

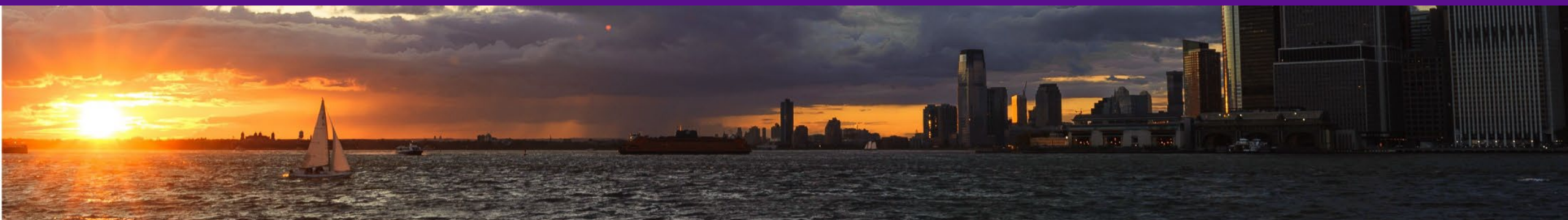


Metabolic Dysfunction-Associated Liver Disease: New Treatments and Future Directions

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Update on the Management of Fatty Liver Disease

Disclosures

Consulting: Aligos, AusperBio, Gilead, GSK, Intercept, Ipsen, Madrigal, Mirum, Vir

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Safety Monitoring Committee: GSK, Precision Biosciences, Takeda

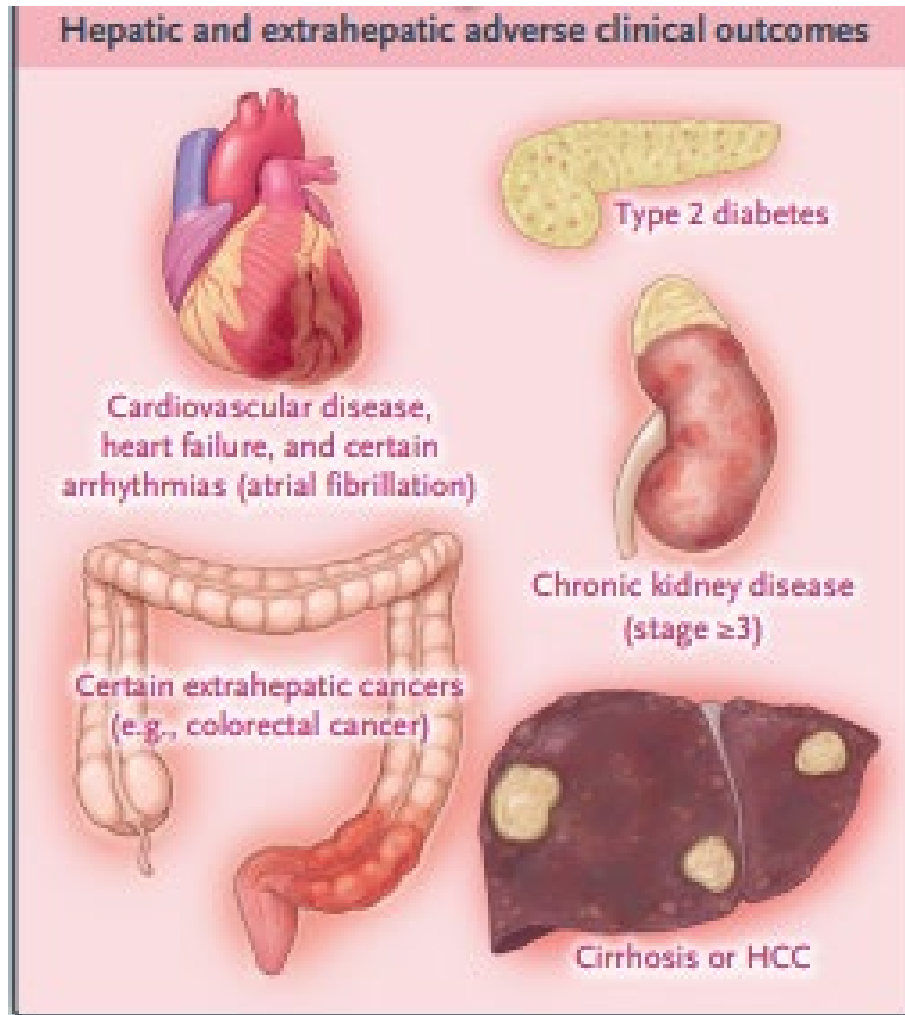
MASLD: Key Points

KEY POINTS

METABOLIC DYSFUNCTION—ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

- MASLD is a multisystem disease that has become a public-health problem worldwide.
- Metabolic dysfunction is key to the pathogenesis and consequences of MASLD.
- The clinical burden of MASLD consists mainly of liver-related disease and death and high rates of fatal and nonfatal cardiovascular disease, chronic kidney disease, type 2 diabetes, and certain extrahepatic cancers, especially extrahepatic gastrointestinal cancers.
- There is a pressing need for drugs to treat MASLD and its more severe form, metabolic dysfunction–associated steatohepatitis (MASH).
- In March 2024, resmetirom, a liver-directed, thyroid hormone receptor beta–selective agonist, was the first drug conditionally approved by the Food and Drug Administration for treating adults with noncirrhotic MASH and moderate-to-advanced fibrosis.
- Incretin-based drugs (especially semaglutide at a dose of 2.4 mg per week) and other metabolism-based pharmacotherapies are showing promise as therapeutic options not only for steatotic liver disease but also for cardiovascular–kidney–metabolic complications that are strongly related to MASLD.

MASLD: Key Hepatic and Extrahepatic Outcomes



Approximate increase in the risk of new-onset adverse clinical outcomes
Type 2 diabetes (if no type 2 diabetes at baseline) — 2.2x
Fatal or nonfatal cardiovascular disease — 1.5x
Heart failure — 1.5x
Atrial fibrillation — 1.2x
CKD (stage ≥ 3) — 1.5x
Extrahepatic cancers — 1.5x
Cirrhosis or HCC — 2–10x

The motivational message for patients: Fatty liver is not just bad for the liver!

Cardiometabolic Renal Syndrome (CKM): Is it Time for CKLM?

Prevalence and Cumulative Incidence Rates of Advanced Liver Fibrosis/LSM/Liver-Related Events by CKM Stage

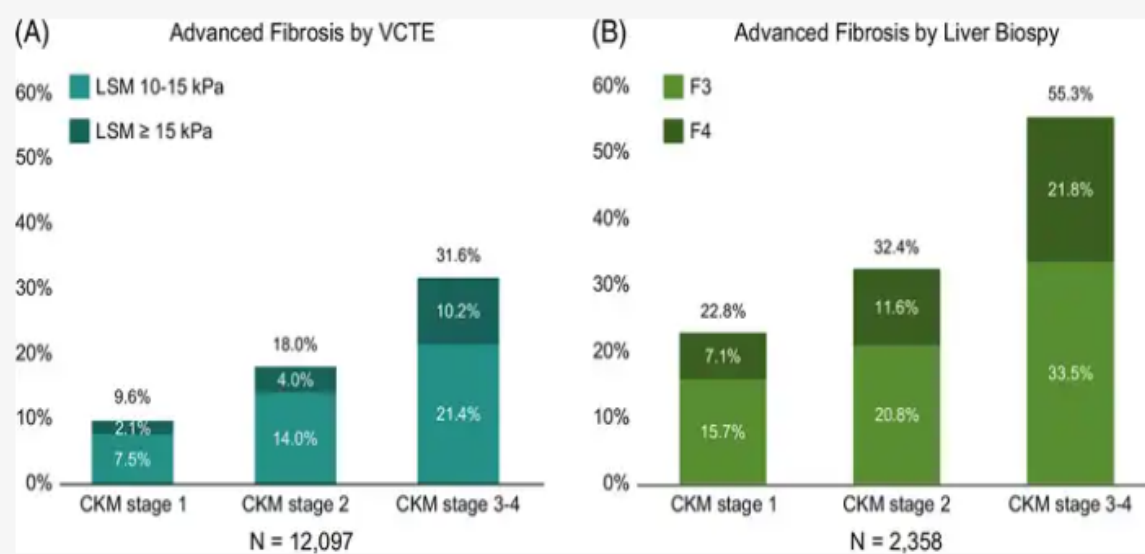


FIGURE 2 Prevalence rates of advanced fibrosis assessed by either vibration-controlled transient elastography or liver histology, stratified by CKM stages in patients with MASLD. Abbreviations: CKM, cardiometabolic-renal syndrome; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

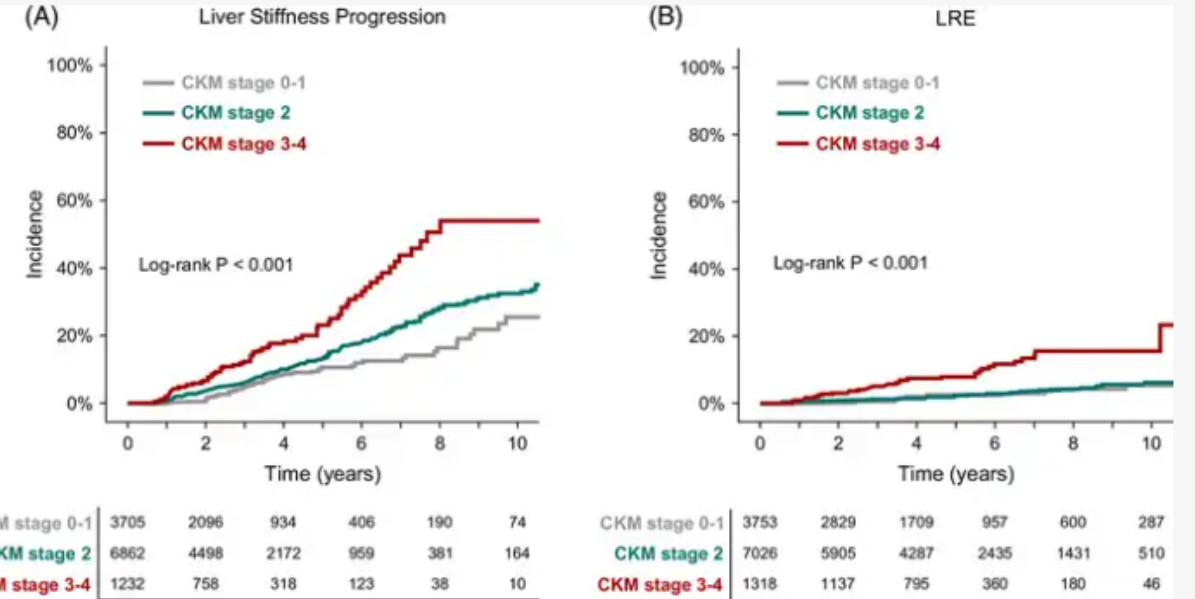
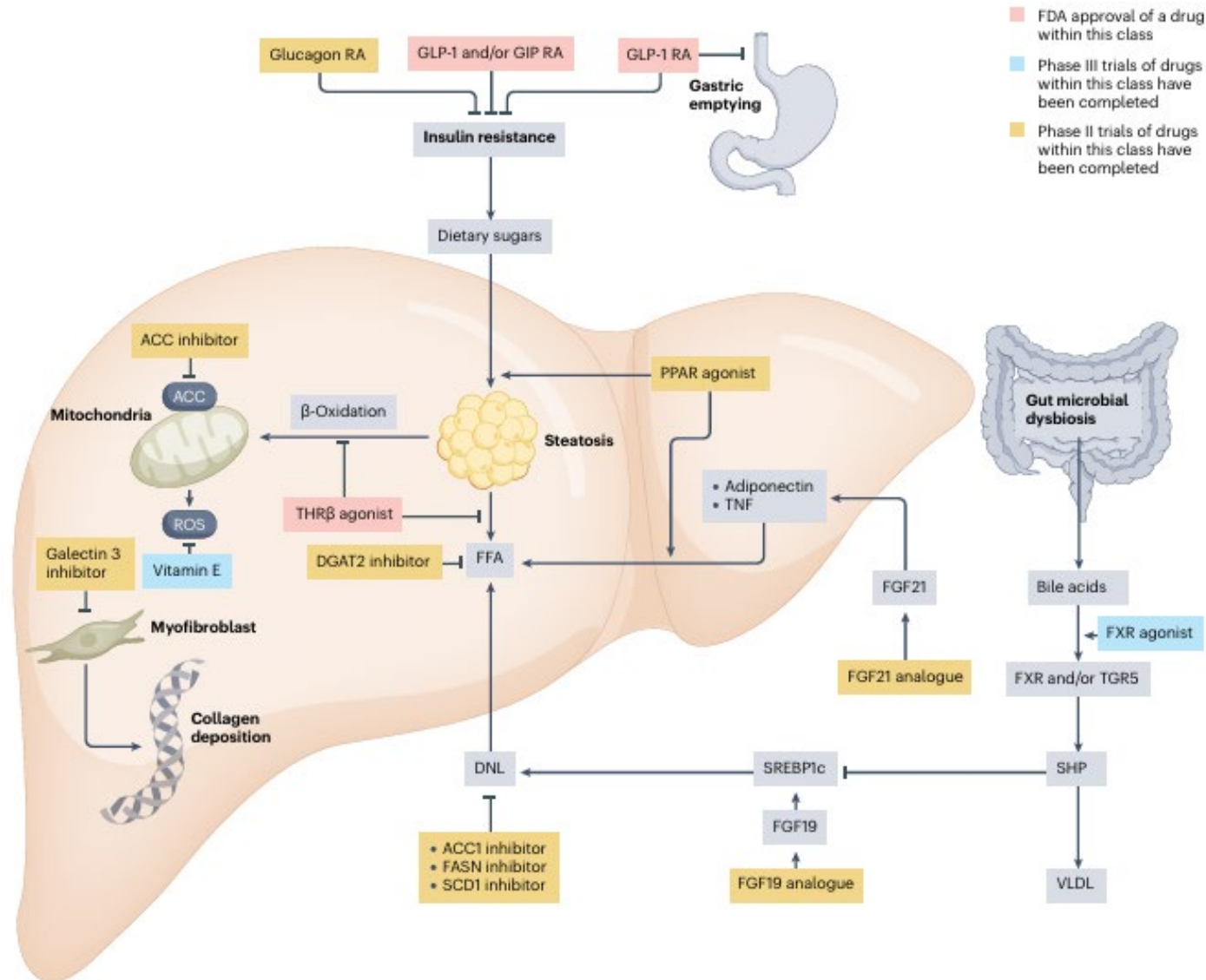


FIGURE 3 Cumulative Incidence rates of (A) liver stiffness progression, and (B) long-term LREs, stratified by CKM stages in patients with MASLD. Abbreviations: CKM, cardiometabolic-renal syndrome; LRE, liver-related events; MASLD, metabolic dysfunction-associated steatotic liver disease.

- CKM stages are independently associated with severity and progression of liver fibrosis in MASLD
- CKM stage 2 significantly increases liver stiffness progression
- CKM stage 3-4 confer the highest risk of liver-related outcomes

Pathogenesis of MASLD: Complicated...

But Allows for Many Opportunities (Including Combinations)

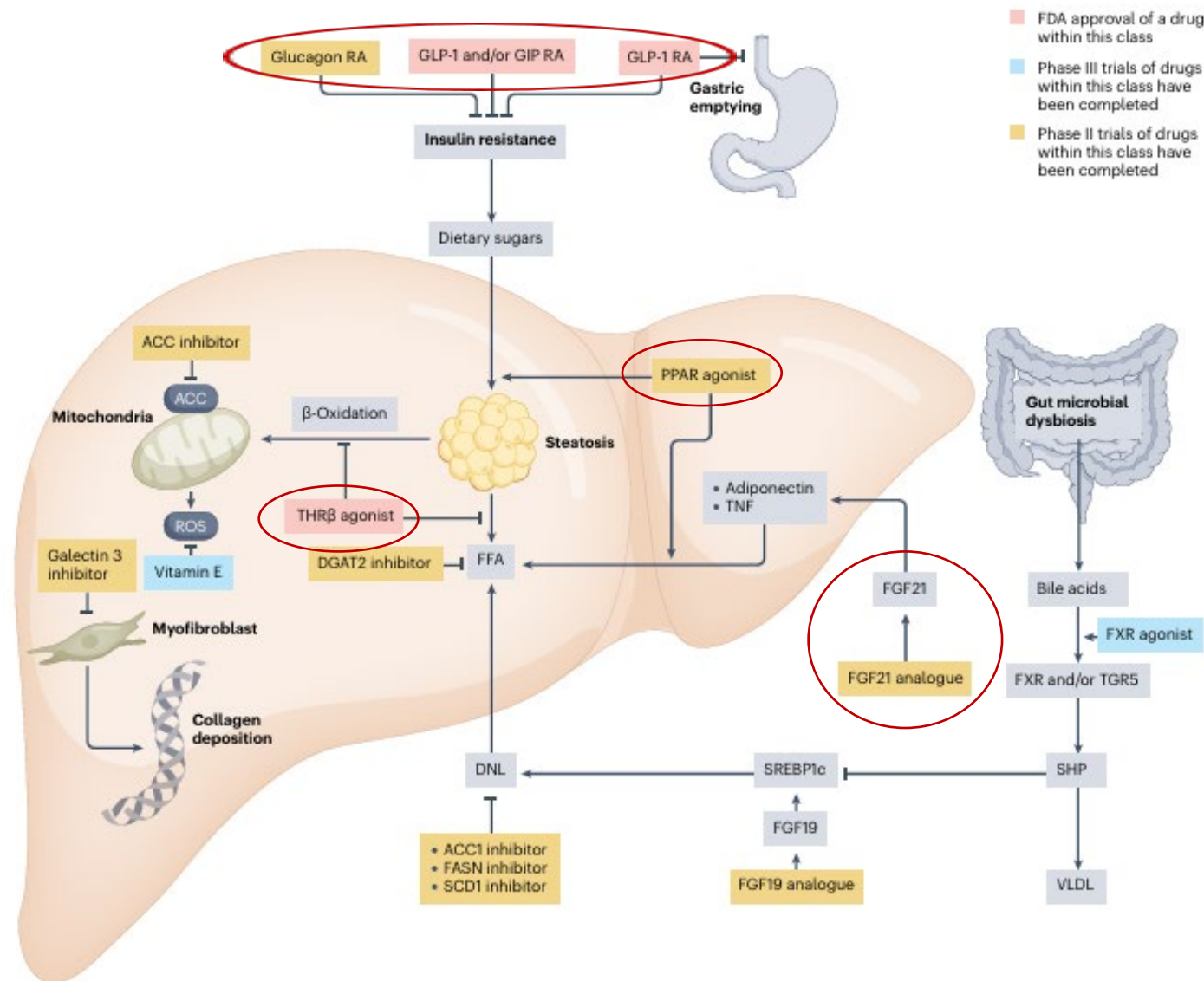


MASH Therapeutic Targets Categorized by Mechanism of Action and Subsequent Biological and Clinical Efficacy in MASH

	Fatty acid synthesis or lipid droplet targeting	Insulin sensitivity/ glucose lowering	Bile acid synthesis	Antiinflammatory	Antifibrotic early stage	Antifibrotic late stage
	• THR-β agonist • FASN inhibitors • FGF21 analog • DGAT inhibitors • KHK inhibitors • siRNA PNPLA3 • PPAR agonist	• GLP-1 agonist • GLP-1/GIP agonist • GLP-1/GIP/glucagon agonist • PPAR agonist • SGLT2 inhibitors • FGF21 analog • ANGPTL3 siRNA • Others	• FGF19 analog • Others	• GLP-1 agonist • GLP-1/GIP agonist • GLP-1/GIP/glucagon agonist • DHA • siRNA PNPLA3 • PPAR agonist • HSD17B13	• FGF21 analog • Glucagon agonist • GLP-1 agonist • GLP-1/GIP agonist • GLP-1/GIP/ glucagon agonist • Anti-JNK-1 • PPAR agonist • Nox inhibitors • FGF19 analog • Others	• FGF21 analog • PPAR agonist • ASK-1 inhibitors • Anti-GAL-3 • Anti-CTGF • FGF21/19 analog • Pentraxin-2 • Anti-IL-17 • Anti-TGF-β
	Steatosis, ballooning, and inflammation			Stage 1–3 fibrosis	Stage 3–4 fibrosis	
Therapeutic goal	Resolution of MASH			Reduction in the rate of progression of fibrosis or improvement in fibrosis		Reversal of advanced fibrosis or improvement in fibrosis

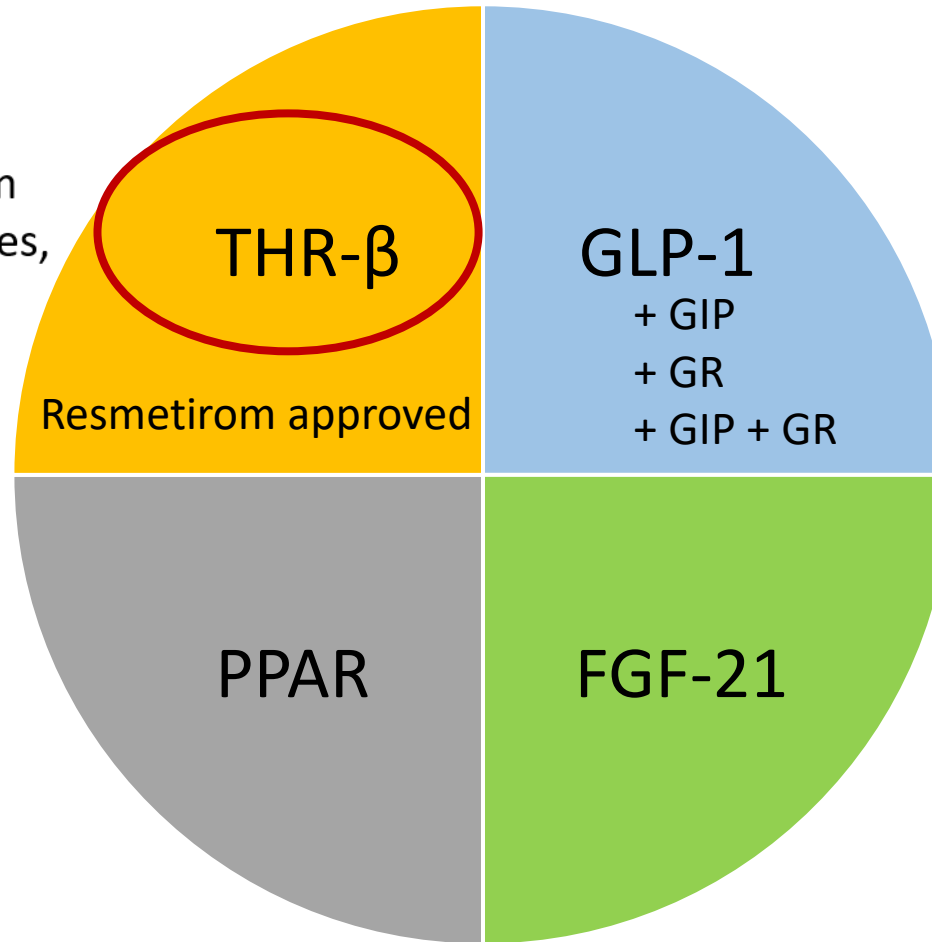
Pathogenesis of MASLD: Complicated...

But Allows for Many Opportunities (Including Combinations)



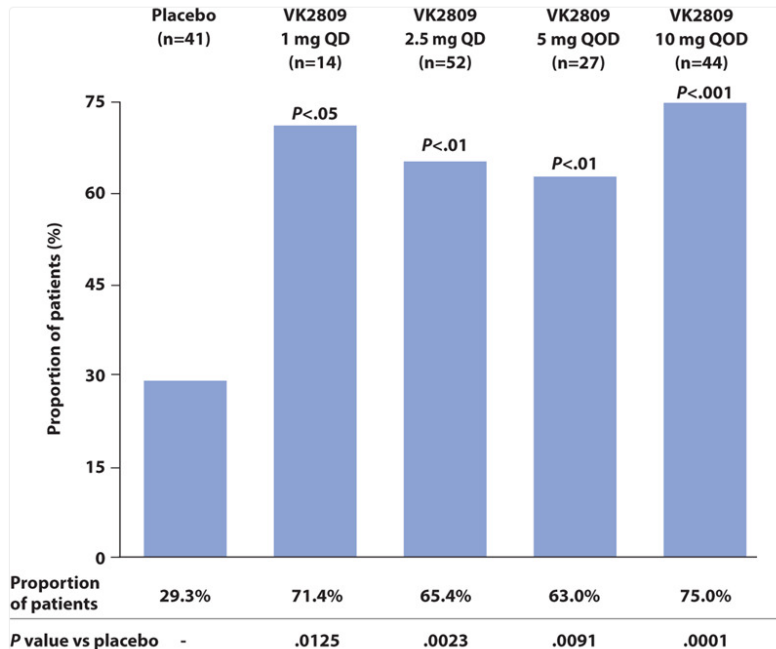
Receptors of Major Interest in MAFLD Drug Development (Not all inclusive)

- Regulates lipid metabolism
- Reduces LDL-C, triglycerides, atherogenic proteins



Results from 52 Week Phase 2b VOYAGE Trial of VK2809 in MASH and Fibrosis

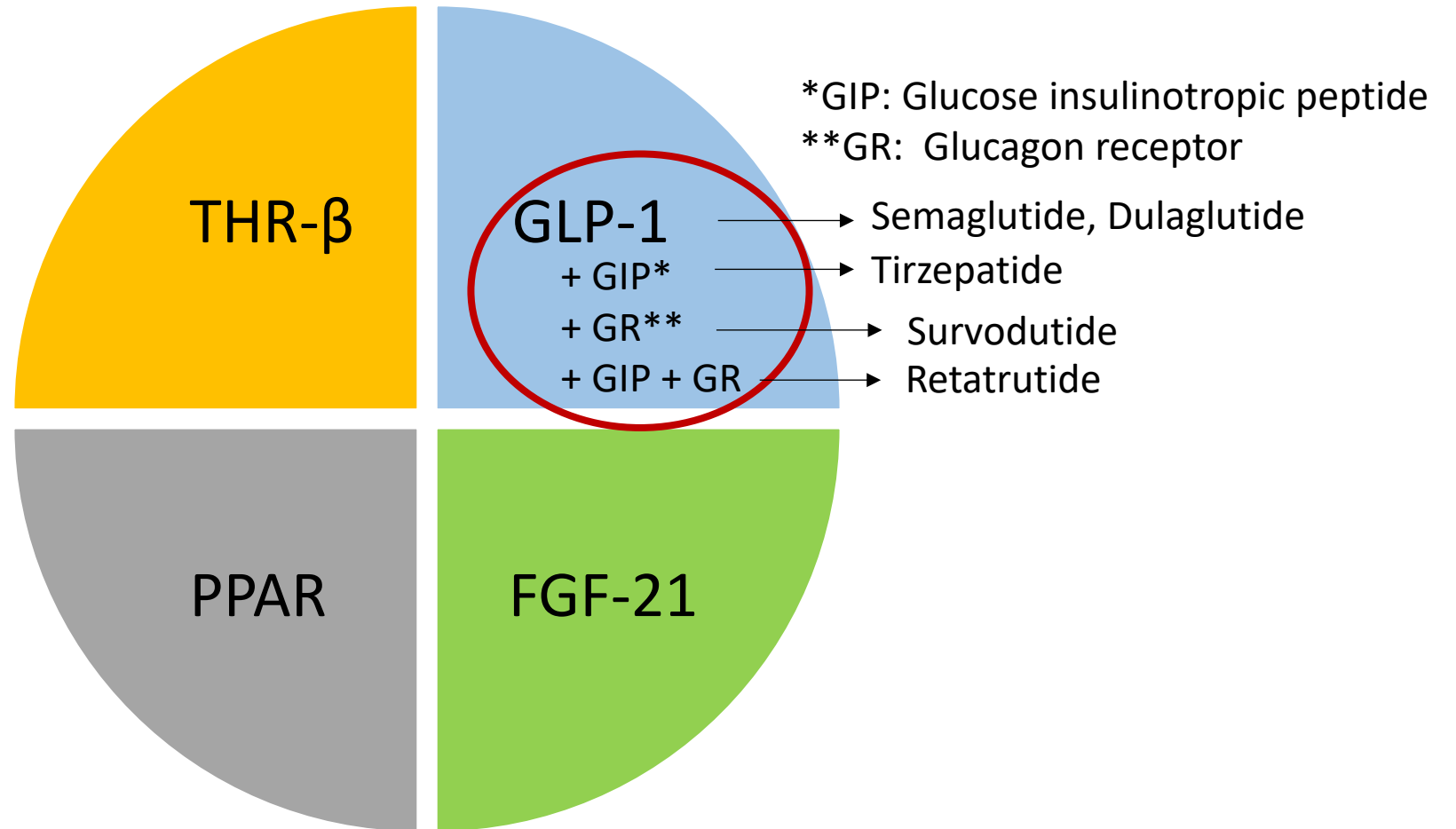
- 4 doses: 1 mg/d, 2.5 mg/d, 5 mg qod, 10 mg qod
- Significant reduction in liver fat at week 12 (primary endpoint)
- Mean relative change in liver fat from BL 37-55% week 52
- NASH resolution at week 52: 63-75% in active arms vs 29% placebo (69% across combined groups)



Proportion of patients (all with baseline MRI and 52 wk biopsy with resolution of MASH without fibrosis worsening)

- Phase 3 trials ongoing

Receptors of Major Interest in MAFLD Drug Development

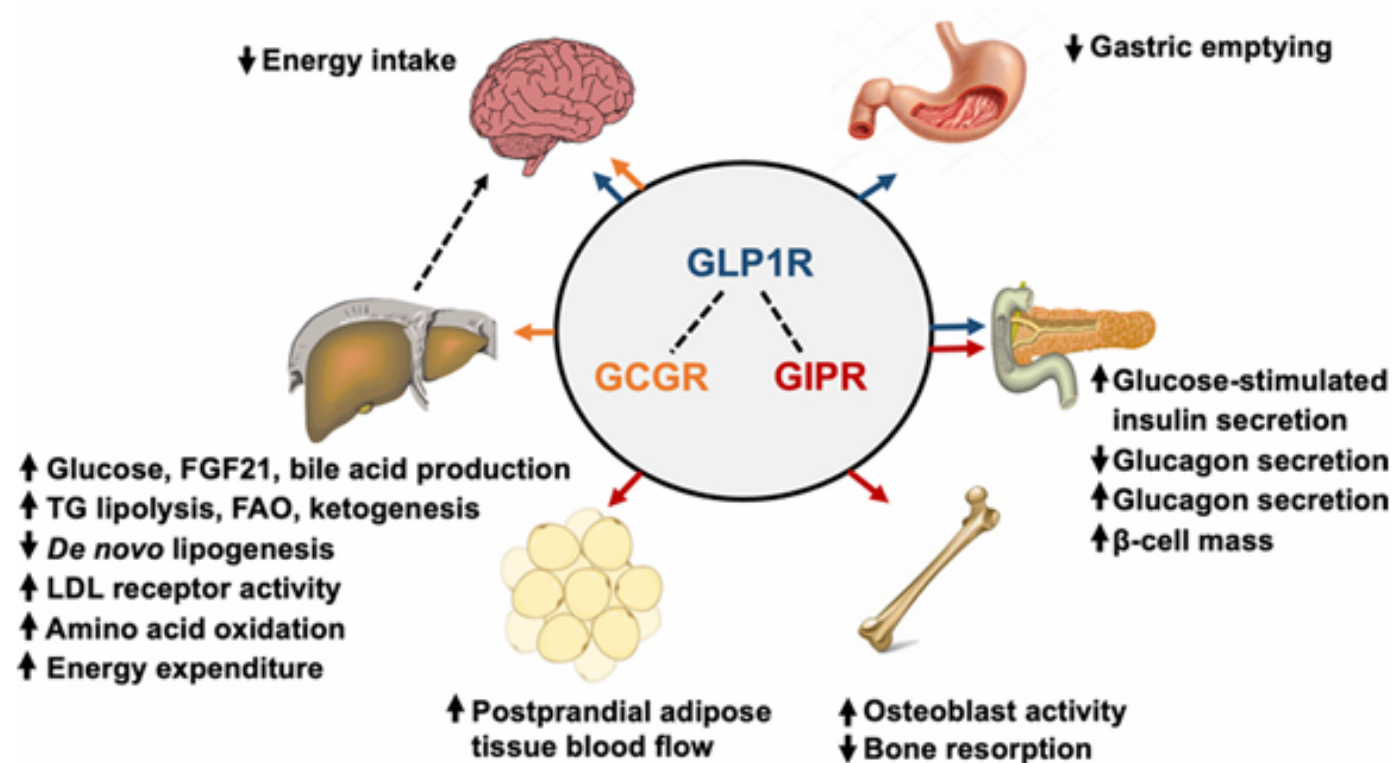


Mechanistic Pathways for GLP-1, GIP, and GCG Receptor Activation

GLP-1R: Glucagon-Like Peptide-1 Receptor

GIPR: Glucagon Insulinotropic Peptide Receptor

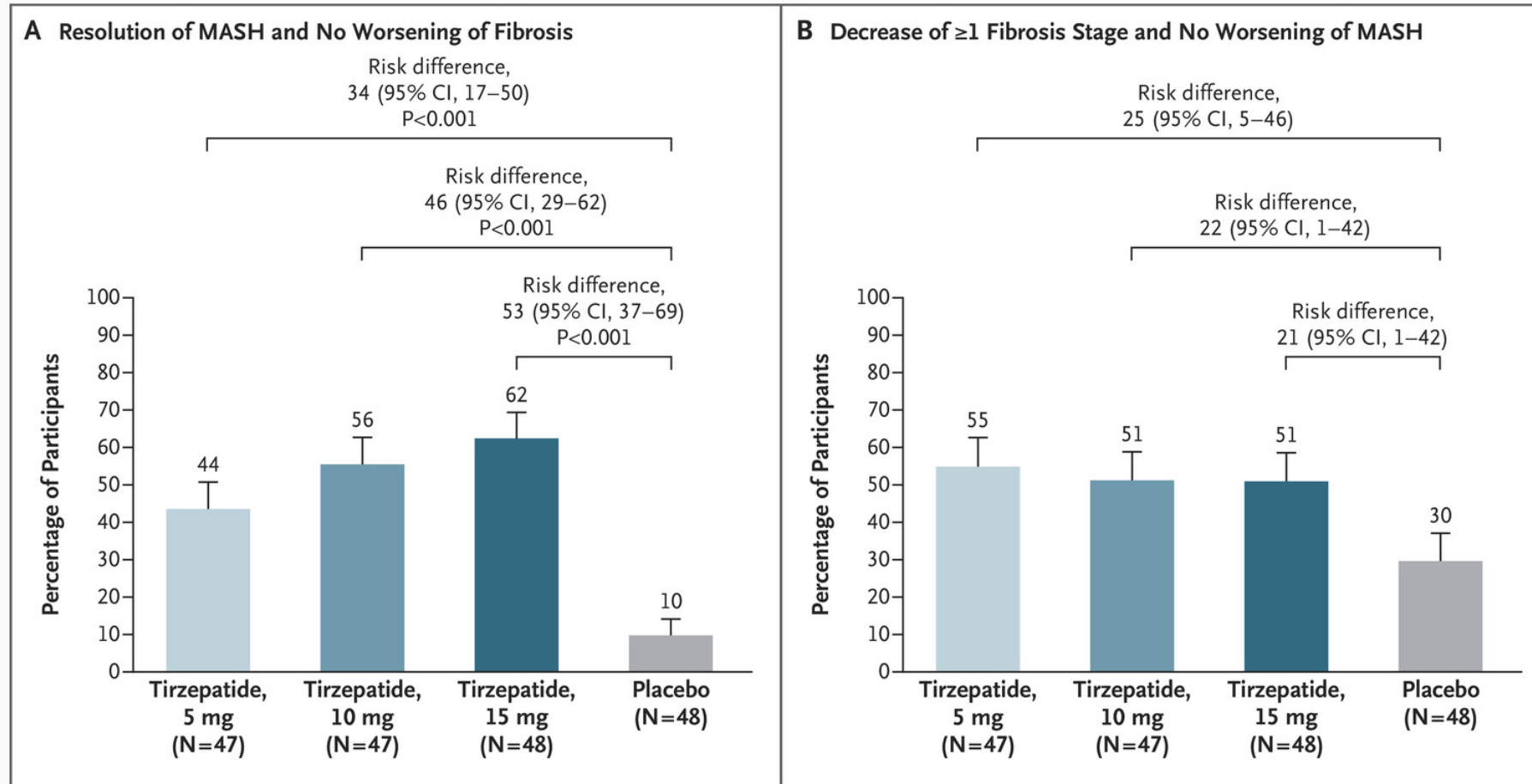
GCGR: Glucagon Receptor



Tirzepatide Once Weekly for the Treatment of MASH (Phase 2)

Tirzepatide 5 mg, 10 mg, 15 mg, vs Placebo for 52 weeks

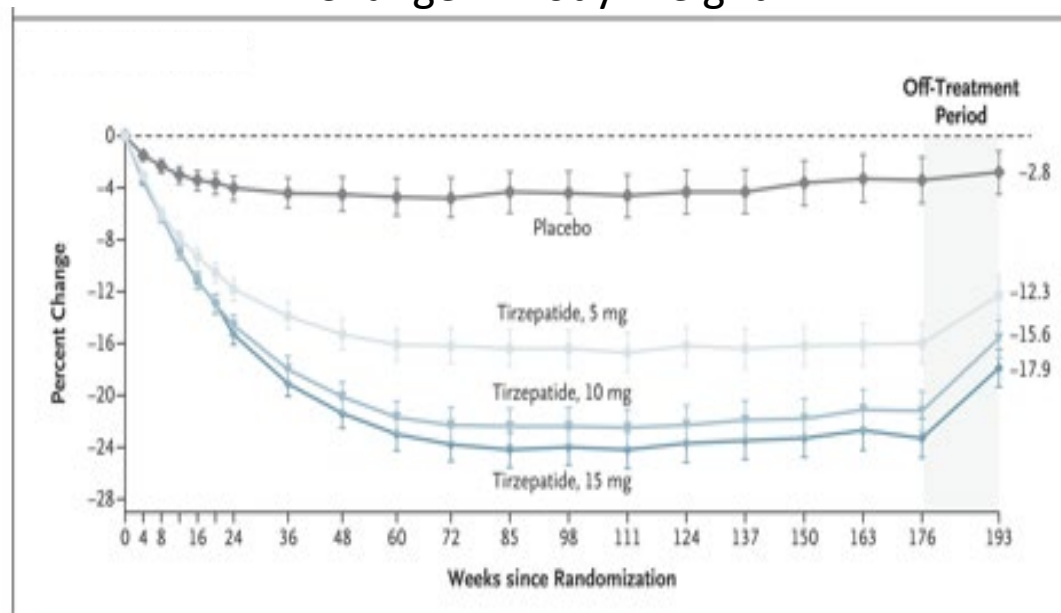
Total n = 190



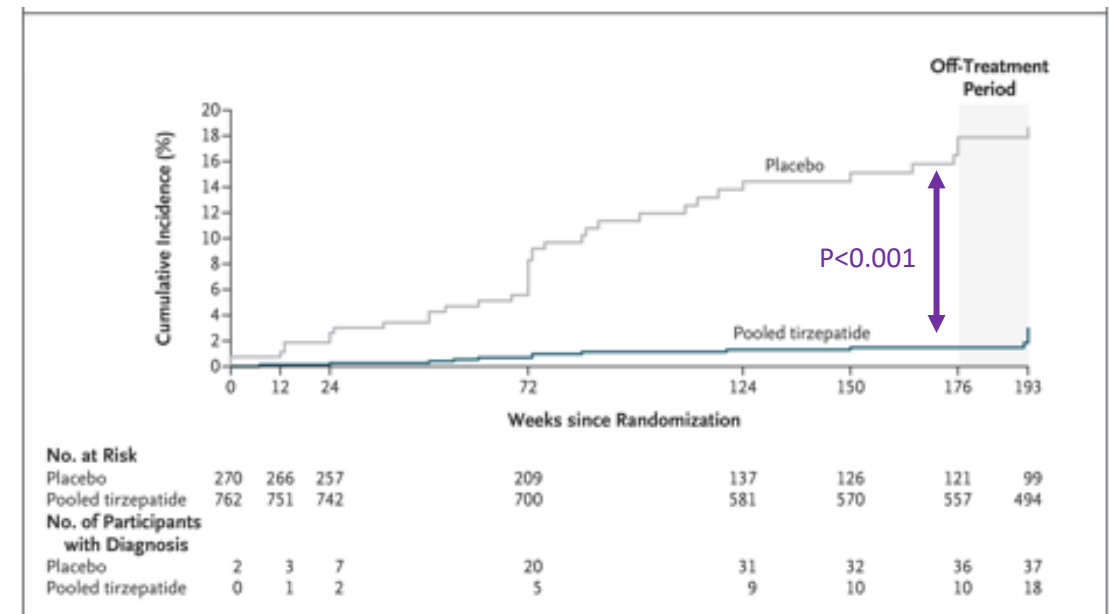
Tirzepatide vs PBO for Obesity and Prevention of T2DM Treatment for 176 Weeks

n=2539 (1032 Prediabetes)

Change in Body Weight



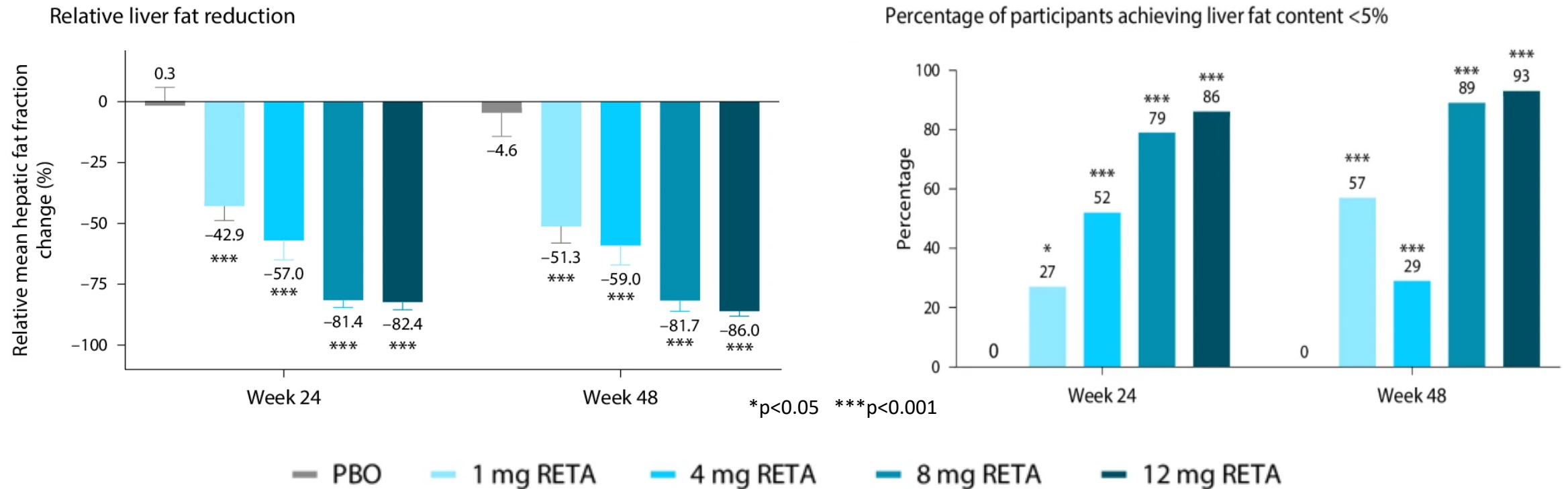
Incidence of Type 2 Diabetes



Tirzepatide can prevent transition from prediabetes to diabetes

Triple Hormone Receptor Agonist Retatrutide for Metabolic Dysfunction-Associated Steatotic Liver Disease: Randomized Phase 2a Trial, n=98

GLP-1 + glucose insulinotropic peptide (GIP) and glucagon receptor agonist



Retatrutide has skipped phase 2b trials and proceeded to phase 3

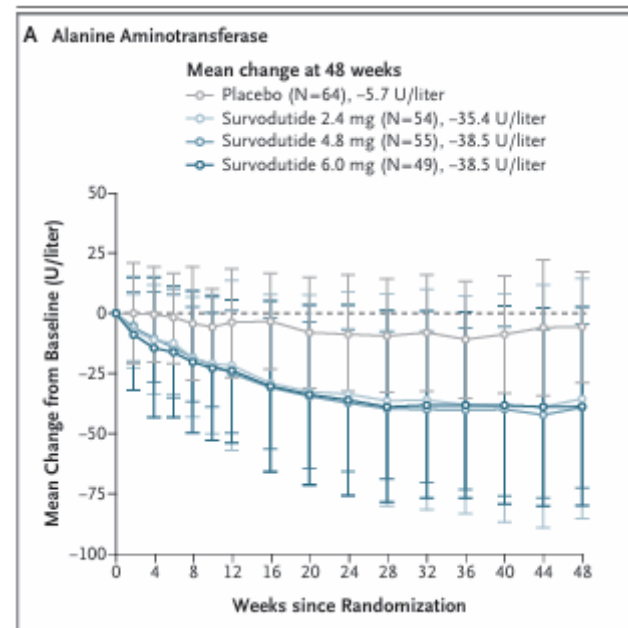
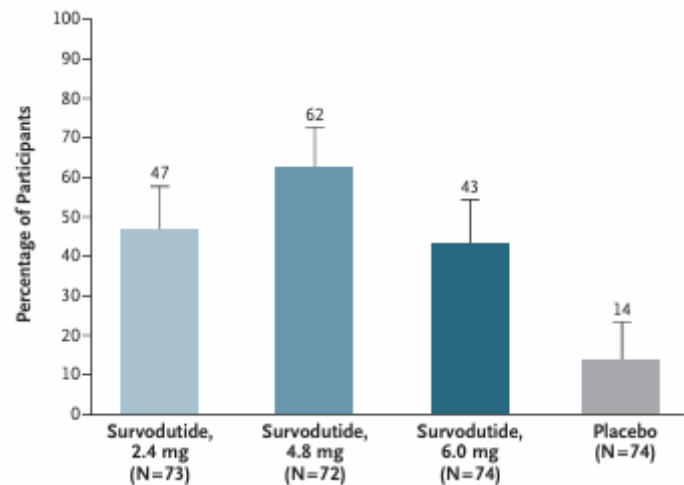
Synergy-Outcomes Study: Tirzepatide vs Retatrutide

Phase 3

- Two parallel groups
- TZP vs placebo
- RETA vs placebo
- Primary treatment period (Week 152)
- Extended maintenance treatment period

Survodutide (GLP-1 + GR Agonist) for MASH With Fibrosis

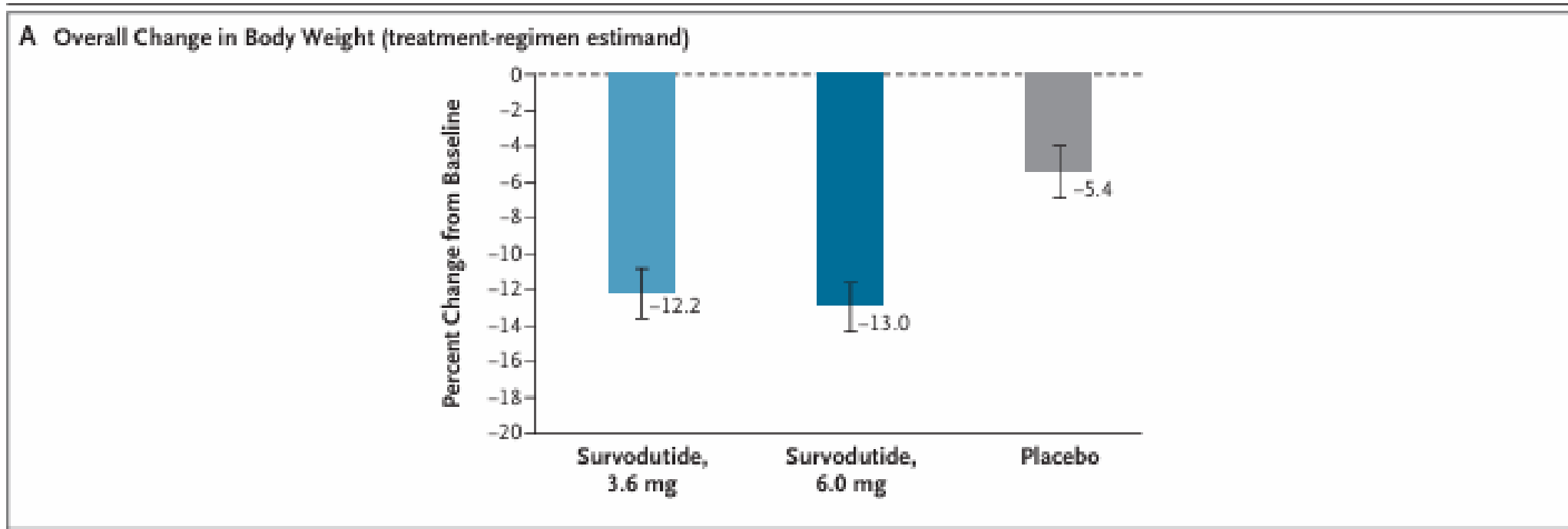
- Placebo or 2.4, 4.8, or 6.0 mg or PBO, n= 293
- 24 week rapid dose-escalation phase, followed by 24 wk maintenance phase
- Primary endpoint: reduction in MASH with no worsening of fibrosis



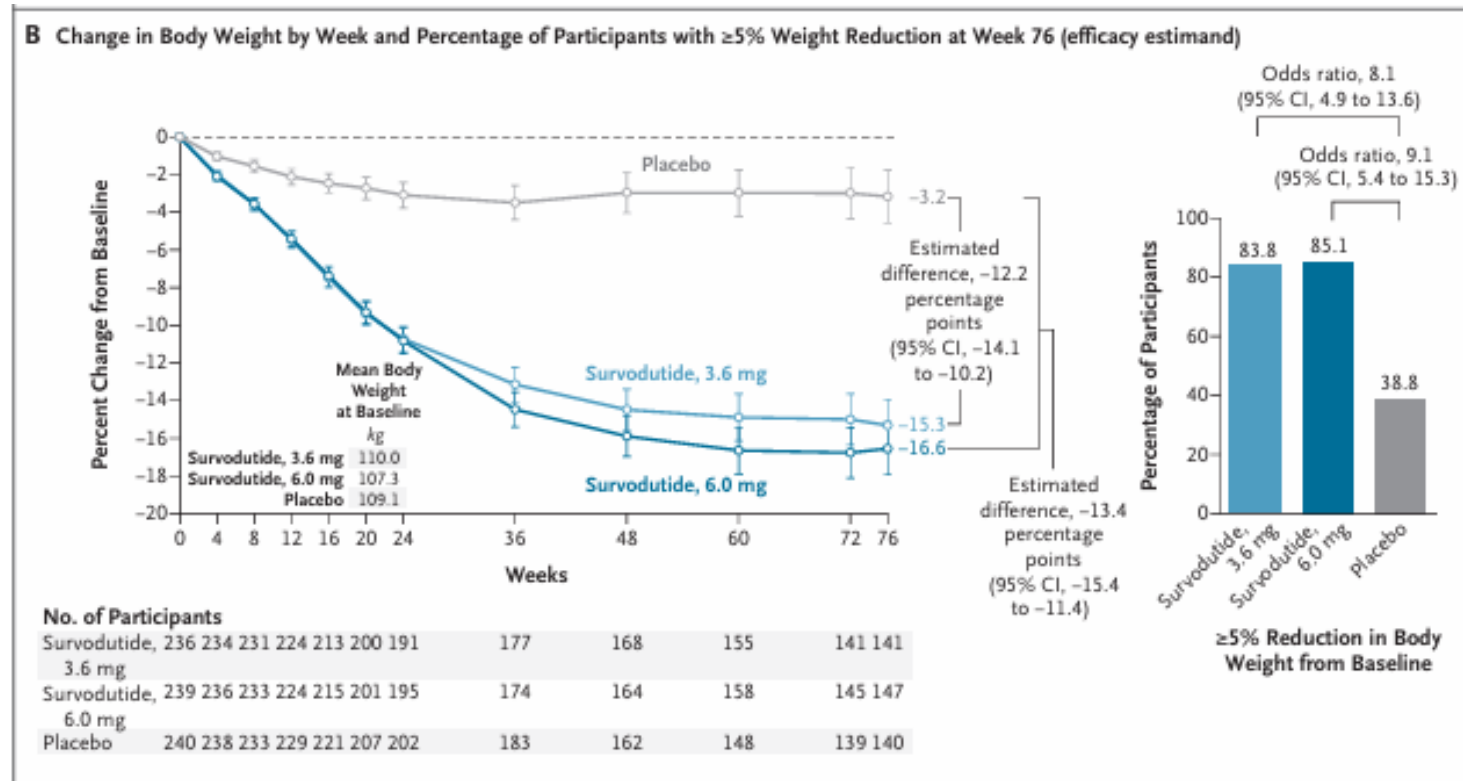
- Improvement in fibrosis 32% vs 18% in 6.0 mg group vs placebo
- Resolution of MASH in 49% of the 6 mg group vs 11% of PBO
- GI side effects (N&V, diarrhea)
- AE leading to d/c 3% PBO vs 16-20% with survodutide

Survodutide Once Weekly for Adults With Obesity: GLP-1 Receptor Agonist + Glucagon Receptor Agonist

- Phase 3, 76 week, double-blind, placebo-controlled, n=725
- Survodutide 3.6 mg vs 6.0 mg vs Placebo (1:1:1)



Survodutide Once Weekly for Adults With Obesity: GLP-1 Receptor Agonist + Glucagon Receptor Agonist



	Survodutide, 3.6 mg (N=241)	Survodutide, 6.0 mg (N=242)	Placebo (N=242)
Adverse event leading to discontinuation of survodutide or placebo	57 (23.7)	60 (24.8)	13 (5.4)
Gastrointestinal adverse event	43 (17.8)	49 (20.2)	7 (2.9)
Adverse events occurring in $\geq 10\%$ of the participants in any trial group†			
Nausea	147 (61.0)	157 (64.9)	42 (17.4)
Vomiting	98 (40.7)	108 (44.6)	15 (6.2)
Diarrhea	77 (32.0)	96 (39.7)	45 (18.6)

Key Areas of Research Interest in GLP-1 Agonist Drug Development in MASH-Related Fibrosis

Understanding mechanism of liver fibrosis improvements in MASH

Optimal ratio of GLP-1 and glucagon receptor agonism for balancing therapeutic efficacy and tolerability in MASH

→ Clinical utility and tolerability of triple agonists over single agonists and dual agonists in MASH

{ Mechanism and functional consequences of muscle loss with GLP-1 agonists

{ Strategies for muscle preservation with concomitant GLP-1 agonist use

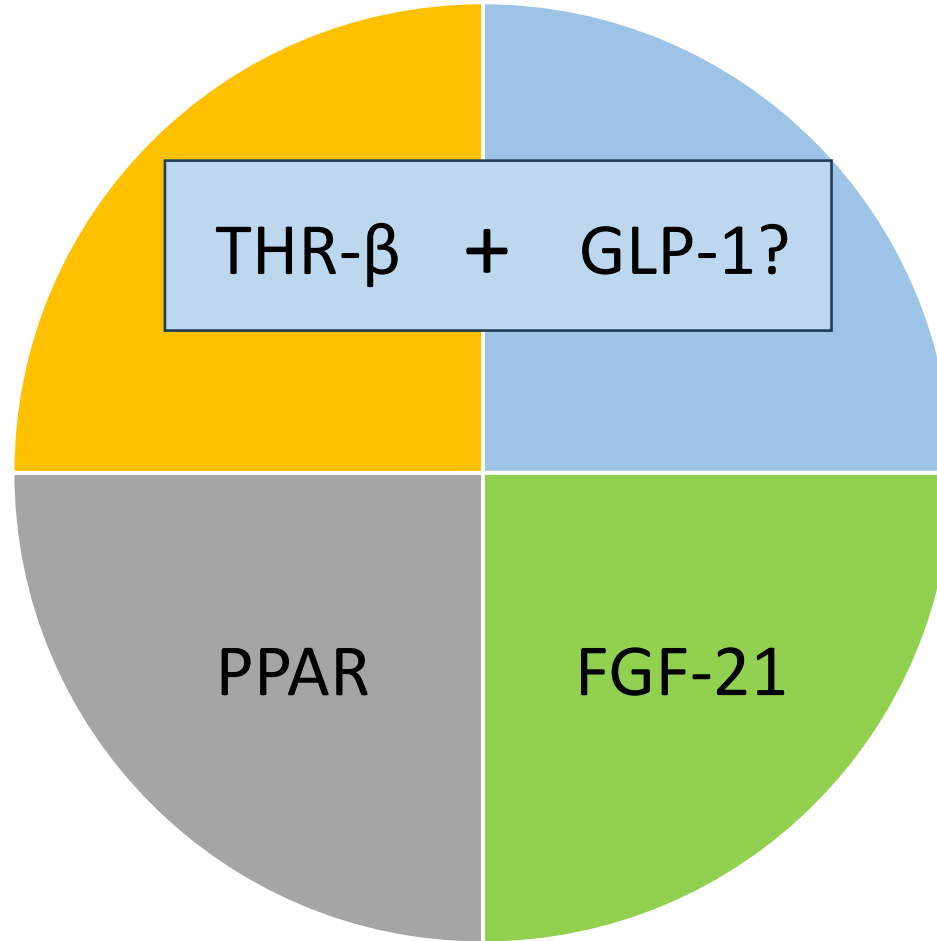
→ Role of combination therapy in GLP-1 agonists with FGF21 analogs and other liver-directed therapies

→ Role of genetic polymorphisms and response to GLP-1 analogs

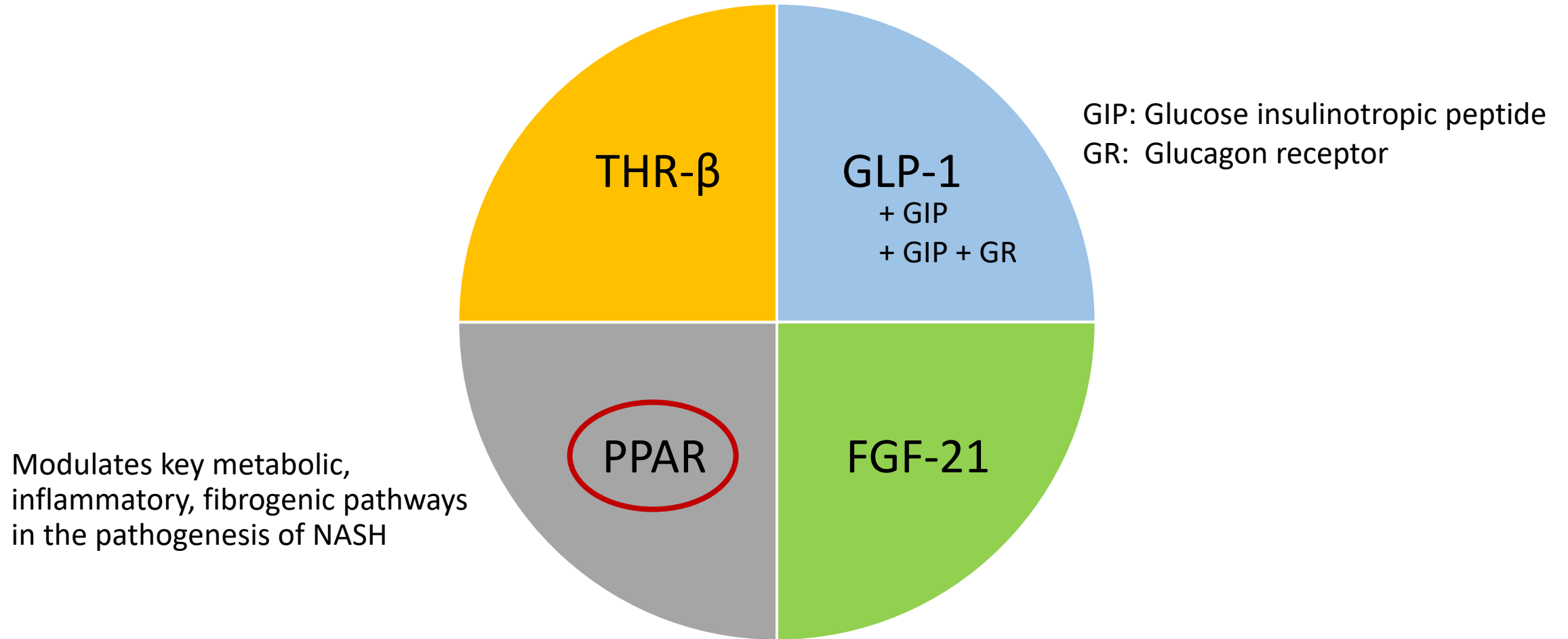
→ Role of GLP-1 in alcohol craving and management of combined metabolic and alcohol-associated steatotic liver disease

Role of GLP-1, GIP, and glucagon-receptor agonists in reversal of cirrhosis and chemoprevention of HCC

Receptors of Major Interest in MAFLD Drug Development



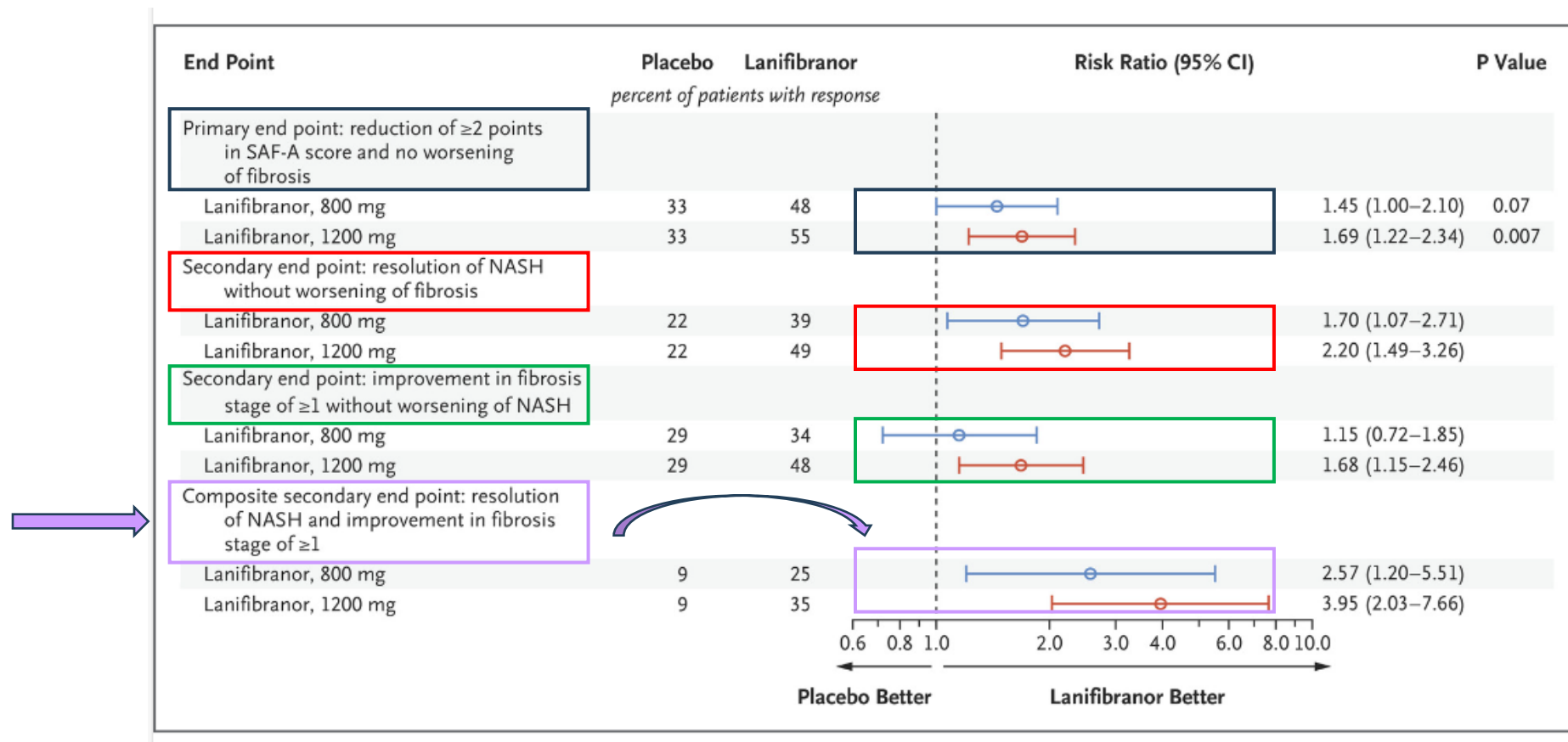
Receptors of Major Interest in MAFLD Drug Development



Efficacy Data From Phase 2b Lanifibranor Study

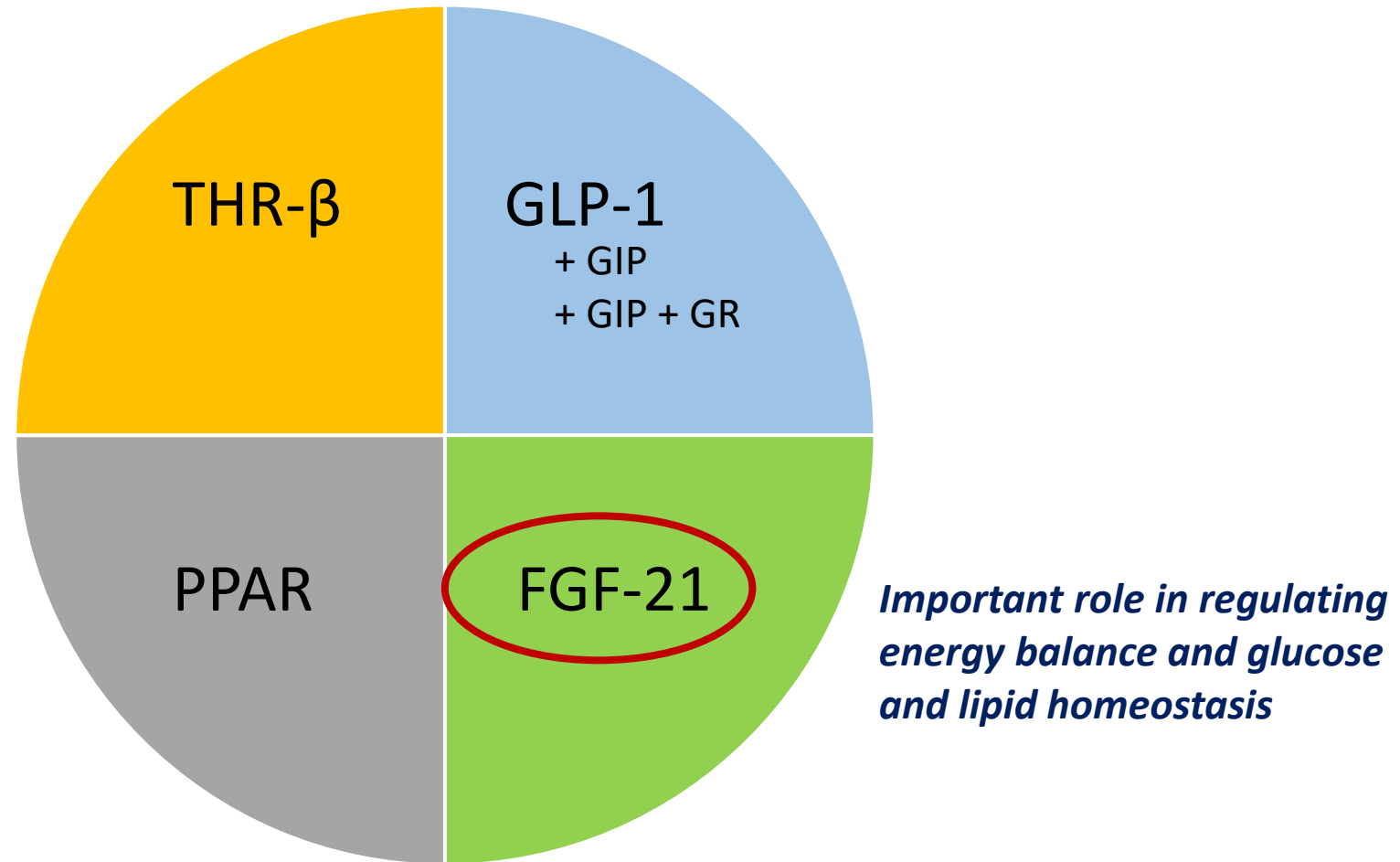
Modulates key metabolic, inflammatory, and fibrogenic pathways in the pathogenesis of MASH

Phase 2b, double-blind, randomized, placebo-controlled trial



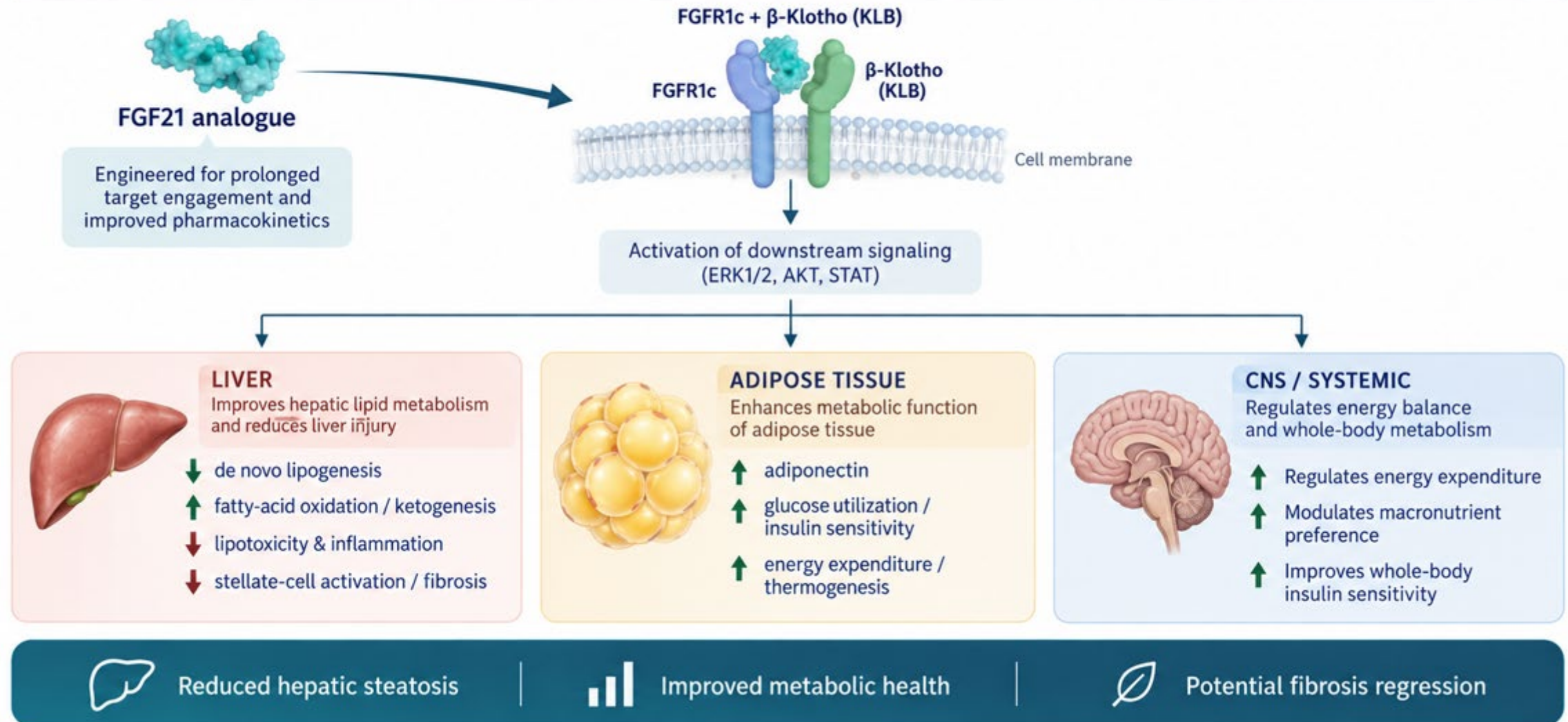
Phase 3 trial in progress

Receptors of Major Interest in MAFLD Drug Development

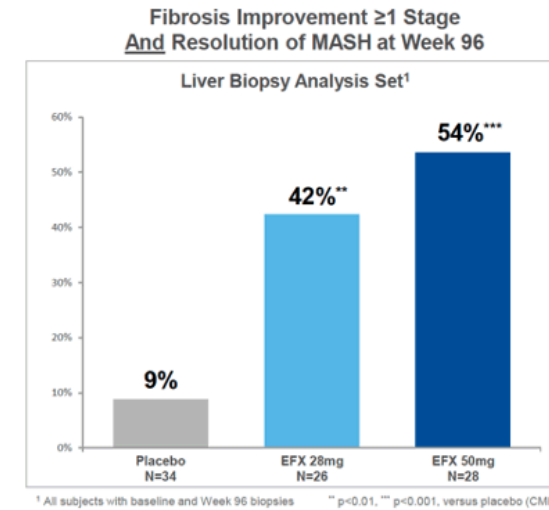
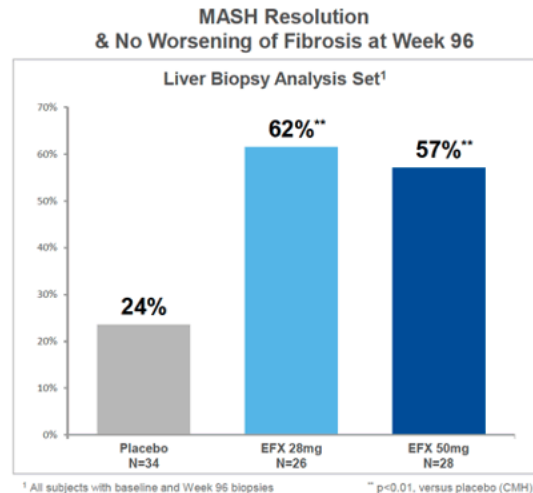
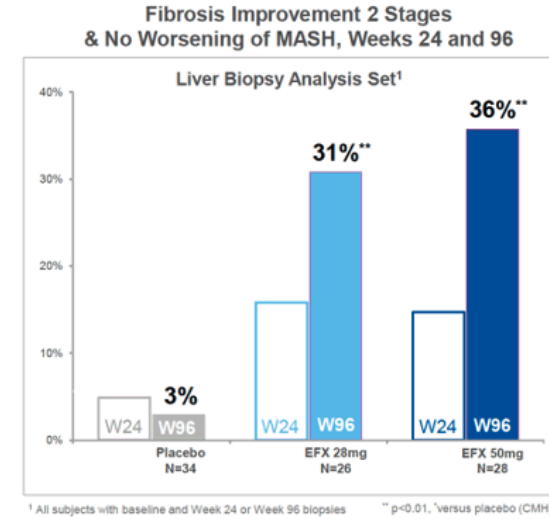
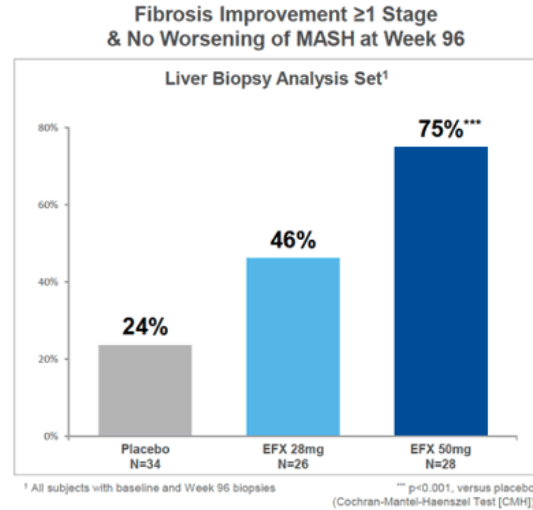
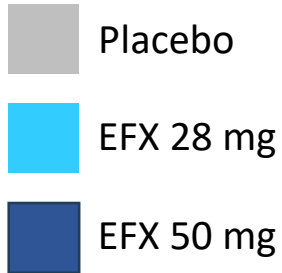


Mechanism of Action: FGF21 Analogues

Targeting metabolic pathways to treat MASH and related cardiometabolic disease



Efruxifermin (FGF-21 Analog) for MASH With Fibrosis Harmony Study (Phase 2b): 96 Week Results



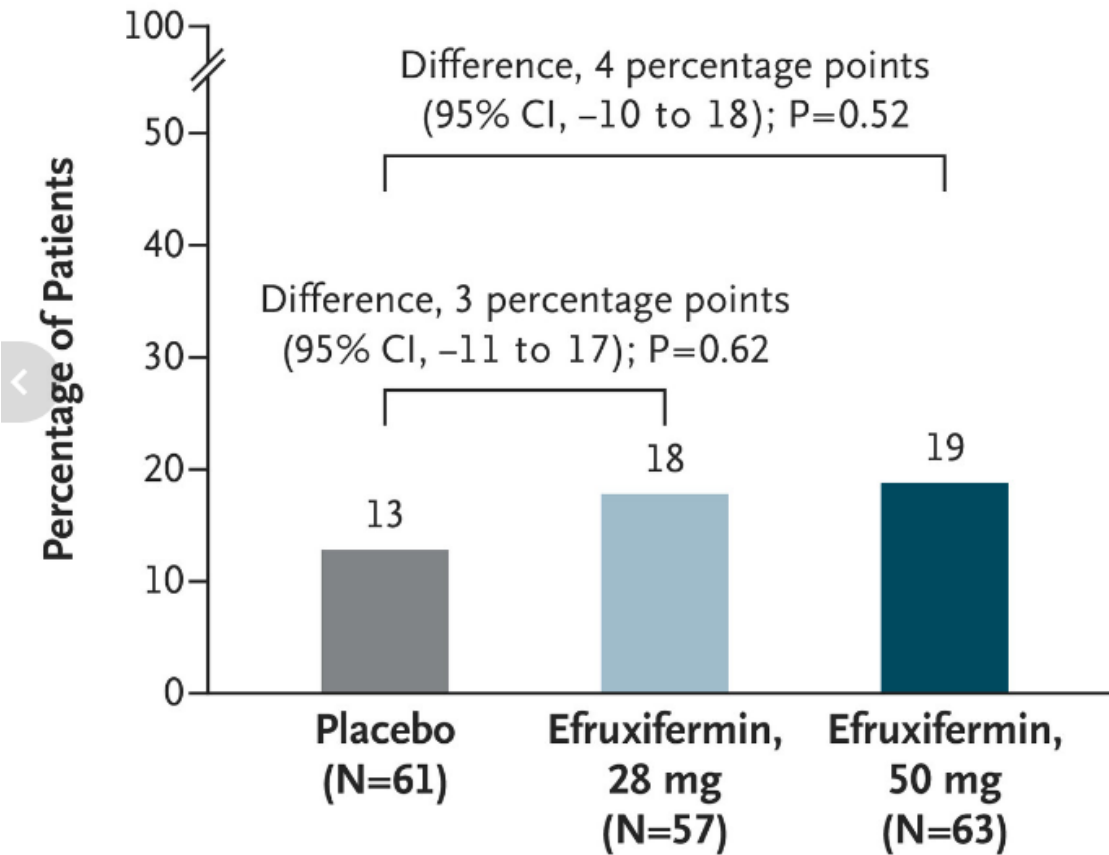
Phase 3 trials
in progress

Harrison SA et al, European Association for the Study of the Liver, Vienna, Austria, June 5-8, 2024

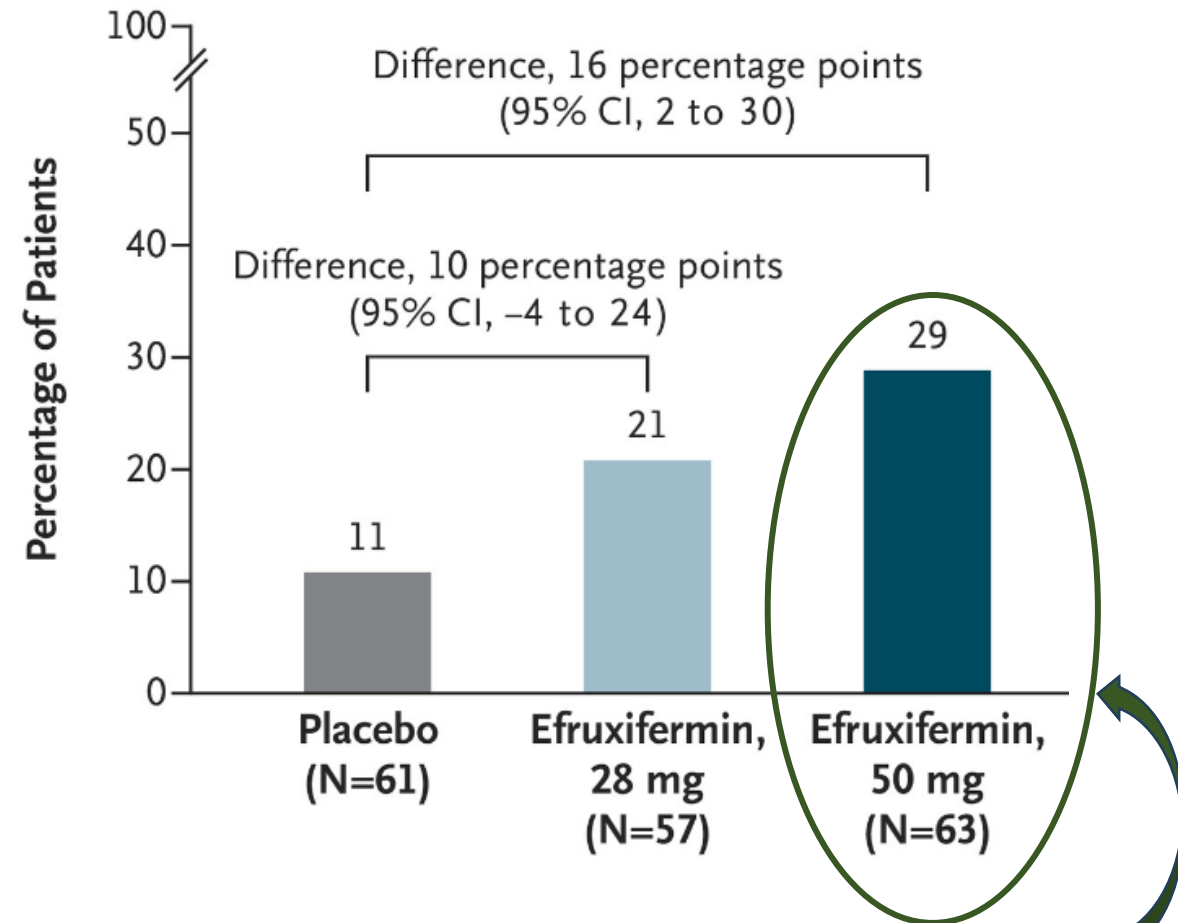
Harrison SA et al, Lancet Gastroenterol Hepatol 2023;8:1080-93

Efruxifermin (FGF-21 Analogue) for MASH Cirrhosis

A Reduction in Fibrosis of ≥ 1 Stage without MASH Worsening at Week 36

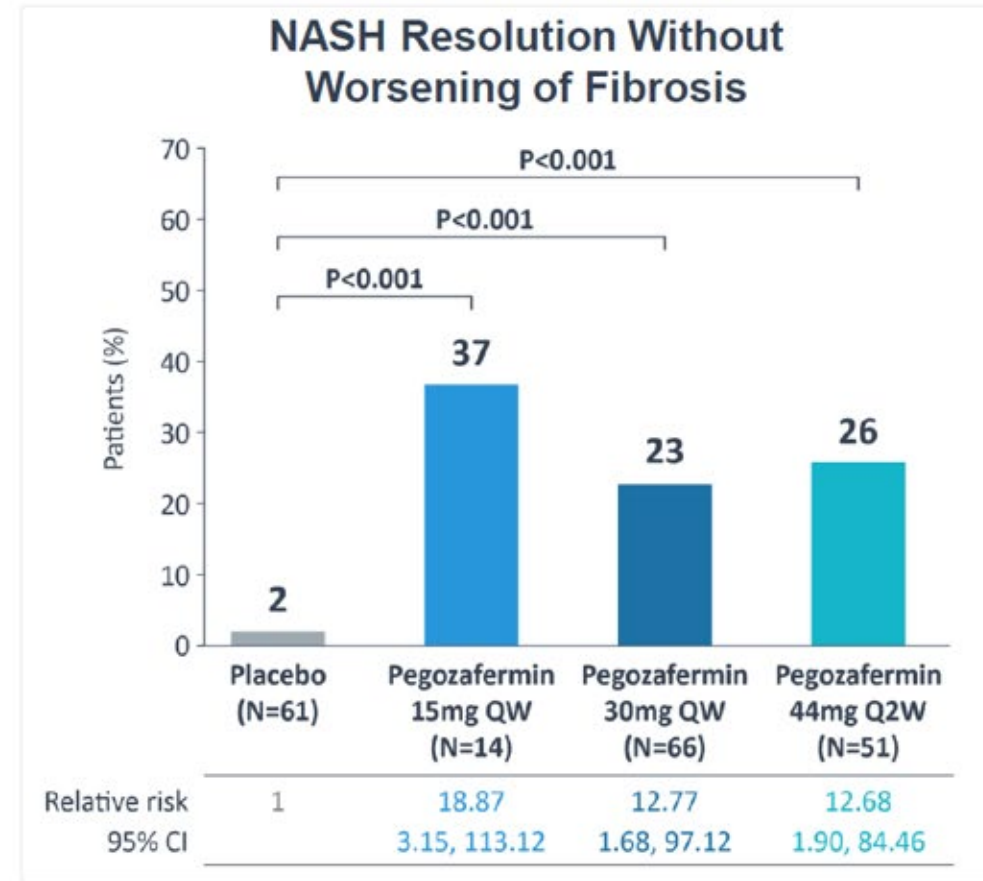
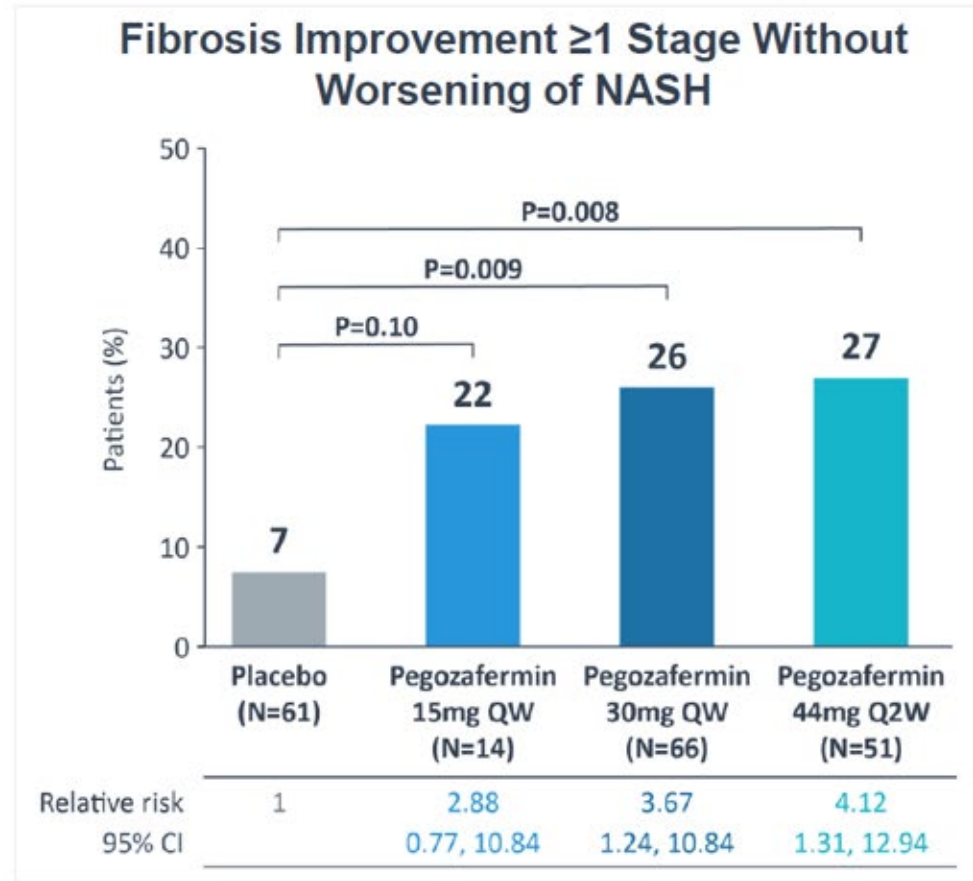


B Reduction in Fibrosis of ≥ 1 Stage without MASH Worsening at Week 96



Significant reduction in fibrosis seen at wk 96

Pegazofermin (FGF-21 Agonist) for F2-3 NASH: Phase 2b



Phase 3 trial is in progress

Key Areas of Research Interest in FGF21 Use in MASH

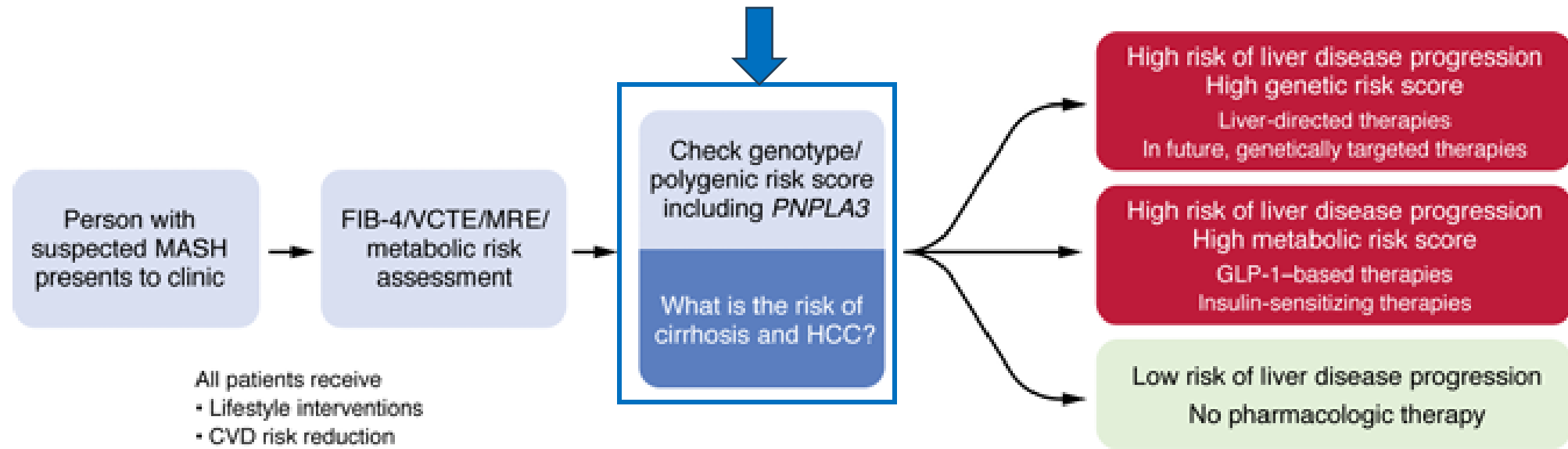
Durability of response and antigenicity

Mechanism and significance of bone turnover

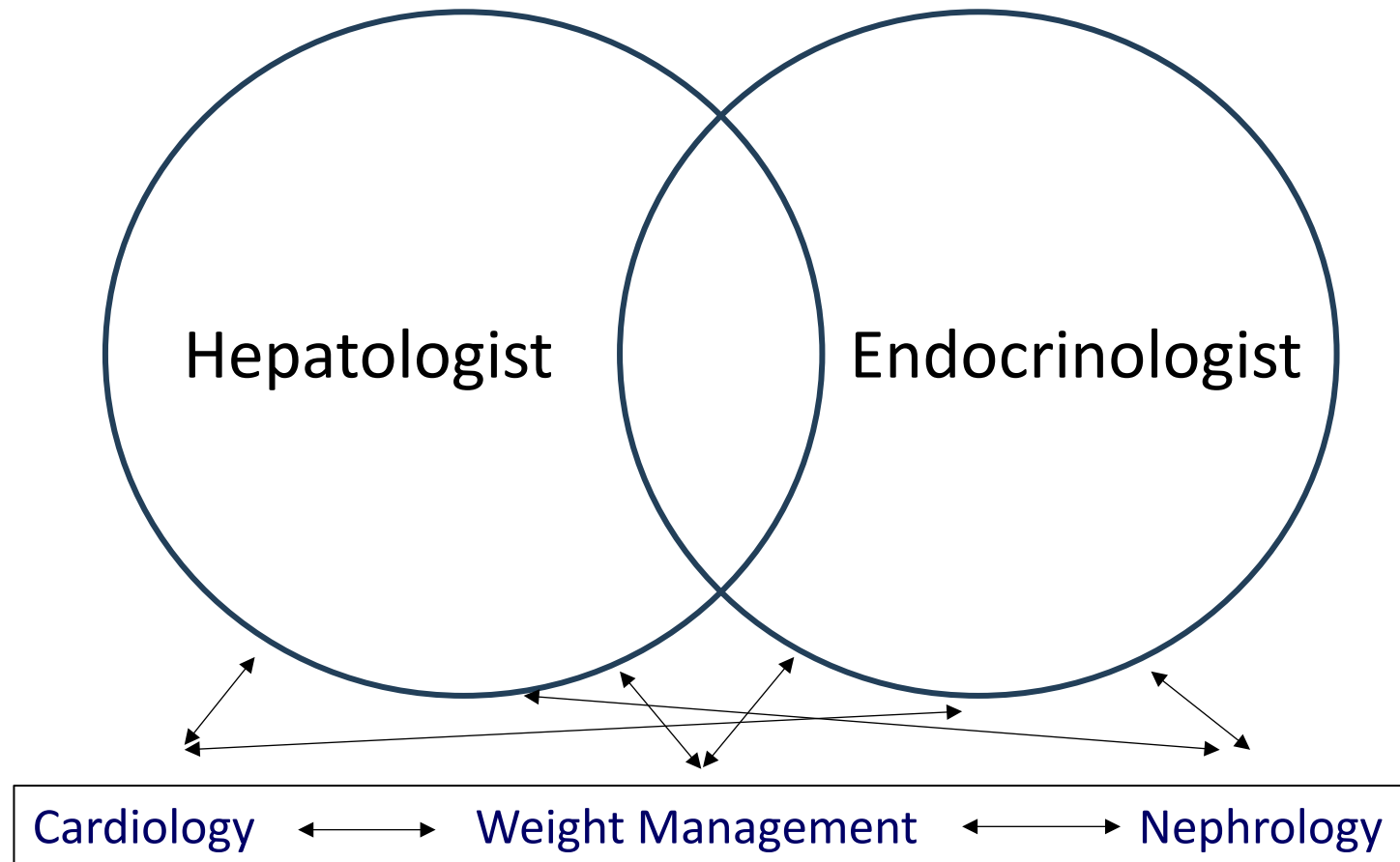
- Role of FGF21 biology in reducing alcohol craving and management of combined metabolic and alcohol-associated steatotic liver disease
 - Strategies for muscle preservation with concomitant GLP-1 agonist use
 - Role of combination therapy in FGF21 analogs with GLP-1 and other therapies
 - Role of genetic polymorphisms and response to FGF21 analogs
 - Role of FGF21 analogs in reversal of cirrhosis and chemoprevention of HCC
-

Another New Horizon: Precision Medicine Paradigm for MASH Treatment From a Genetic Viewpoint

Several genetic polymorphisms have been identified as associated with MAFLD/MASH



Expansive Perspective of the Hepatologist's Role



SGLT2 Inhibitor Use and Liver-Related Events: A Meta-analysis

Methods:

- Eight cohort studies
- n=626,104 with T2DM



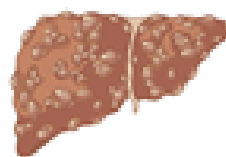
n=228,298 SGLT2 inhibitor new users

n=397,806 other DM medication new users

Outcomes: SGLT2 Inhibitors vs. Other Diabetes Medication

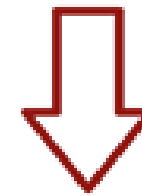
Major Adverse Liver Outcomes

HR 0.83
(95% CI 0.72-0.95)



Liver-Related Death

HR 0.64
(95% CI 0.50-0.82)



Conclusions: SGLT2 inhibitor use was associated with significant risk reduction in major adverse liver outcomes in comparison with use of DPP-4 inhibitors, metformin, or pioglitazone but not GLP-1 receptor agonists.

DM, diabetes mellitus; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

Several other studies, including a small RCT (BMJ 2025), support this conclusion

Statins are Beneficial for the Liver in Patients with MASLD

- ~ 8000 patients followed for median 4.6 years
- 40.5% on a statin
- Compensated advanced CLD (cACLD) in 17% of patients (LSM > 10 kpa)
- Cox regression models stratified by cACLD and statin use
- Lower risk of liver-related outcomes and liver stiffness progression in statin users in all comparisons (cACLD and non-ACLD)($p < 0.001$)
- *Consistent with growing body of literature on statins and liver prognosis*
- *Many physicians still think statins are “bad” for the liver*

Challenges in Current MASH Trials

- Trials are usually of long duration (years)
- Regulators want to see improved clinical outcomes (fewer liver–related events)
- Placebo arms in an era of available drugs (some approved for this indication, others not)
- Impact of lifestyle interventions
- We need your support!