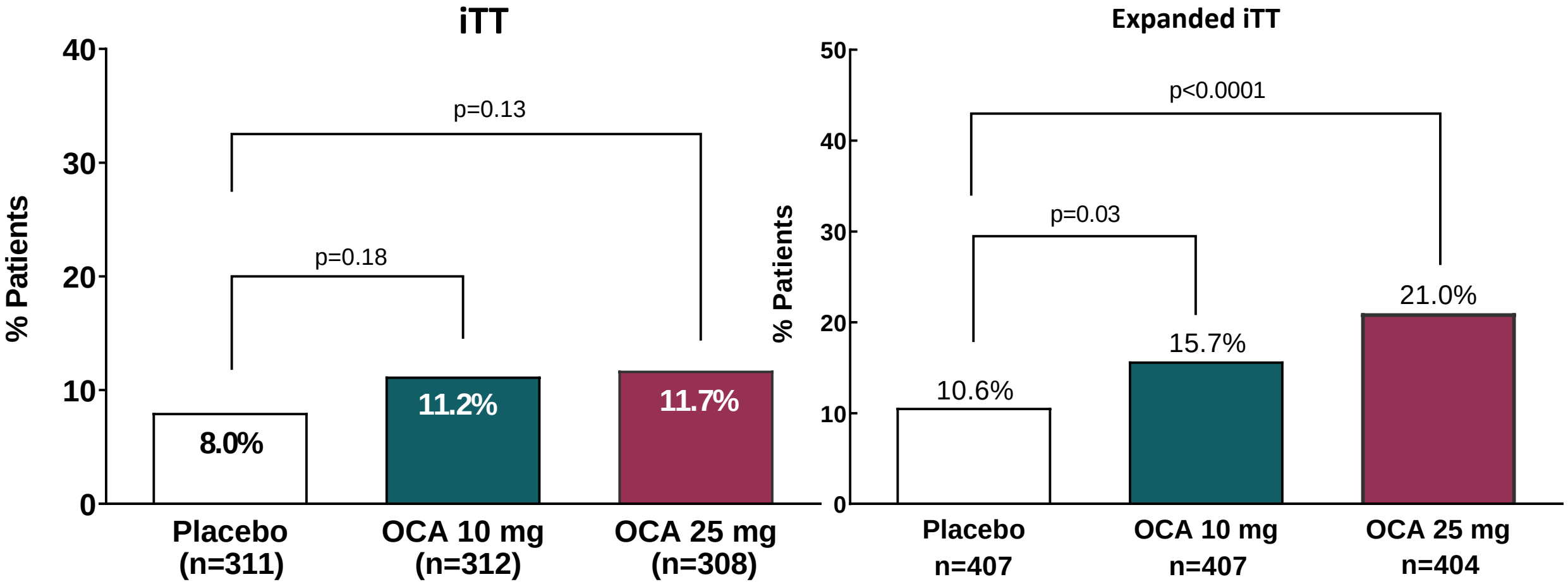
Younossi et al, Lancet 2019

REGENERATE NASH FIBROSIS STUDY

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 ≥1 Stage with No Worsening of NASH

Primary Endpoint:

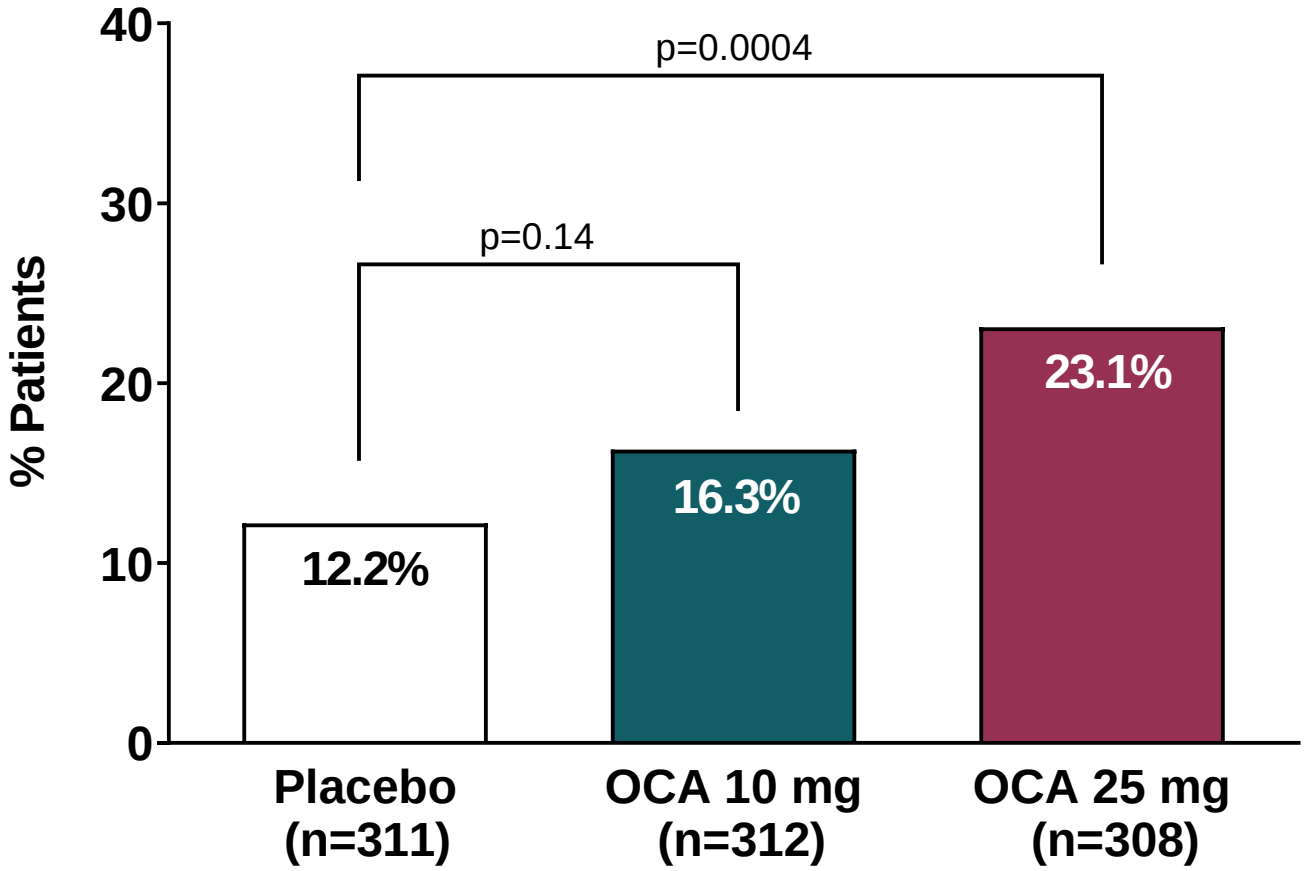


Expanded ITT Population, N=1,218.
Primary endpoint definition: Fibrosis improvement by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation, or steatosis).
This primary endpoint was met in the Primary ITT Population.
P values are nominal.

REGENERATE
NASH FIBROSIS STUDY

Resolution of Definite NASH with No Worsening of Fibrosis

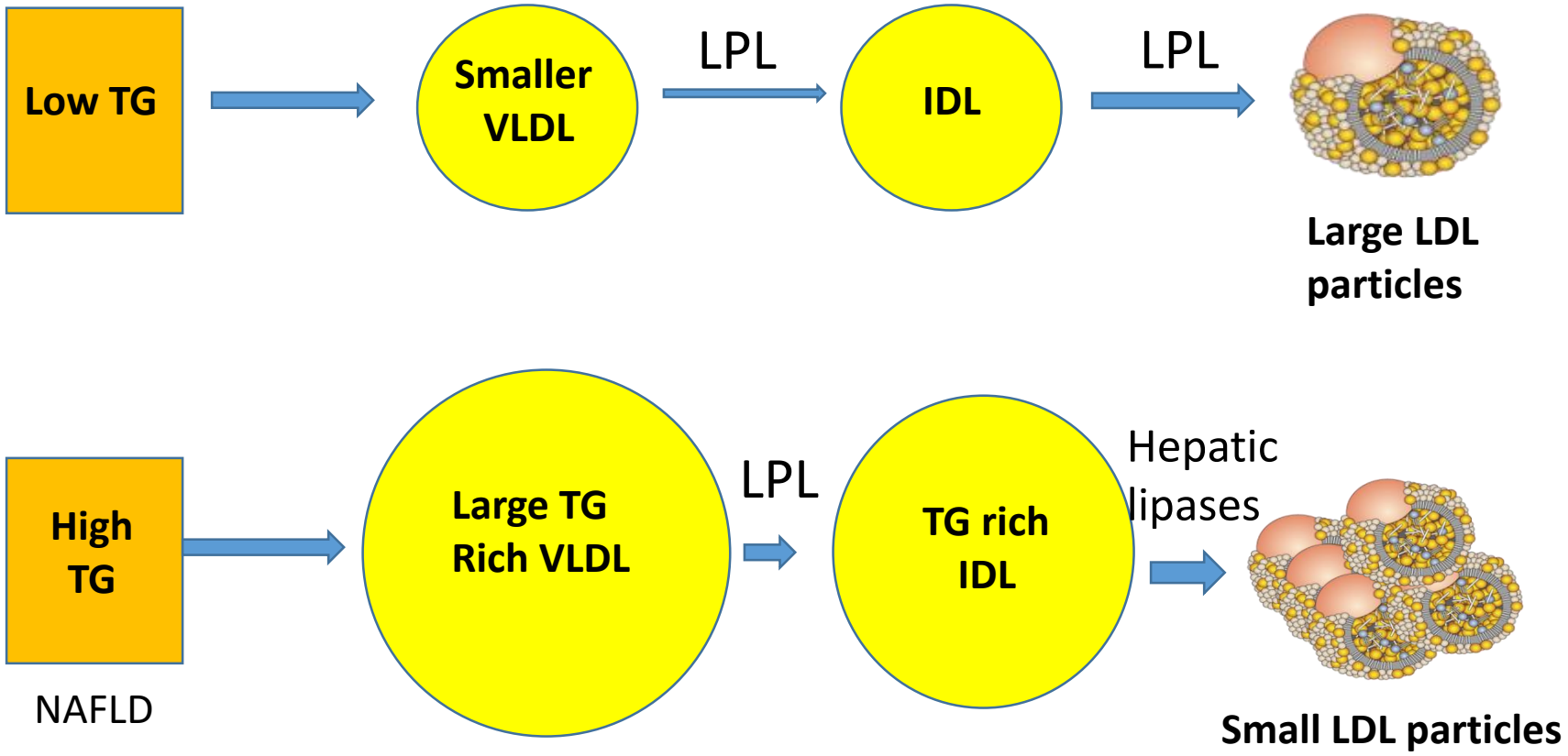
*Overall Pathologist Assessment: ITT Population**



REGENERATE
NASH FIBROSIS STUDY

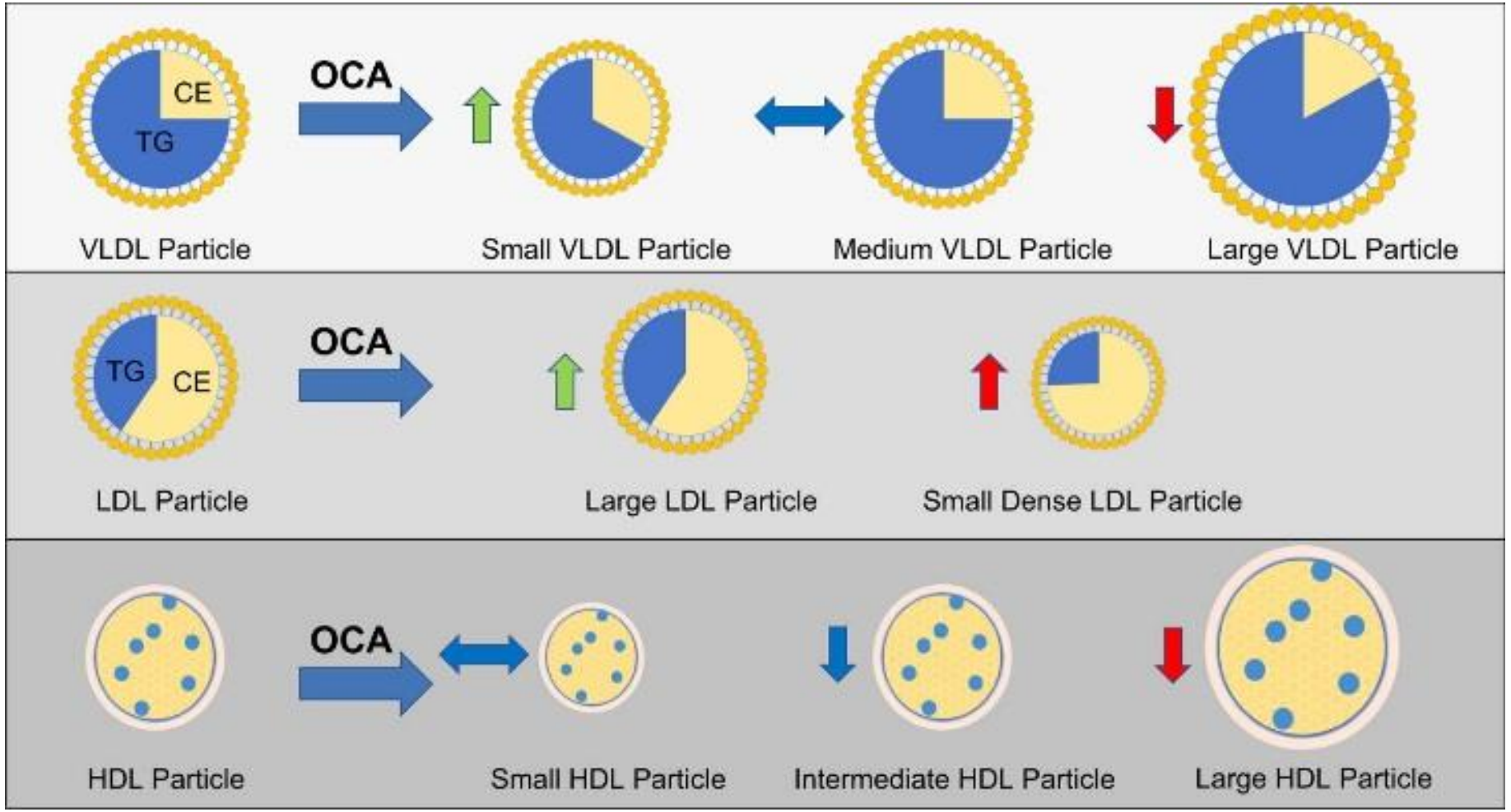
*Post-hoc analysis with endpoint defined as: (i) overall pathologist assessment of “no steatohepatitis,” and (ii) no increase in fibrosis stage from baseline. P values are nominal.

Steatosis is Central in Development of Atherogenic Lipoproteins



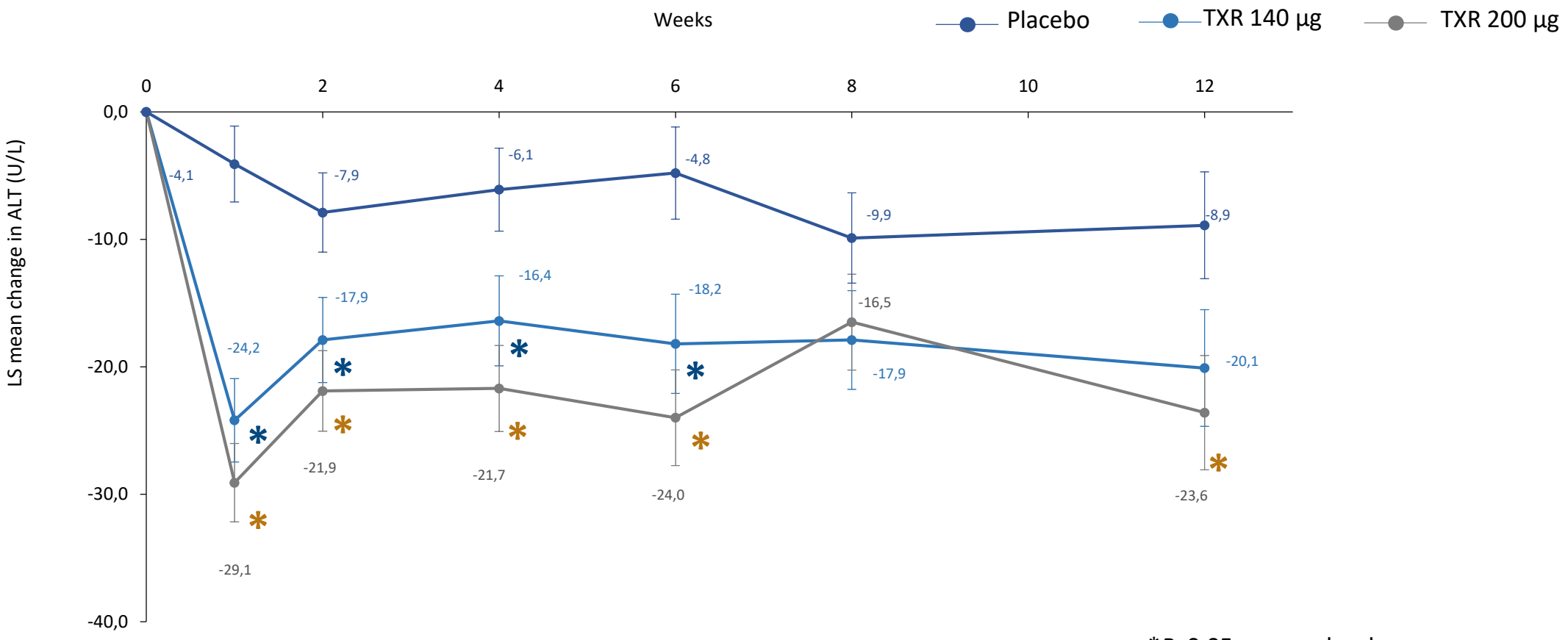
Berneis et al. J Lipid Res 2002

Impact of OCA on lipoproteins



Siddiqui et al, J Hepatol. 2019 Oct 18. pii: S0168-8278(19)30607-5.

Tropifexor- a small molecule FXR agonist also improves ALT



*P<0.05 versus placebo

LDL-C INCREASES WITH INCREASING TROPIFEXOR EXPOSURE

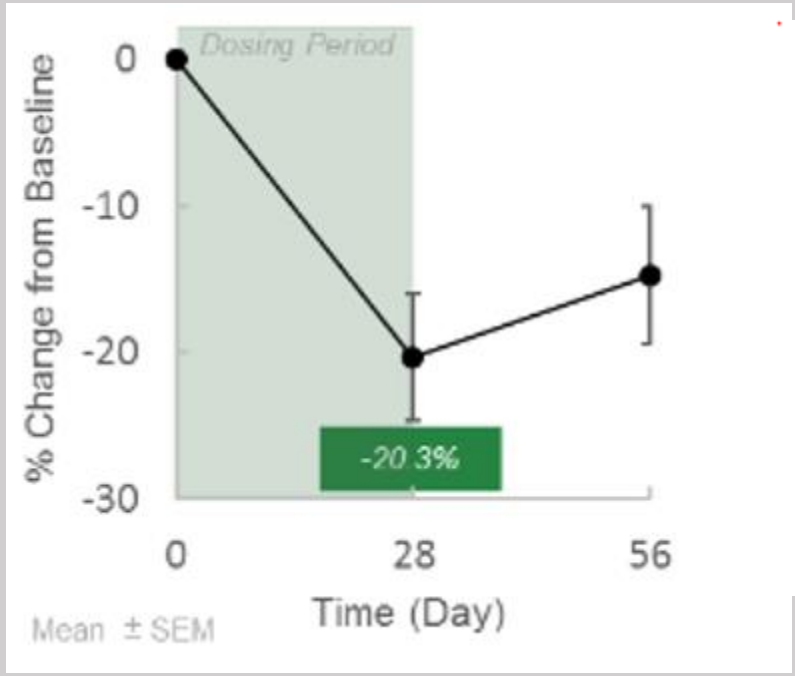
Data are presented as LS mean change (SE) with 2-sided *P* values by repeated measures ANCOVA
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; LS, least square; SE, standard error; TXR, tropifexor; W, week

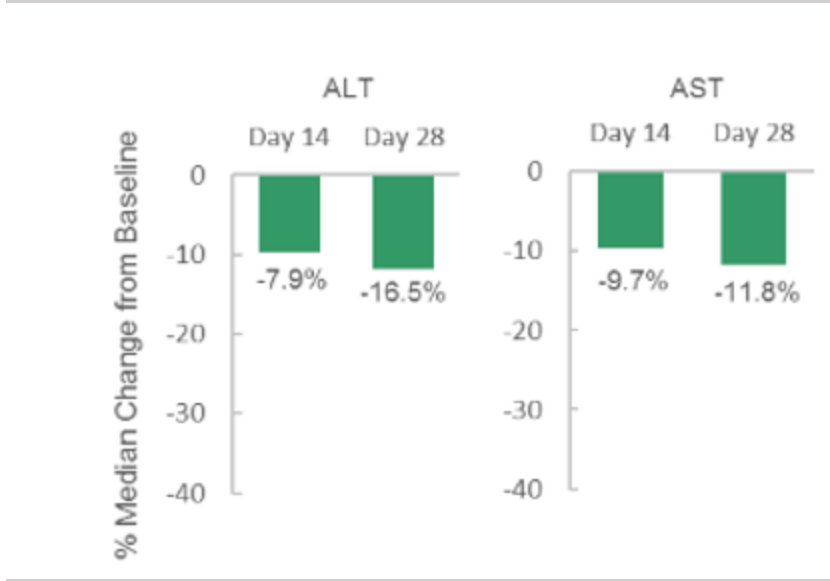
Sanyal et al, AASLD 2019

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.



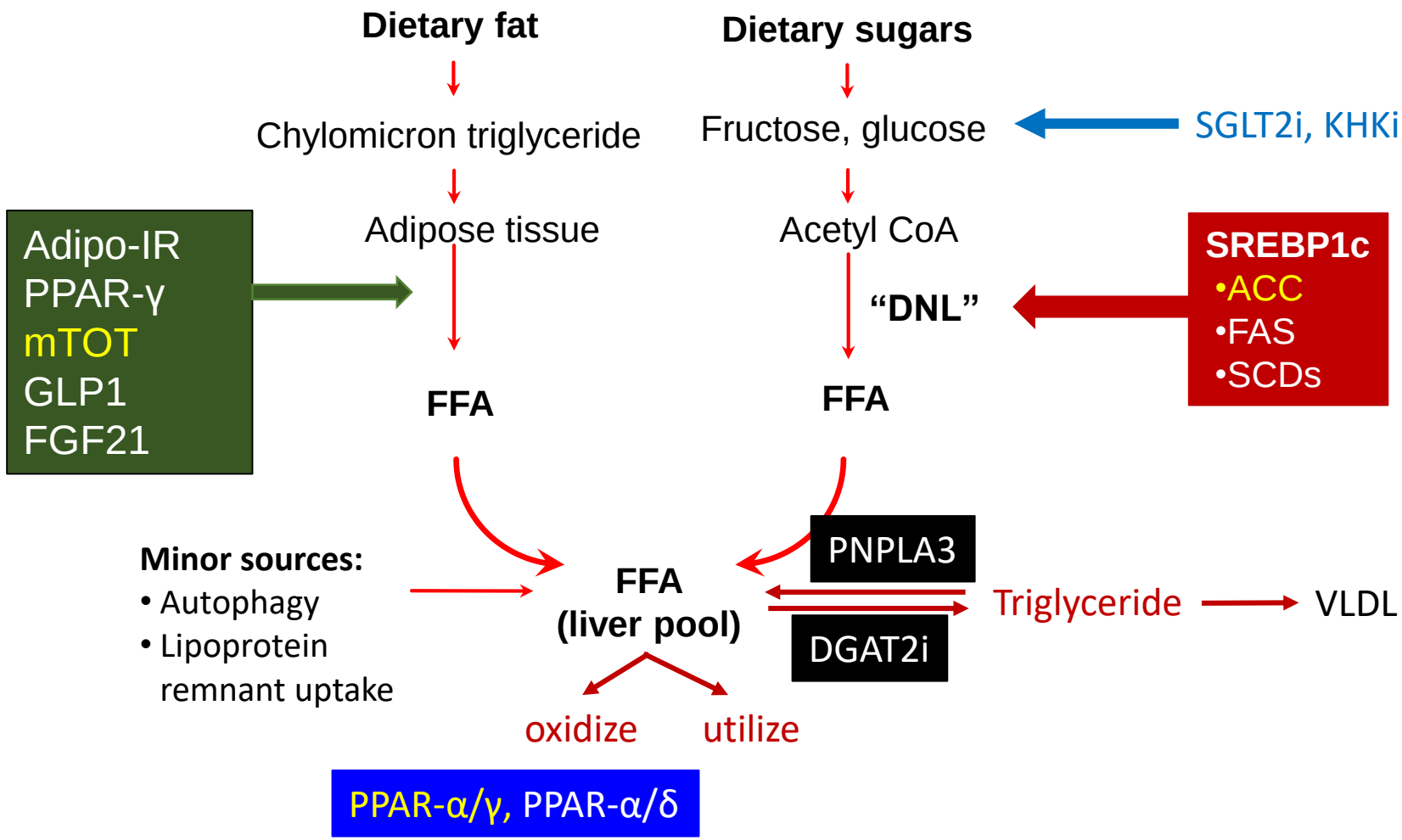


Harrison et al, AASLD 2019

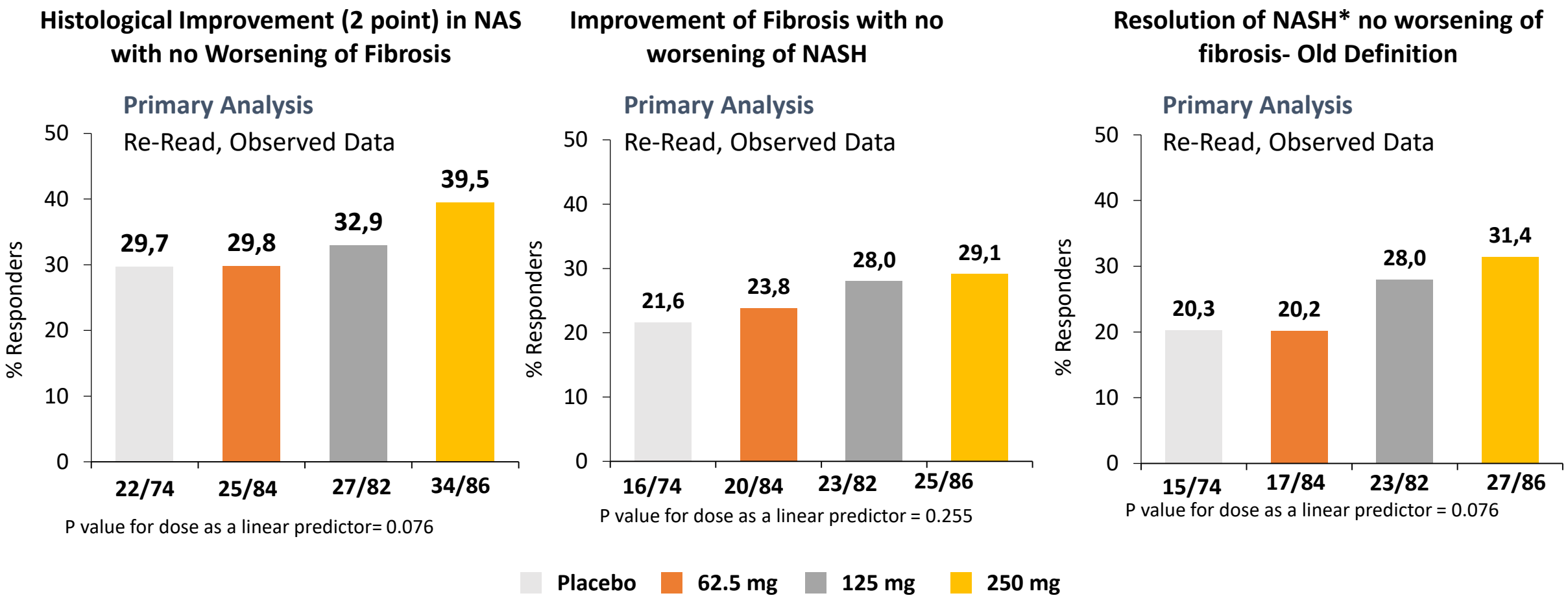
Phase II and drugs in early development

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

Metabolic substrate loading promotes energy storage as triglyceride



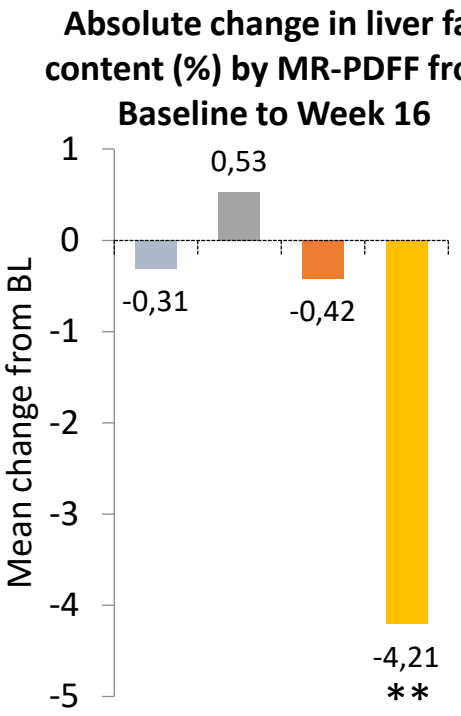
Results of MSDC-0602K in a large Phase 2b NASH study demonstrate improvement in markers of insulin resistance, glucose metabolism, serum aminotransferases, non invasive markers of NASH and histopathology

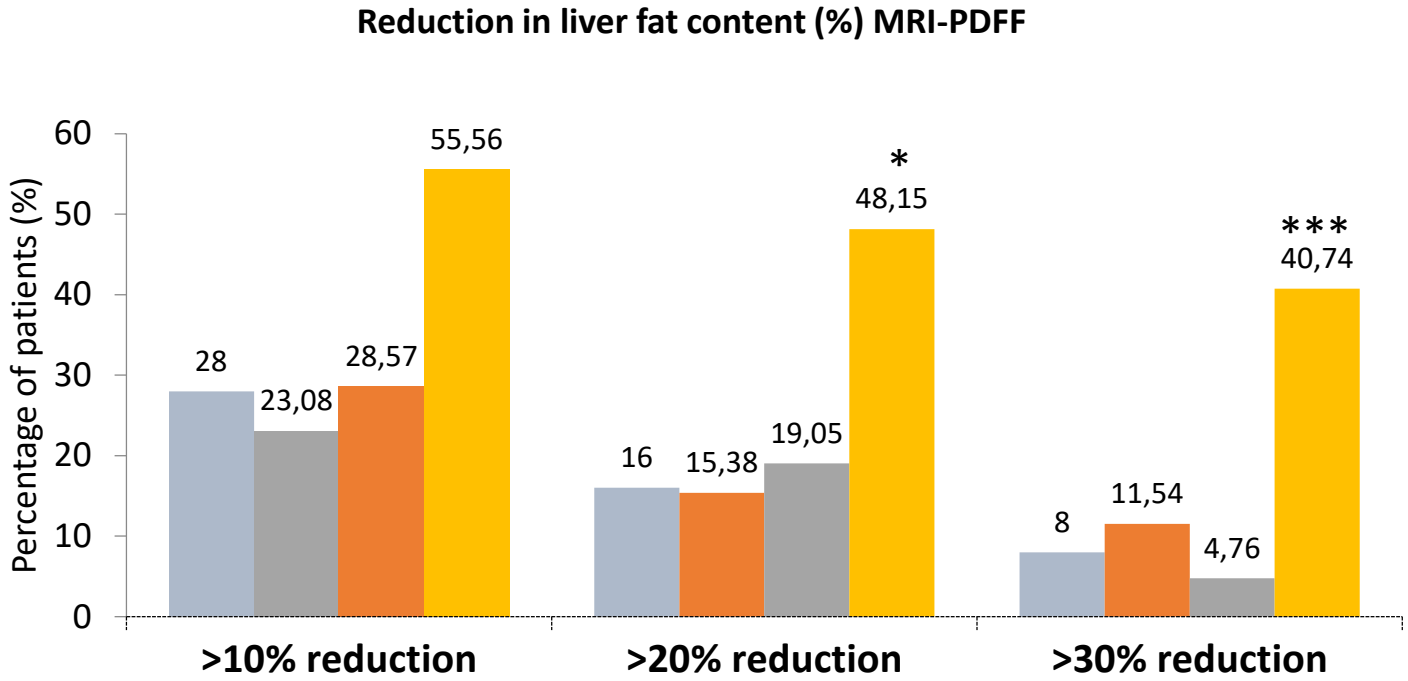


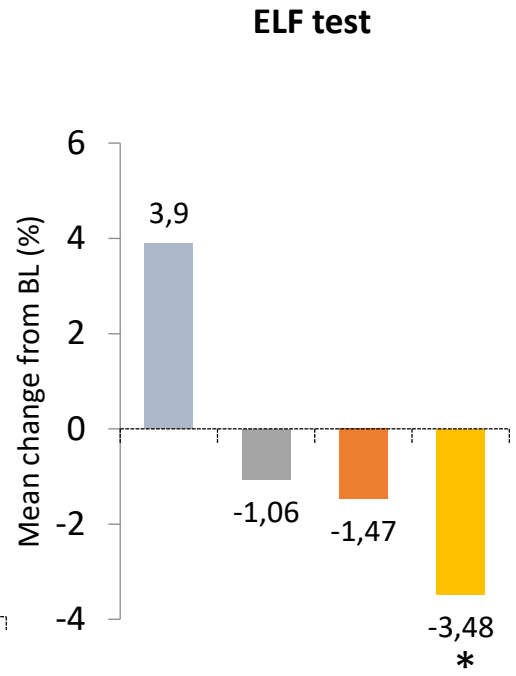
*Resolution of NASH is defined as a ballooning score of 0 and an inflammation score of 0-1 without worsening of fibrosis.

Harrison S, et al. AASLD 2019, Boston, USA. #LO1

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)







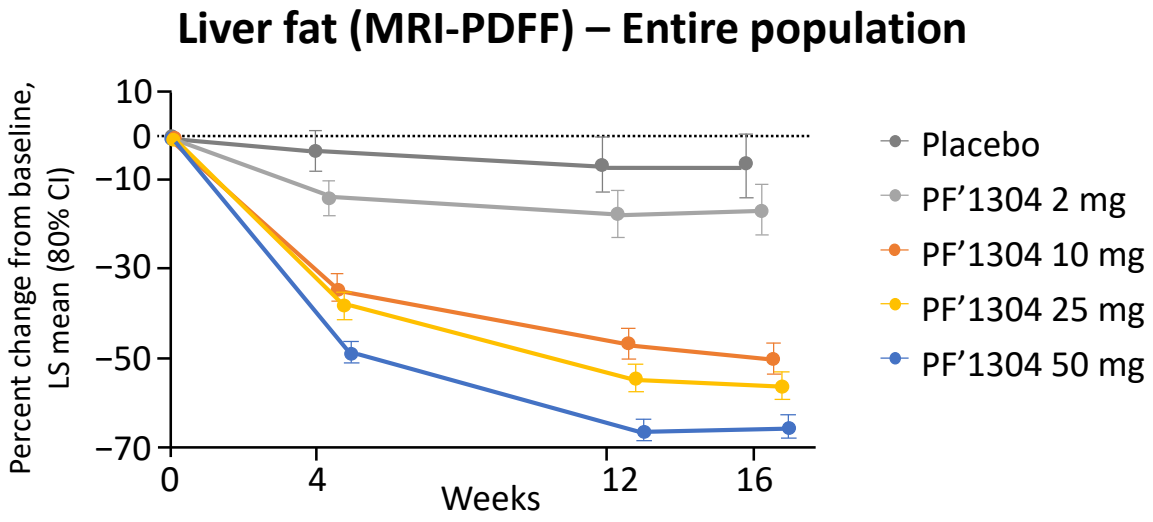
*p≤0.05, **p≤0.01, ***p≤0.001.

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

Gawrieh S, et al. AASLD 2019, Boston, USA. #LO10

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

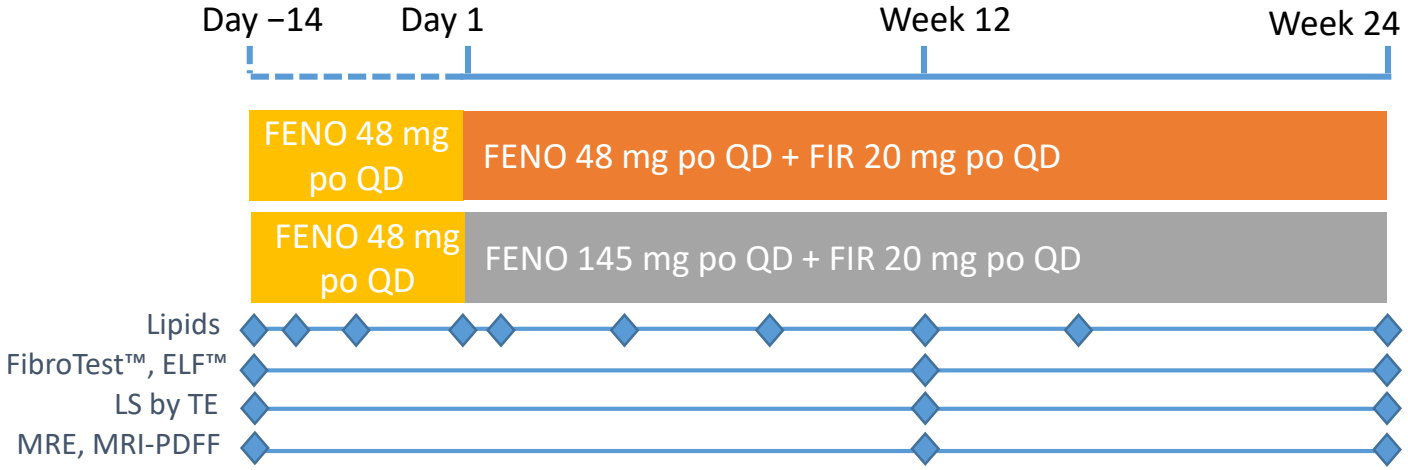


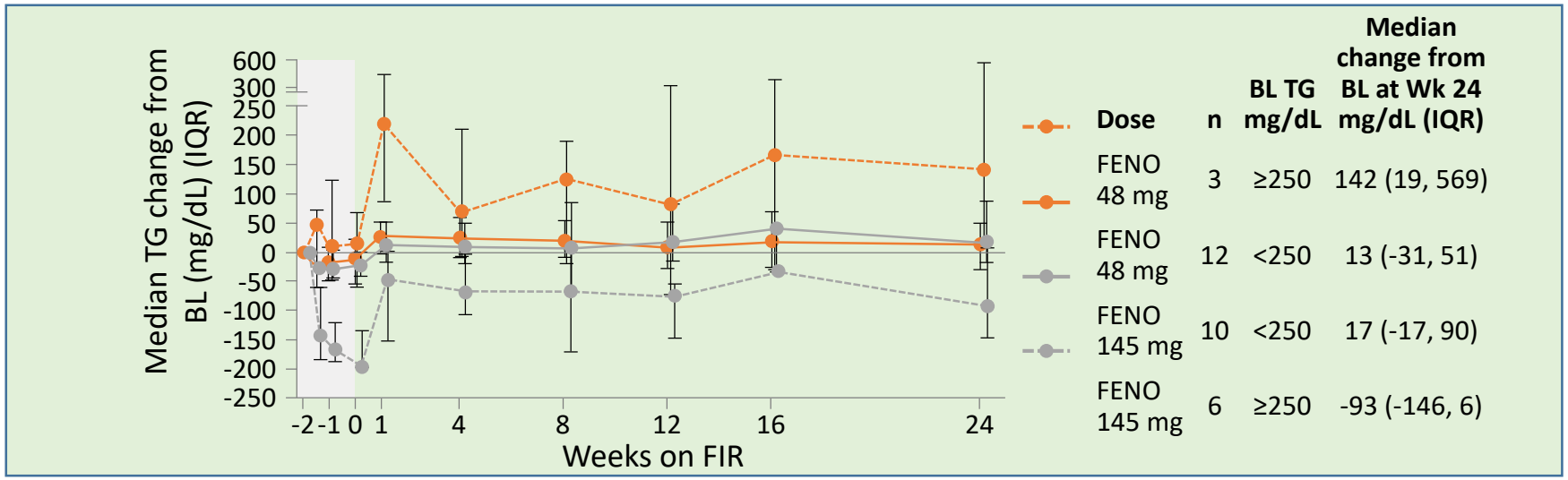
Proportion of patients who achieved relative reduction in MRI-PDFF ≥30% at Week 16

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



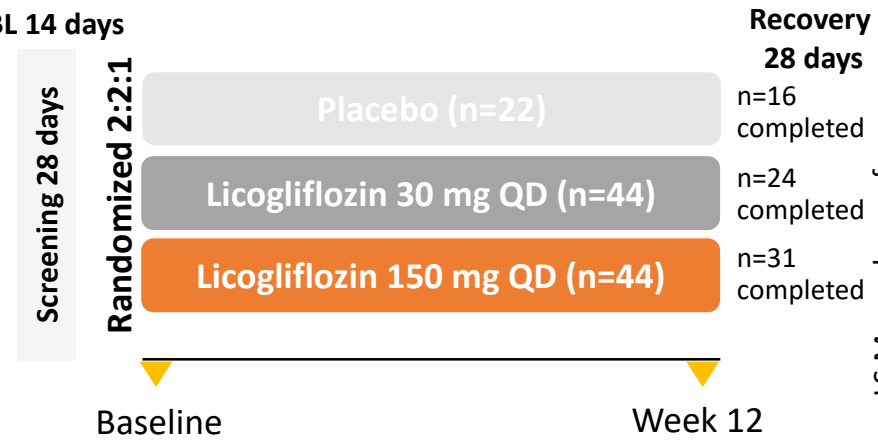


Dose	n	BL TG mg/dL	Median change from BL at Wk 24 mg/dL (IQR)
FENO 48 mg	3	≥250	142 (19, 569)
FENO 48 mg	12	<250	13 (-31, 51)
FENO 145 mg	10	<250	17 (-17, 90)
FENO 145 mg	6	≥250	-93 (-146, 6)

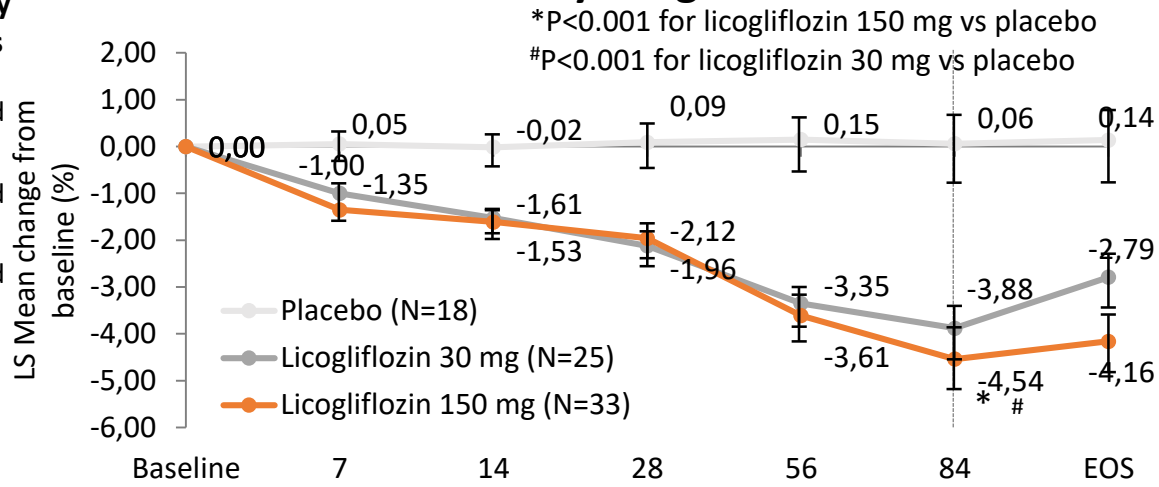
Lawitz E, et al. AASLD 2019, Boston, USA. #LP5

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

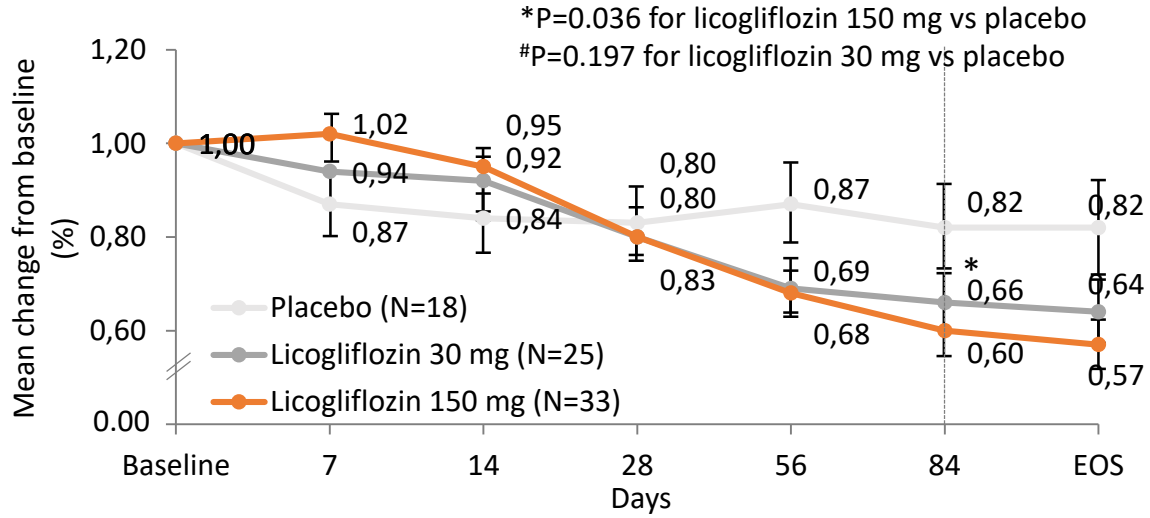
110 enrolled subjects with histologically confirmed or phenotypic NASH (BMI ≥27kg/m² in non-Asians or ≥23 kg/m² in Asians, ALT ≥35 (females) and T2D



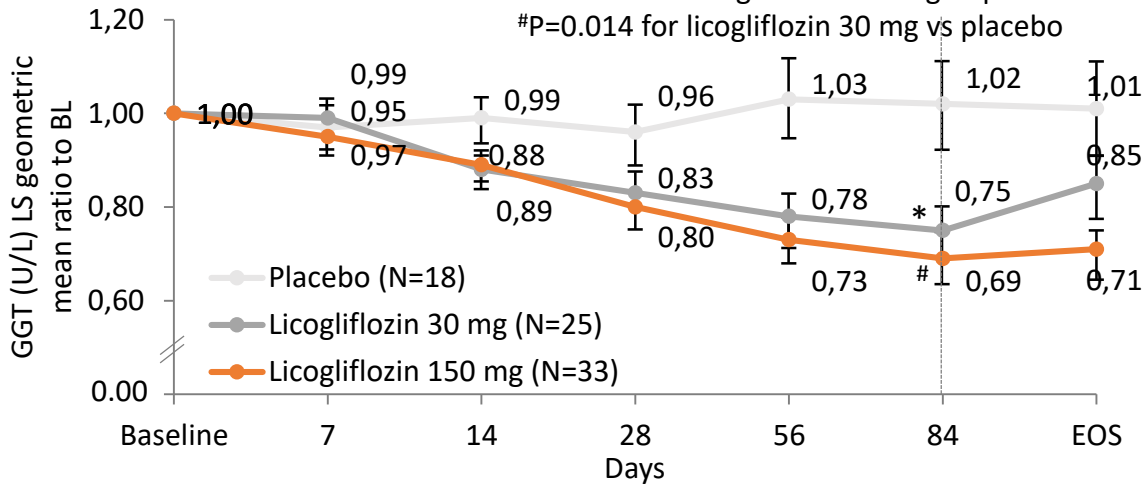
Body weight



Primary endpoint: Change in ALT up to Week 12



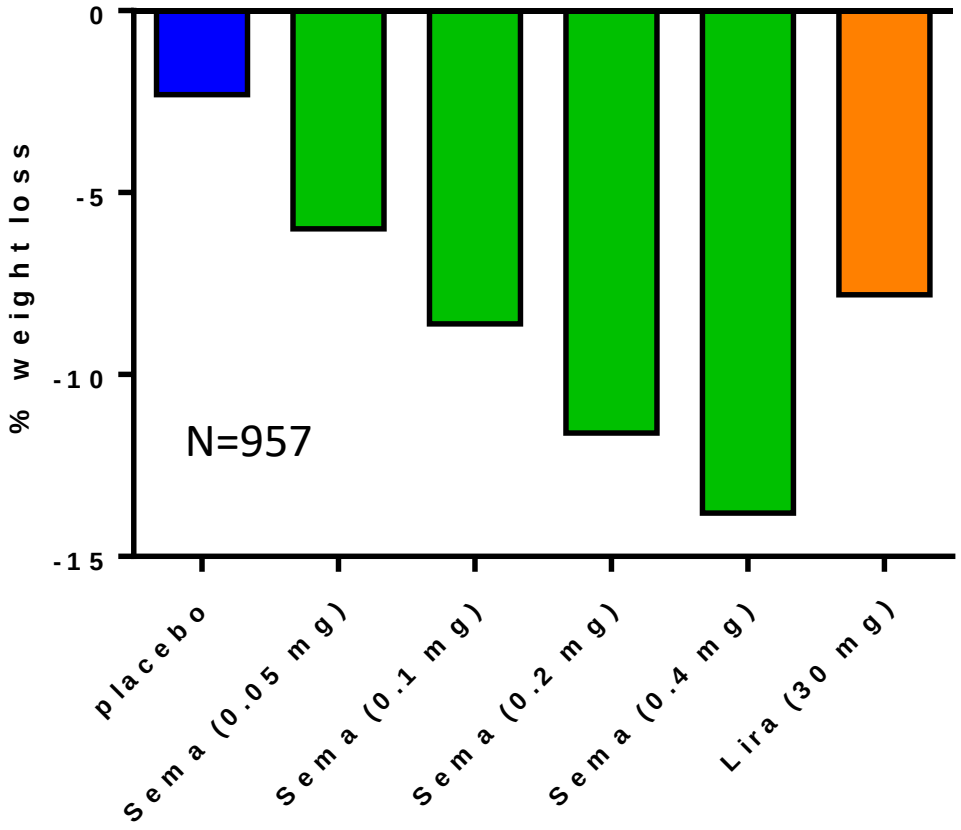
GGT



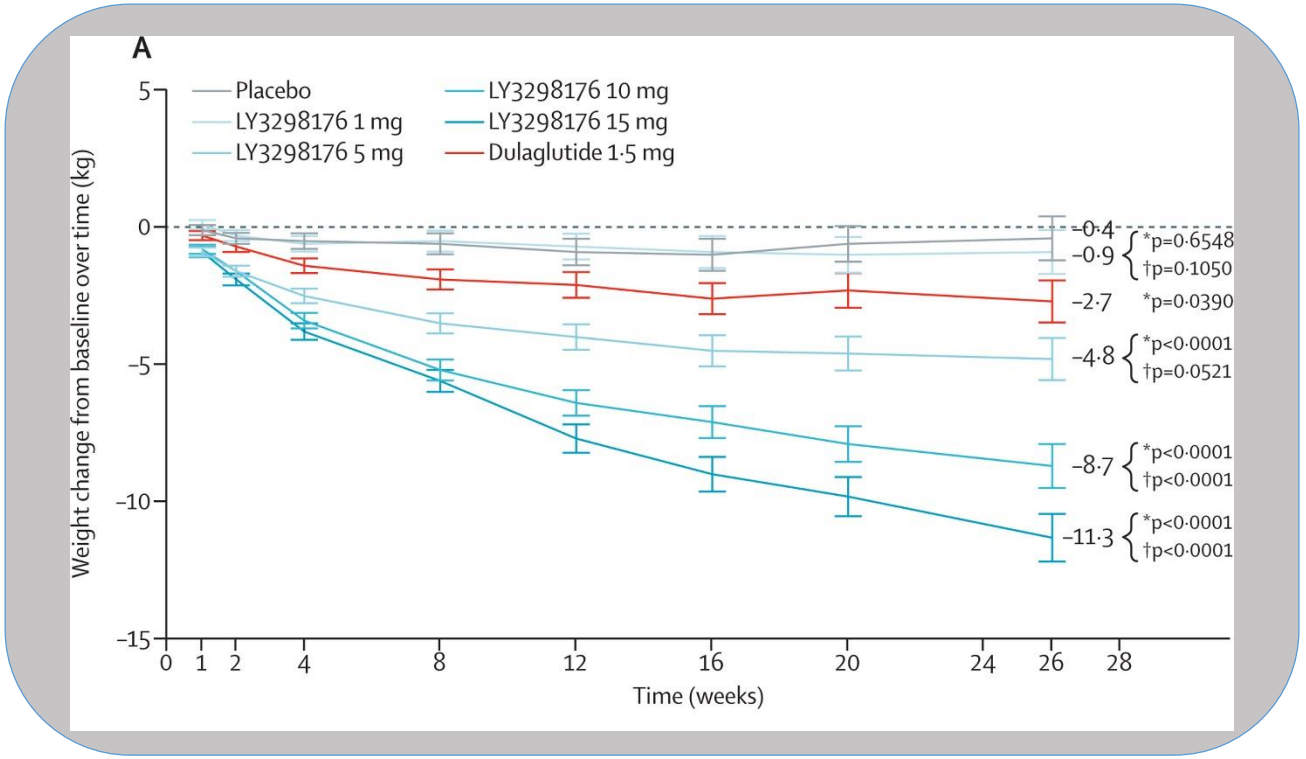
Harrison S, et al. AASLD 2019, Boston, USA. #LO7

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

P< 0.005 after multiple comparison for all Semaglutide groups



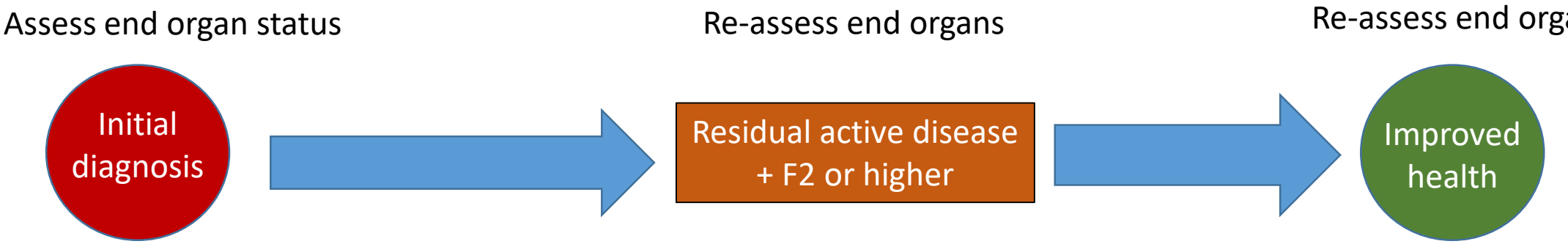
O'Neill et al, Lancet. 2018 Aug 25;392(10148):637-649.



GLP-1/GIP agonist (terzepatide)

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

VCU Health™