Treatment Updates in MASH

Andres Gomez-Aldana MD

Transplant Hepatologist

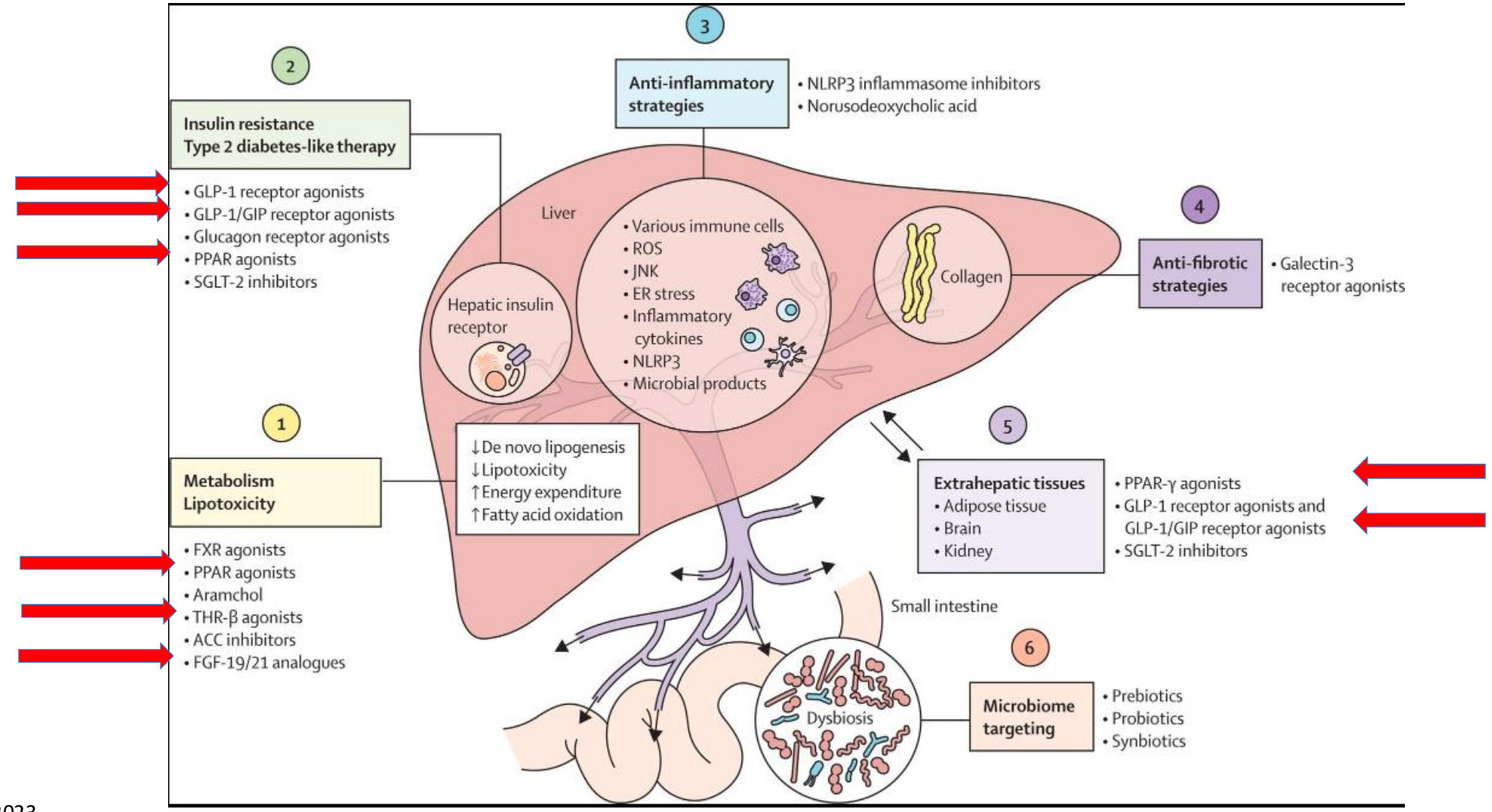
Texas Liver Institute

UIW - UTHSCSA

Texas Liver Institute

UT Health San Antonio Long School of Medicine

This is a very active area of research….

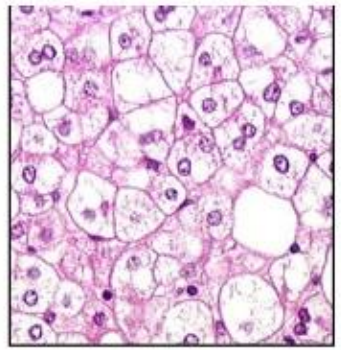


The Lancet, 2023.

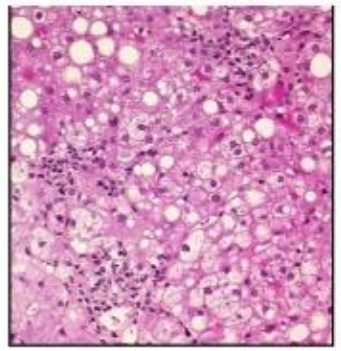
FDA Endpoints for Drug Approval
Evaluate at Week 24 versus baseline

MASH resolution (Total absence of ballooning/absent or mild inflammation)
Without worsening of **fibrosis** (increase of ≥1 stage)

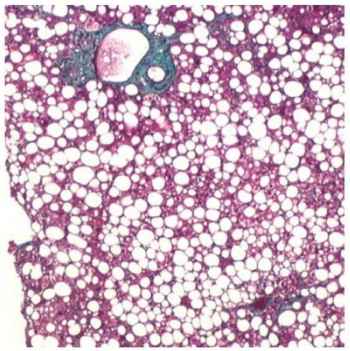
Improvement (reduction) in fibrosis of at least one stage,
Without worsening of **MASH** (Increased ballooning, inflammation, or steatosis)



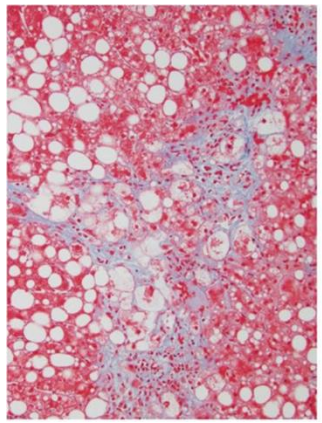
Ballooning



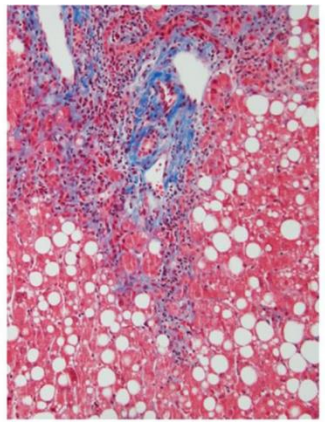
Inflammation



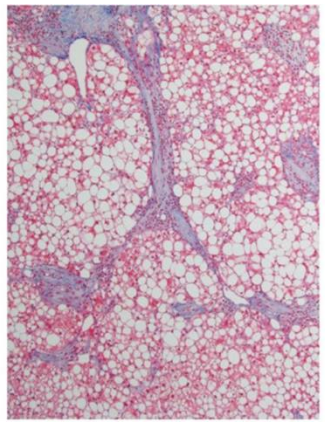
Steatosis



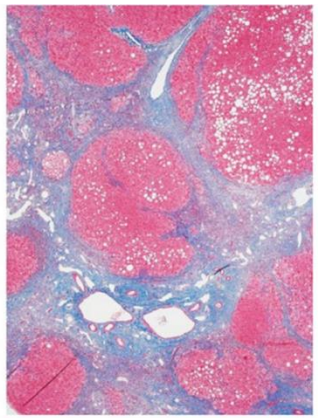
Perisinusoidal
1



Periportal
2



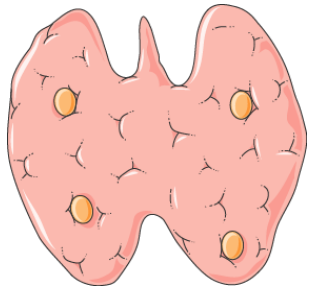
Bridging
3

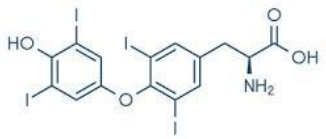


Cirrhosis
4

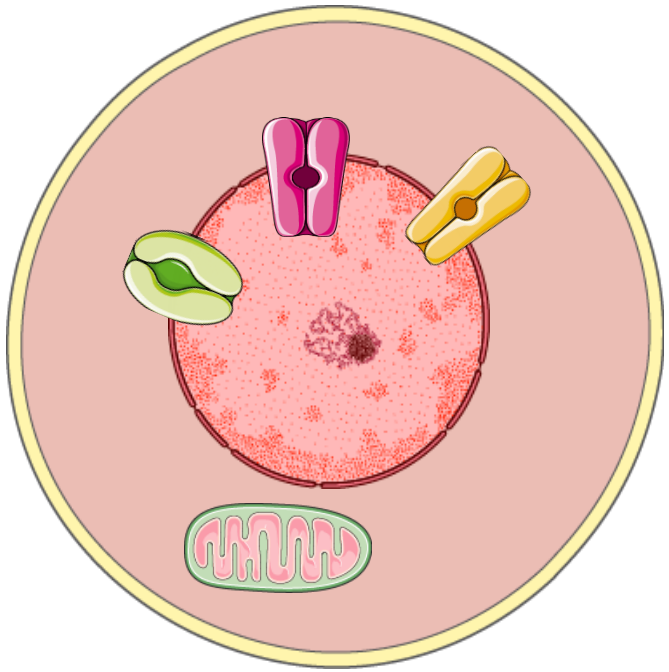
Thyroid Hormone Receptor-β (THR-β) Agonists in Late-Stage Development

Class	Agent	Description	Development phase
THR-β agonists	Resmetirom	THR-β agonist	MASH with F4/cirrhosis
	VK2809	THR-β agonist	





thyroxine



THR - α

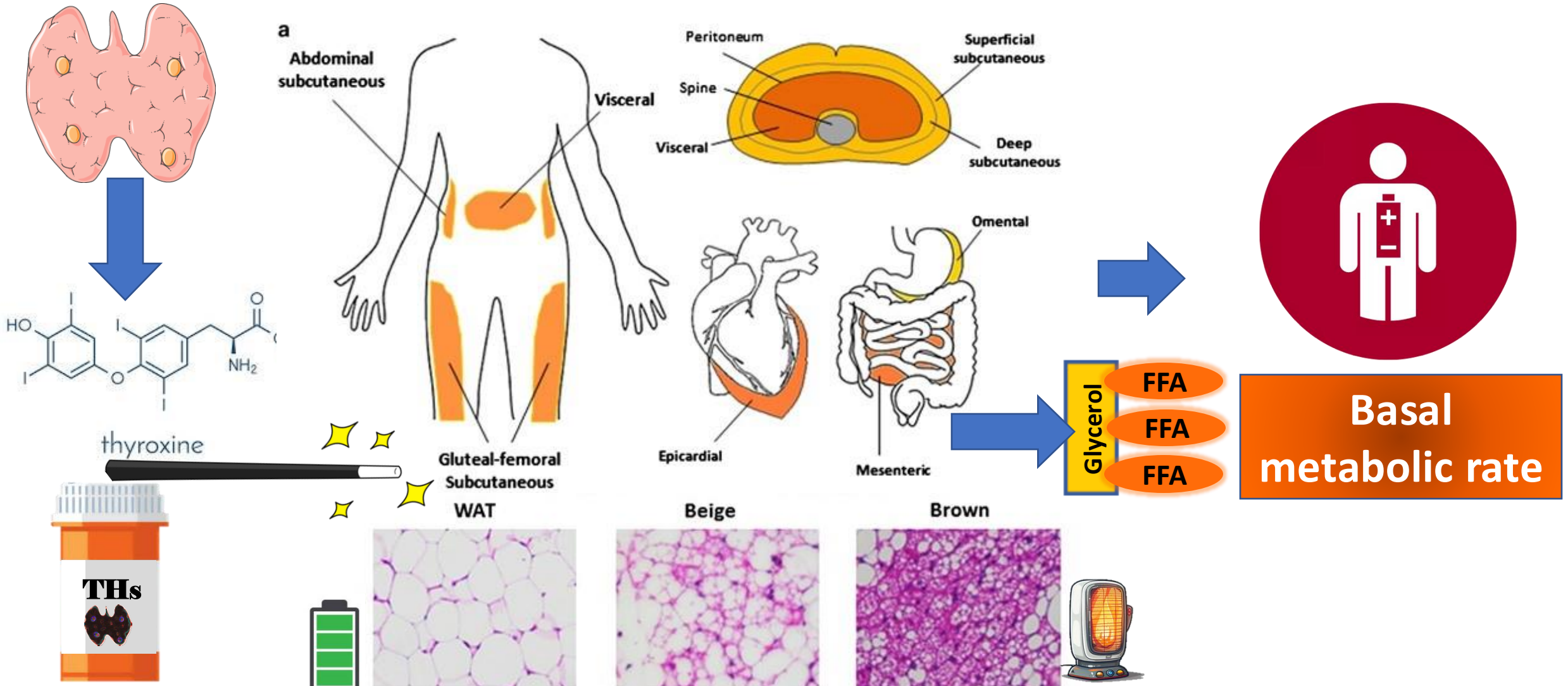
Bones, brain, heart, skeletal muscle, and adipose tissue.

THR - β

liver, kidney, pituitary gland, and retina

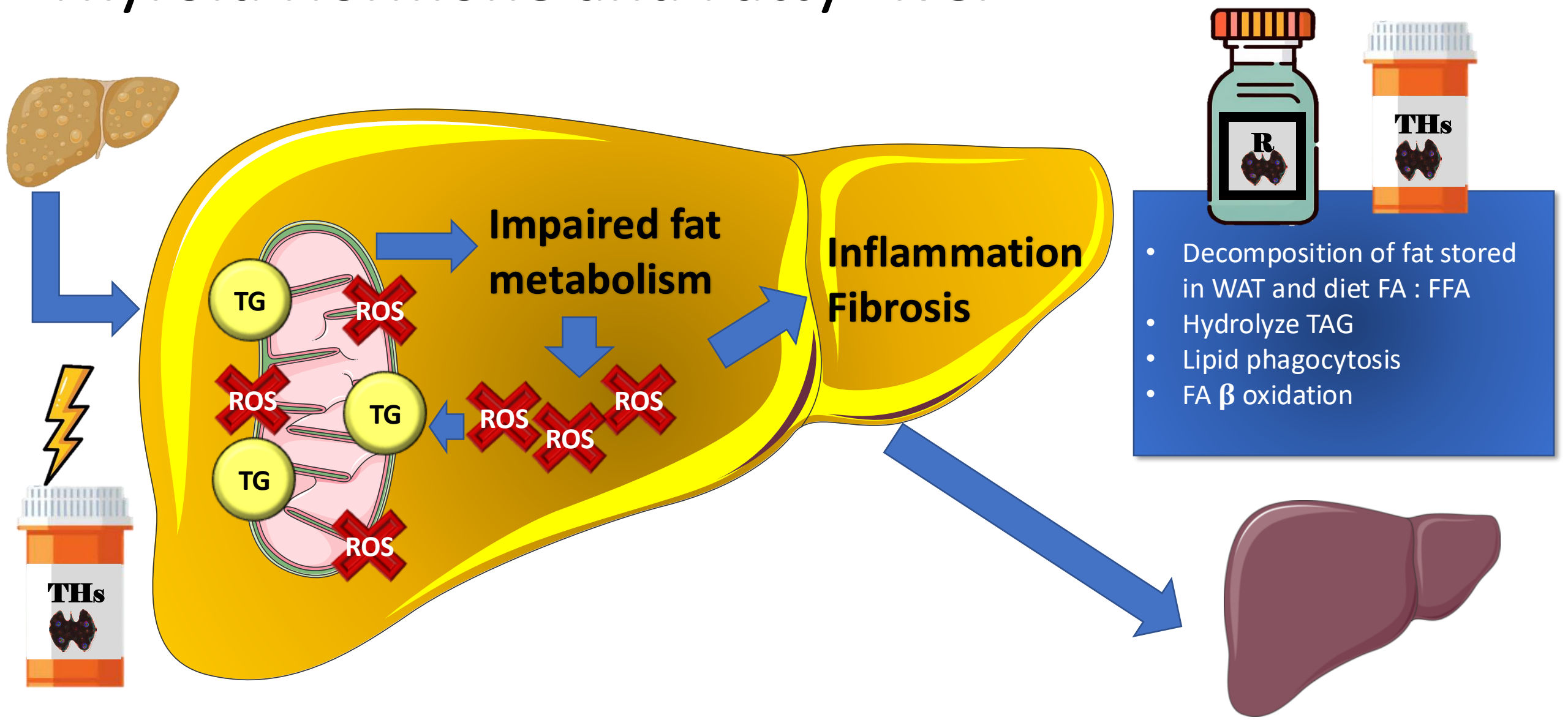
Kwok KH. Exp Mol Med. 2016;48 :e215.

Thyroid Hormone Receptor-β (THR-β) Agonists



Kwok KH. Exp Mol Med. 2016;48 :e215.

Thyroid Hormone and Fatty Liver



Begriche K. Mitochondrion 2006 ;6:1-28

Resmetirom is the First FDA Approved Drug for MASH

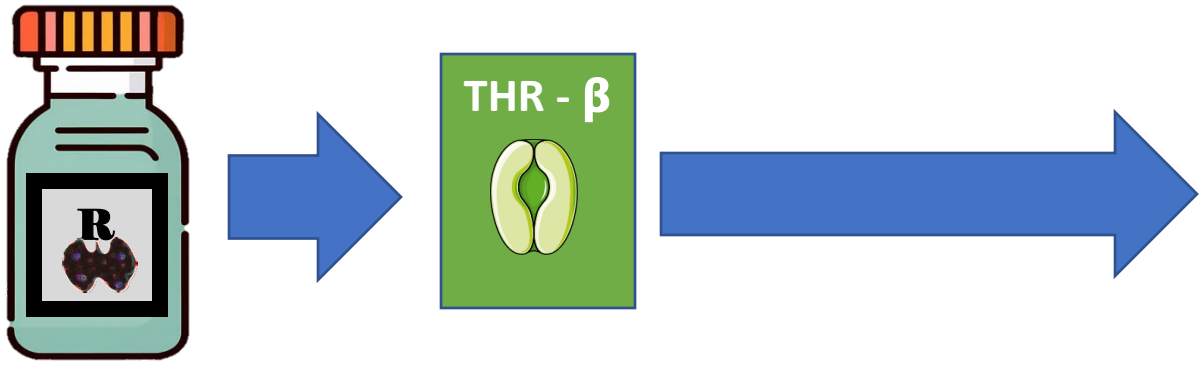
Oral, partial agonist of thyroid hormone receptor-beta (THR-β)[1]

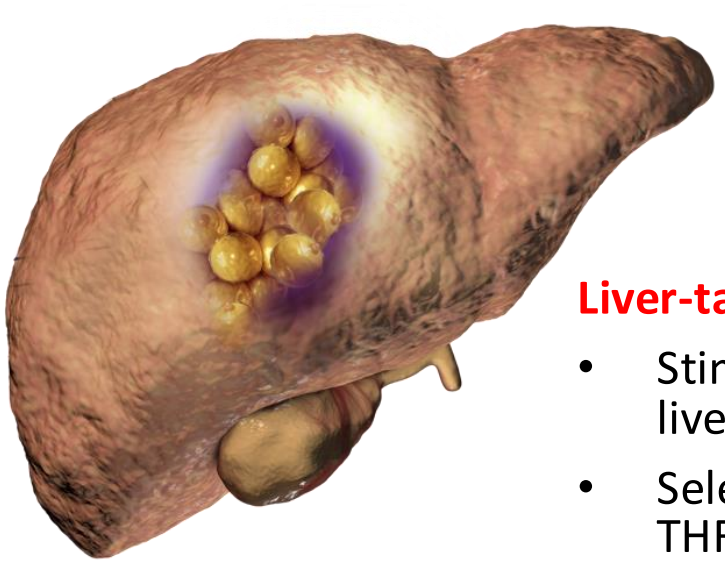
Approved March 2024, for the treatment of adults with **NASH[a] and moderate-to-advanced fibrosis**

[a]*NASH* used due to publication date.

1. Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509; 2. Rezdiffra (remetirom) [prescribing information]. Madrigal Pharmaceuticals, Inc.; West Conshohocken, PA; 2024.

Resmetirom Mechanism of Action





Liver-targeted activity

- Stimulates THR-β receptors in the liver
- Selectively effective in activating THR-β over THR-α outside the liver (heart and bones)

↓ Hepatic Steatosis

↓ Intrahepatic triglycerides
↑ Stimulates lipophagy
↑ Stimulates mitochondrial biogenesis
↓ Lipogenesis

Fibrogenesis

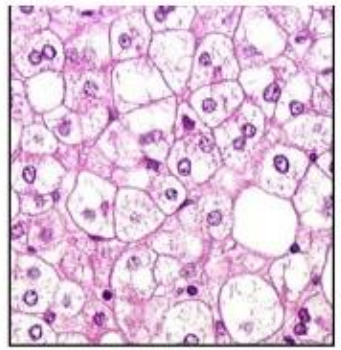
↓ TGF-β signaling

1. Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509; 2. Rezdiffra (resmetirom) [prescribing information]. Madrigal Pharmaceuticals, Inc.; West Conshohocken, PA; 2024.

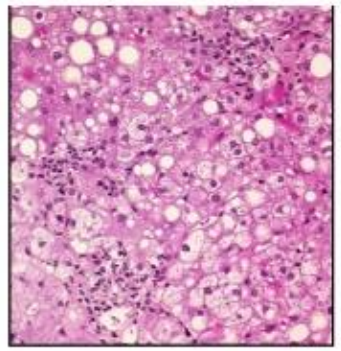
FDA Endpoints for Drug Approval
Evaluate at Week 24 versus baseline

MASH resolution (Total absence of ballooning/absent or mild inflammation)
Without worsening of **fibrosis** (increase of ≥1 stage)

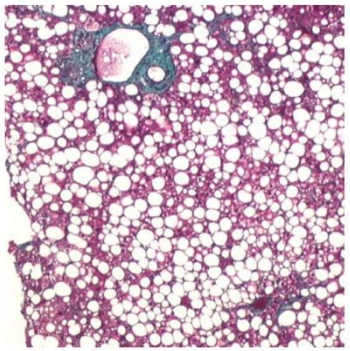
Improvement (reduction) in fibrosis of at least one stage,
Without worsening of **MASH** (Increased ballooning, inflammation, or steatosis)



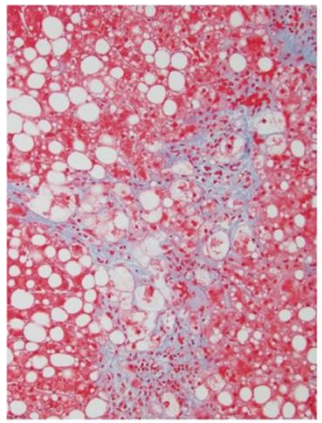
Ballooning



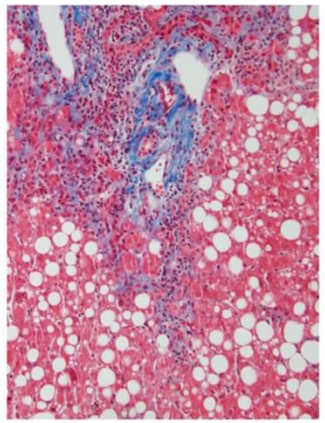
Inflammation



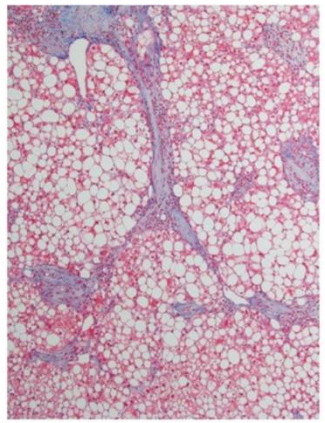
Steatosis



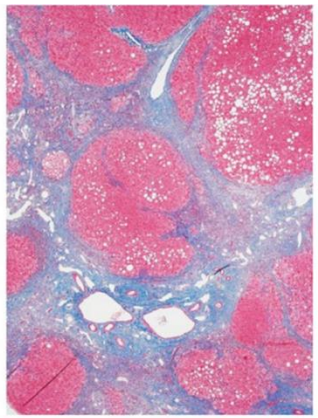
Perisinusoidal
1



Periportal
2



Bridging
3



Cirrhosis
4

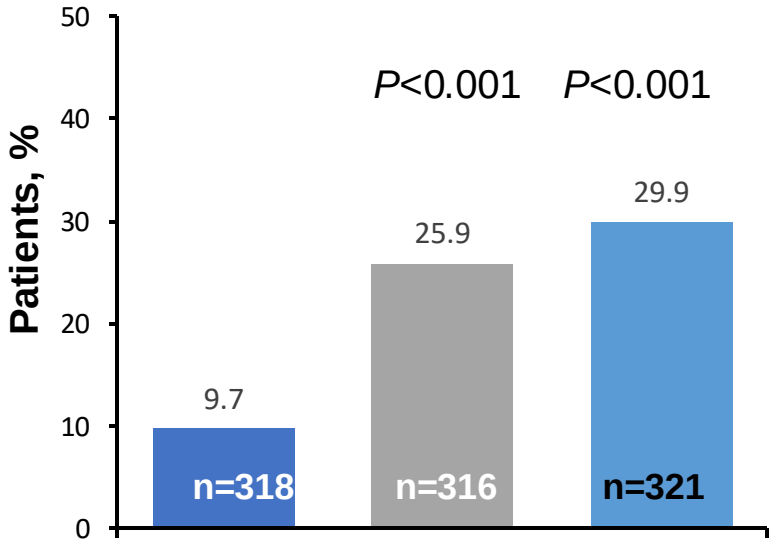
Resmetirom Phase 3 (MAESTRO) Study: Patient Population

Characteristic	Overall (N=966) %
Fibrosis stage F1b F2 F3	 5.1 33.0 61.9
Type 2 diabetes	67.0
Hypertension	78.1
Dyslipidemia	71.3
Statin use	48.9
GLP-1 receptor agonist use	14.3

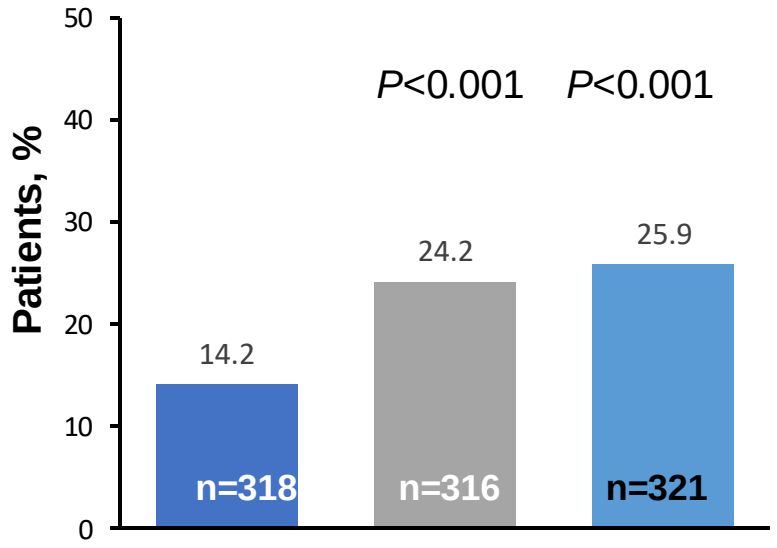
Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509.

Resmetirom Phase 3 (MAESTRO) Study: Primary and Key Secondary Endpoints

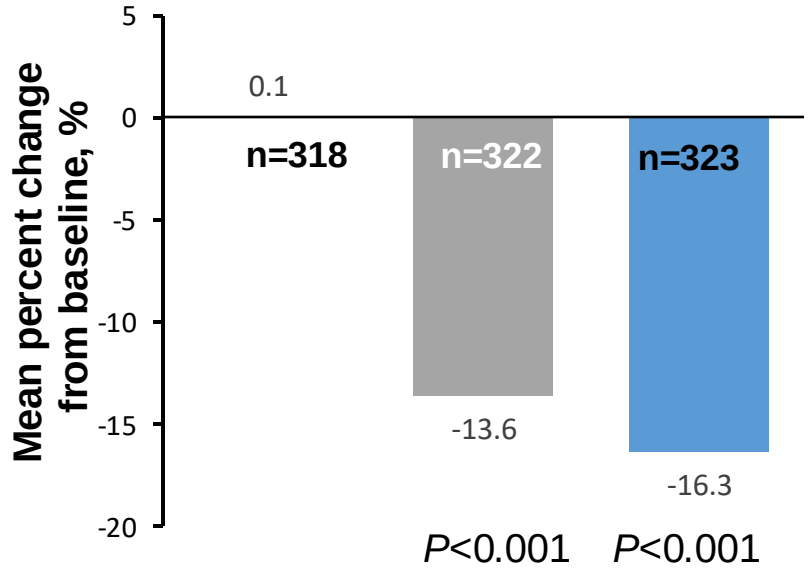
NASH resolution with no worsening of fibrosis



Fibrosis improvement by ≥1 stage with no worsening of NAFLD activity score



Percent change in LDL cholesterol at week 24



Placebo Resmetirom 80 mg Resmetirom 100 mg

Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509.

Resmetirom: Phase 3 (MAESTRO Study): Safety Summary

Adverse events >10% of patients in any group

	Resmetirom 80 mg (n=322) %	Resmetirom 100 mg (n=323) %	Placebo (n=321) %
Diarrhea	**27.0**	**33.4**	**15.6**
COVID-19	21.4	16.7	20.6
Nausea	**22.0**	**18.9**	**12.5**
Arthralgia	14.9	10.8	12.5
Back pain	10.9	8.4	11.8
Urinary tract infection	10.2	8.4	8.4
Fatigue	10.2	8.0	8.7
Pruritus	8.1	11.5	6.9
Vomiting	8.7	10.8	5.3

NOTE: Increases in mean ALT and AST (<1.5x baseline) were observed in the first 4 weeks after initiating resmetirom treatment. Values returned to baseline ~8 weeks after initiating treatment.

Harrison SA et al. *N Engl J Med*. 2024 Feb 8;390(6):497-509.

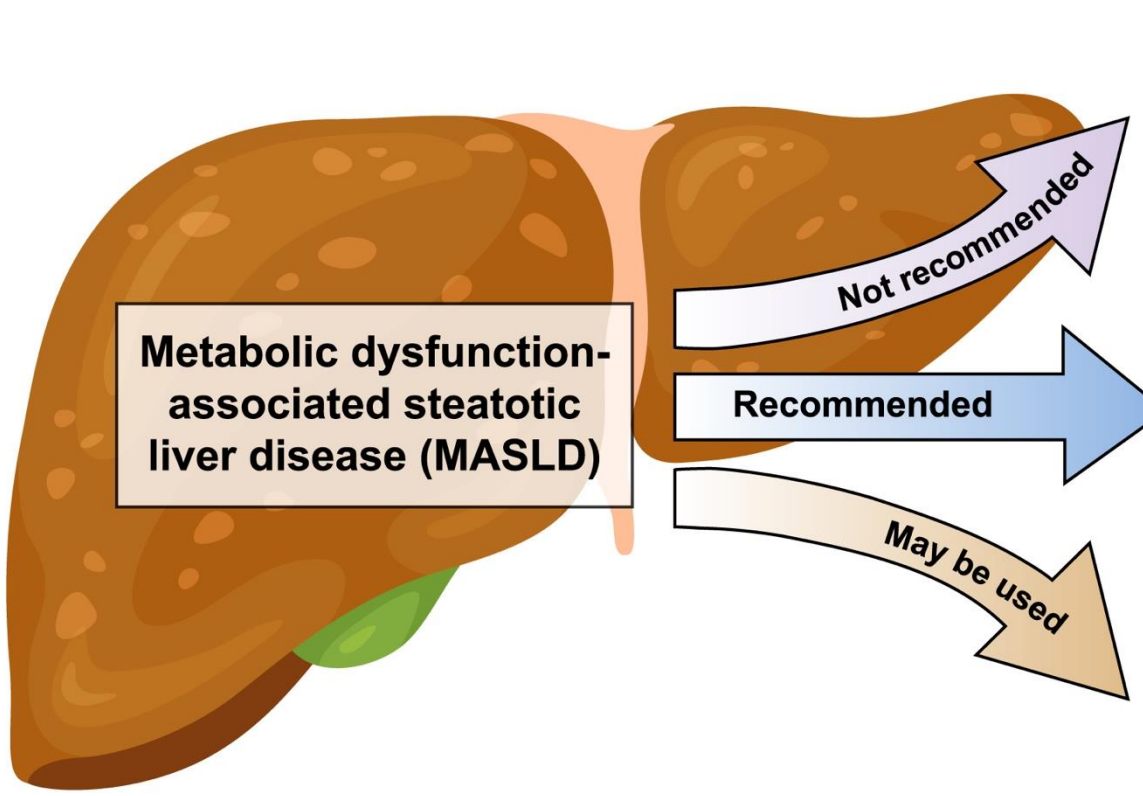
Resmetirom Dosing and Other Considerations

DOSE

< 100 kg (220 lbs)	> 100 kg (220 lbs)
80 mg QD	100 mg QD

Rezdiffra (resmetirom) [prescribing information]. Madrigal Pharmaceuticals, Inc.; West Conshohocken, PA; 2024.

AASLD Practice Guidance: Selection of Patients for Resmetirom Therapy



- Cirrhosis, including LSM via VCTE >20 kPa or MRE >5 kPa
- Concomitant active liver disease
- Excess alcohol use (>20/30 g/d in women/men)
- Active thyroid disease

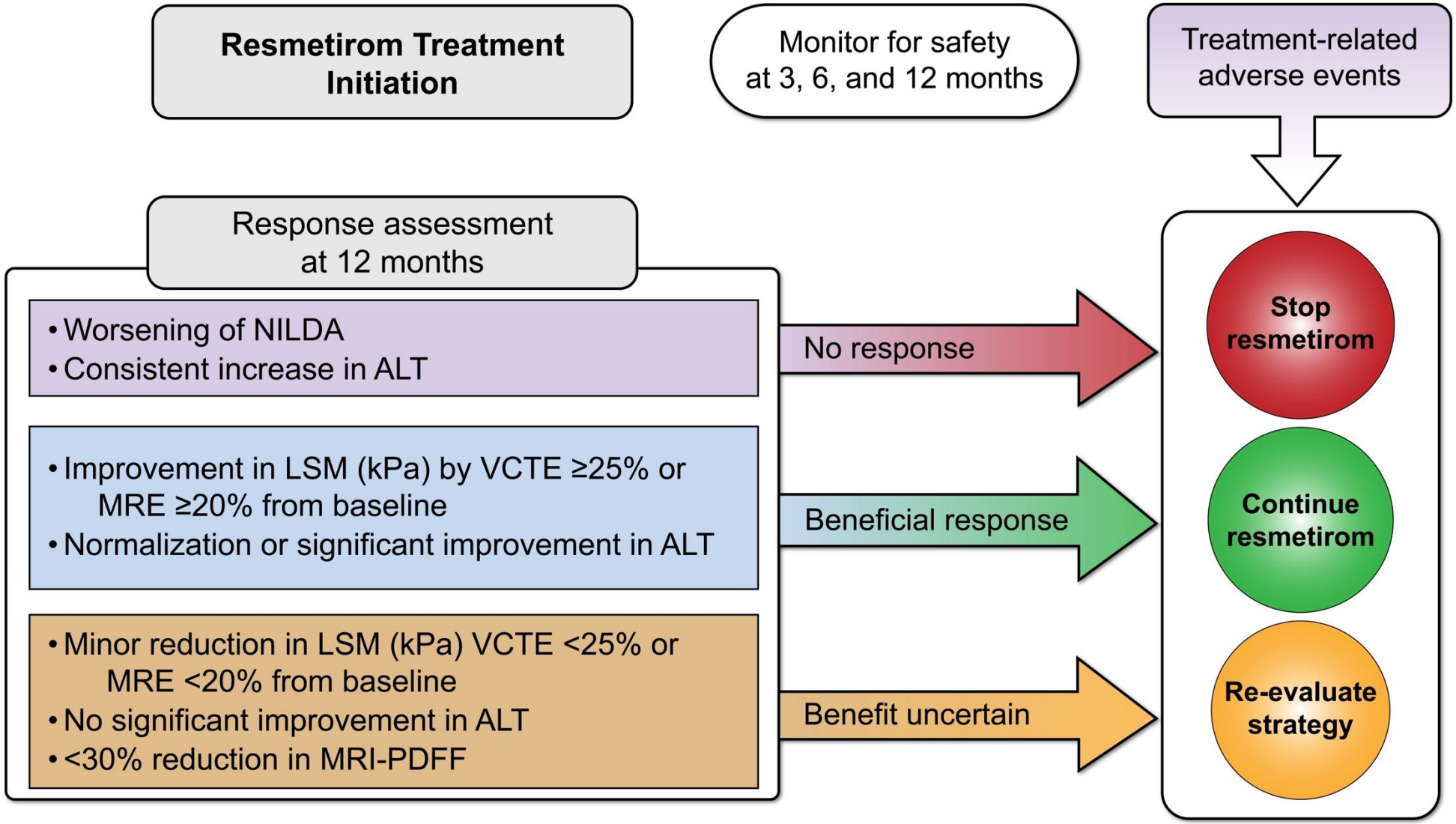
Imaging-based NILDA	VCTE: LSM 8 kPa - 15 kPa MRE: LSM 3.1 kPa - 4.4 kPa
Liver histology	MASH with F2-F3

- Individualized decisions by a specialist experienced in liver fibrosis for:
  - LSM values outside the recommended ranges
  - Other NILDA data consistent with F2-F3

NILDA=Non-invasive liver disease assessment

Modified from: Chen, VL et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology* ():10.1097/HEP.0000000000001112, October 18, 2024. | DOI: 10.1097/HEP.0000000000001112

AASLD Practice Guidance: Assessment for Treatment Outcome in Patients Receiving Resmetirom



Modified from: Chen, VL et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology* ():10.1097/HEP.0000000000001112, October 18, 2024. | DOI: 10.1097/HEP.0000000000001112

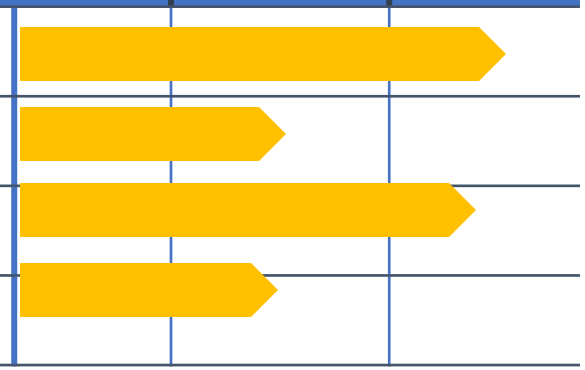
AASLD Practice Guidance: Safety and Efficacy Assessment at Baseline and During 12 Months of Treatment With Resmetirom

	Safety/Efficacy assessments	Safety assessments		Efficacy assessments	
Timeframe	**Hepatic function panel**	**Thyroid function**	**Lipid profile**	**Noninvasive measurement of liver stiffness**	**MRI-PDFF**
Before treatment initiation	✓	✓	✓	✓	Consider
3 months	✓				
6 months	✓	✓	✓		
12 months	✓	✓	✓	Repeat if imaging NILDA was used at baseline	Consider repeating if baseline data are available

NILDA=Non-invasive liver disease assessment

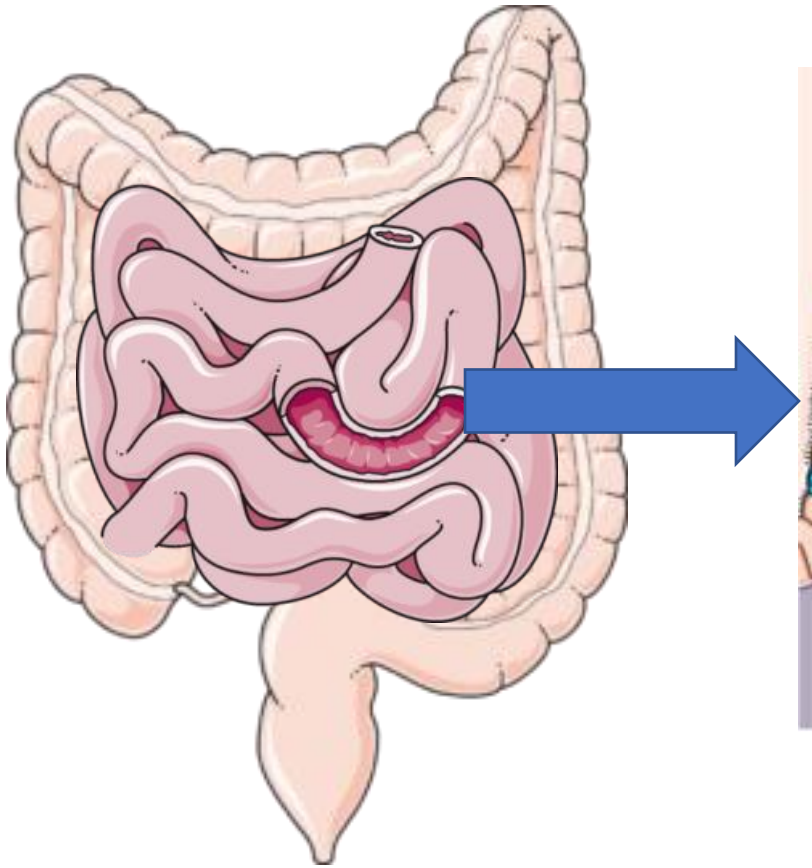
Modified from: Chen, VL et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology* ():10.1097/HEP.0000000000001112, October 18, 2024. | DOI: 10.1097/HEP.0000000000001112

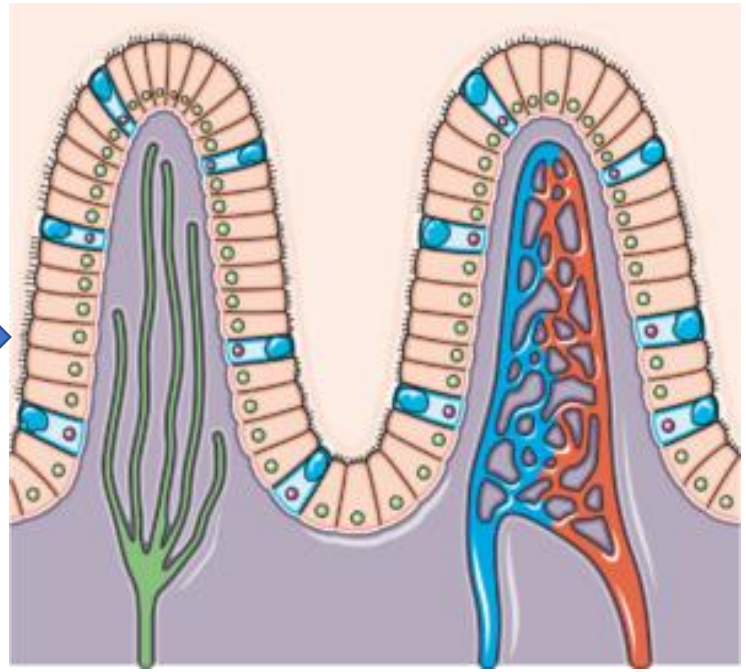
MASH Therapies on the Horizon

Class	Agent	Description	Development phase
GLP1R agonists	Semaglutide	GLP-1 agonist	
	Tirzepatide	Dual GLP1 and GIP agonist	
	Survodutide	Dual GLP-1 and GCG agonist	
	Pemvidutide	Dual GLP-1 and GCG agonist	

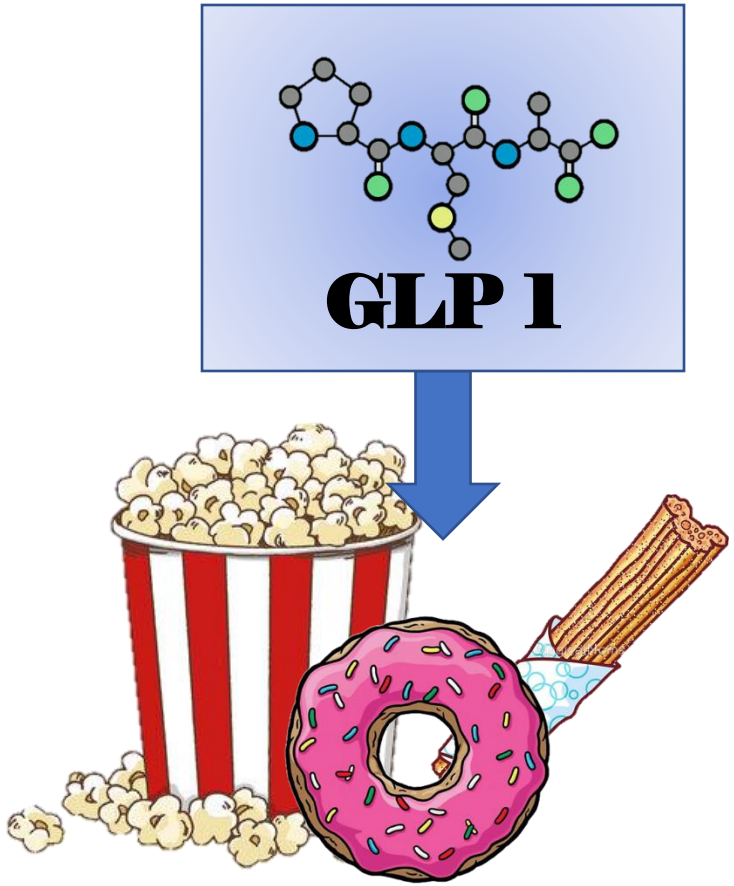
FASN, fatty acid synthase; FGF-21, fibroblast growth factor-21; GCG, glucagon receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide; PPAR, peroxisome proliferator-activated receptor.

Glucagon-Like Peptide-1 (GLP-1)





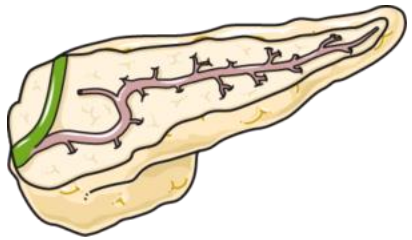
Enteroendocrine cells



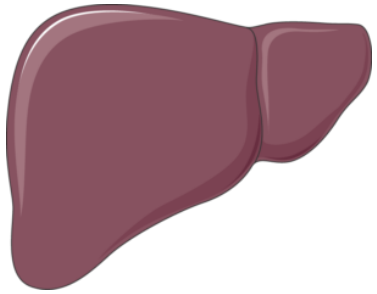
Glucose intake

Nevola R. Int J Mol Sci. 2023; 24:1703

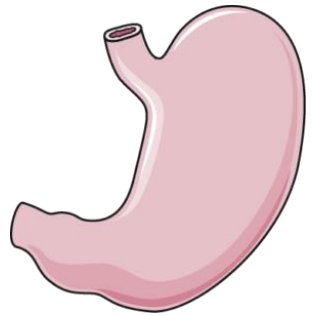
Glucagon-Like Peptide-1 (GLP-1)



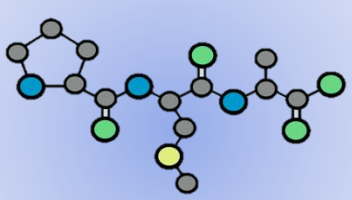
↑ Insulin Synthesis
↑ Insulin Secretion
↓ Blood Glucose
↑β cell proliferation



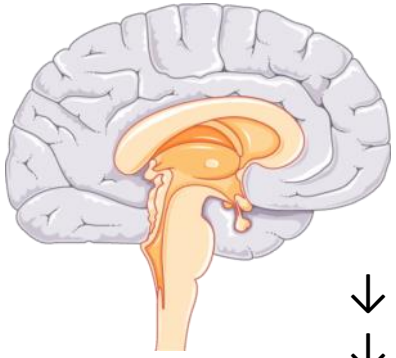
↓ Hepatic steatosis
↓ Liver glucose production
↓ Plasma Liver enzyme level



↓ Gastric emptying
↓ GI Peristalsis

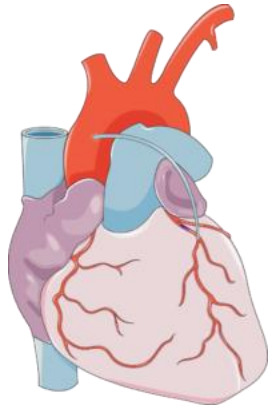


GLP 1



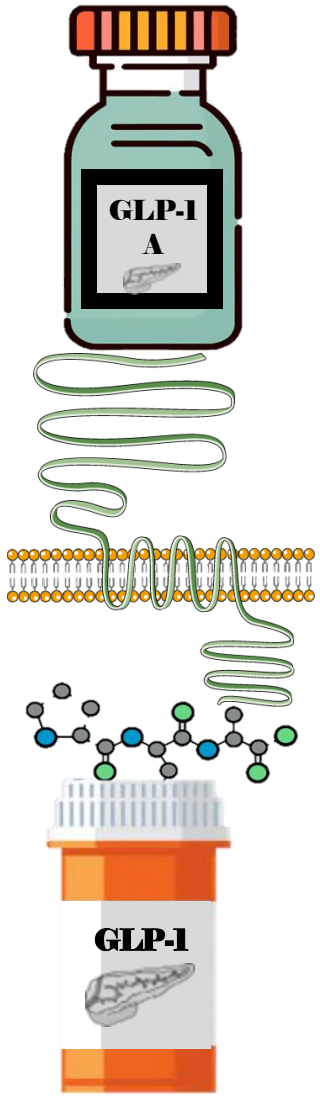
↓ Reward behavior
↓ Reduces food intake

↑ Nitric Oxide
↓ Oxidative stress
↓ Atherogenesis



Nevola R. Int J Mol Sci. 2023; 24:1703

Glucagon-Like Peptide-1 (GLP-1) and Liver



↓ Appetite
↑ Satiety

↓ HbA1C

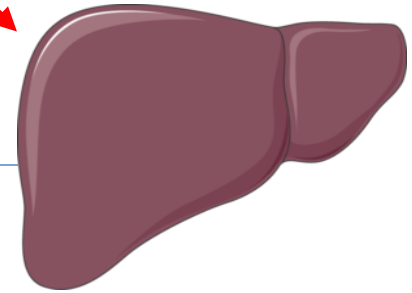
↓Low- grade systemic inflammation

↓ Caloric intake

↓ Body weight

↓ Insulin Resistance

Hepatic FAs storage



↑ Insulin signaling

↑ Adiponectin

↓ ER stress
FAM3A overexpression
FXR Activation
LXR activation

↑ Autophagy and lysosomal function
↑ Lipolysis and FAs oxidation
↑ Autophagy and lysosomal function
↓ De novo lipogenesis
↓ Liver inflammation

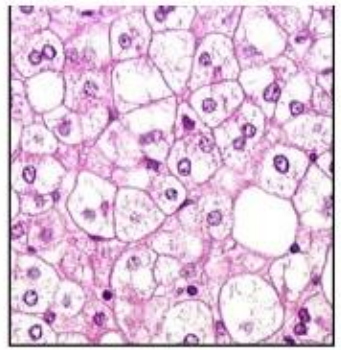
↓ Hepatic cytolysis
↓ Hepatic steatosis
↓ Steatohepatitis
↓ Progression of fibrosis

Nevola R. Int J Mol Sci. 2023; 24:1703

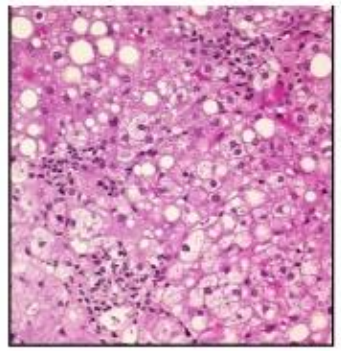
FDA Endpoints for Drug Approval
Evaluate at Week 24 versus baseline

MASH resolution (Total absence of ballooning/absent or mild inflammation)
Without worsening of **fibrosis** (increase of ≥1 stage)

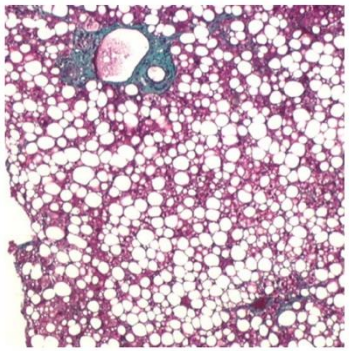
Improvement (reduction) in fibrosis of at least one stage,
Without worsening of **MASH** (Increased ballooning, inflammation, or steatosis)



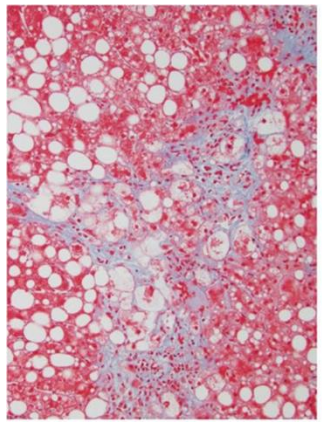
Ballooning



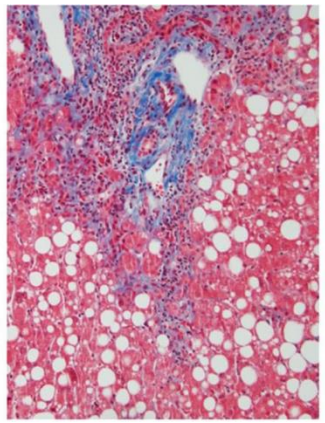
Inflammation



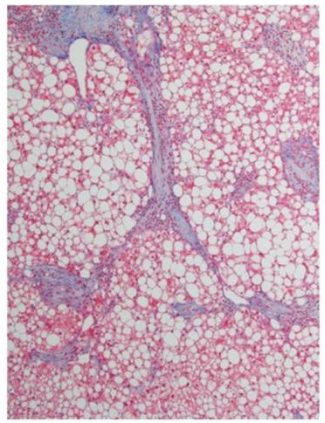
Steatosis



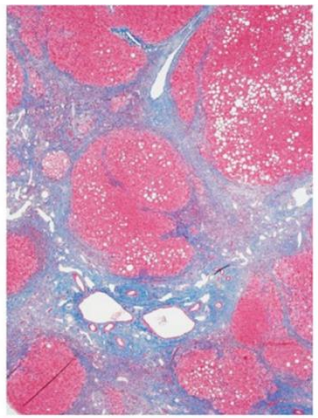
Perisinusoidal
1



Periportal
2

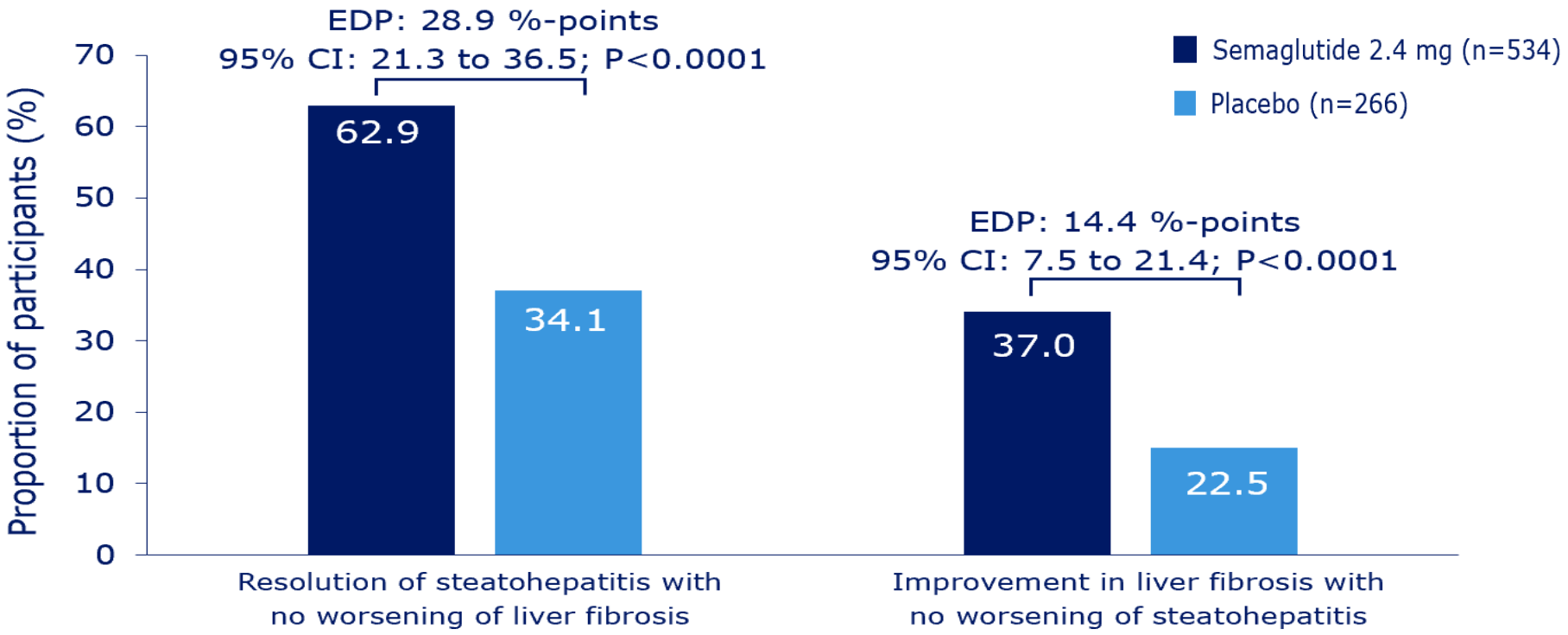


Bridging
3



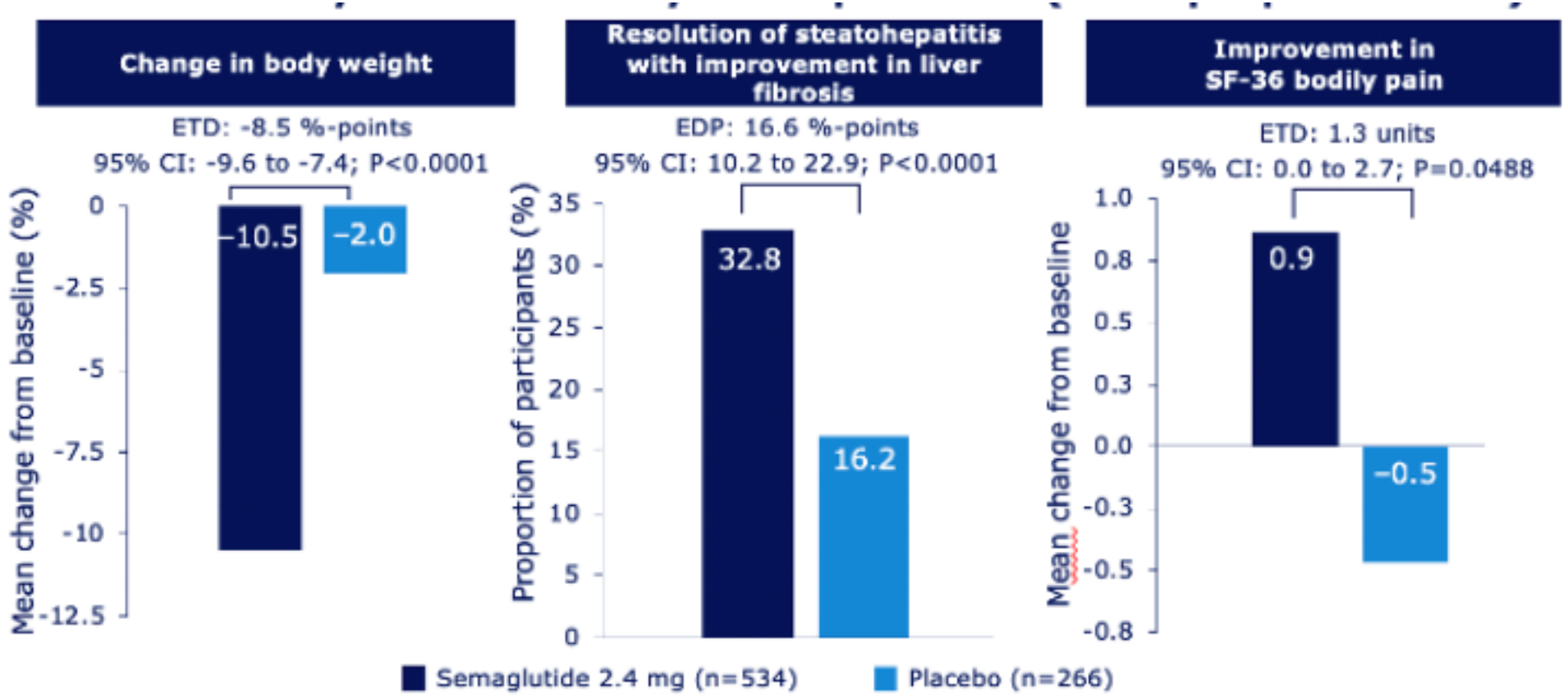
Cirrhosis
4

Phase 3 Semaglutide: Primary Endpoints



Newsome P et al, The Liver Meeting, AASLD 2024, LB abstract 5018.

Phase 3 Semaglutide: Confirmatory Secondary Endpoints



CI, confidence interval; EDP, estimated difference in responder proportions; ETD, estimated treatment difference; ITT, intention-to-treat; SF-36, Short Form-36.

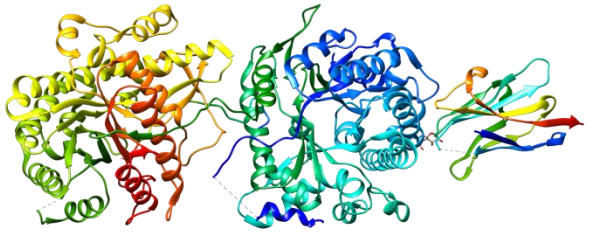
Newsome P et al, The Liver Meeting, AASLD 2024, LB abstract 5018.

Phase 3 Semaglutide: Safety

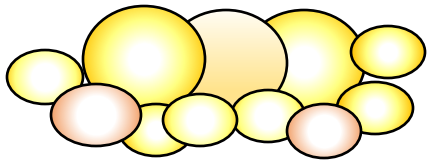
	Semaglutide 2.4 mg (N=800)	Placebo (N=395)
	n (%)	n (%)
All AEs	690 (86.3)	315 (79.7)
Fatal AEs	3 (0.4)	6 (1.5)
Serious AEs	107 (13.4)	53 (13.4)
AEs leading to trial discontinuation	21 (2.6)	13 (3.3)
AEs affecting ≥10% of participants		
Nausea	290 (36.3)	52 (13.2)
Diarrhea	215 (26.9)	48 (12.2)
Constipation	178 (22.3)	33 (8.4)
Vomiting	149 (18.6)	22 (5.6)
COVID-19	134 (16.8)	74 (18.7)
Decreased appetite	112 (14.0)	11 (2.8)

Newsome P et al, The Liver Meeting, AASLD 2024, LB abstract 5018.

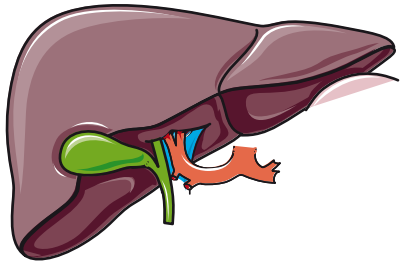
Fibroblast Growth Factor 21 (FGF-21)



FGF-21



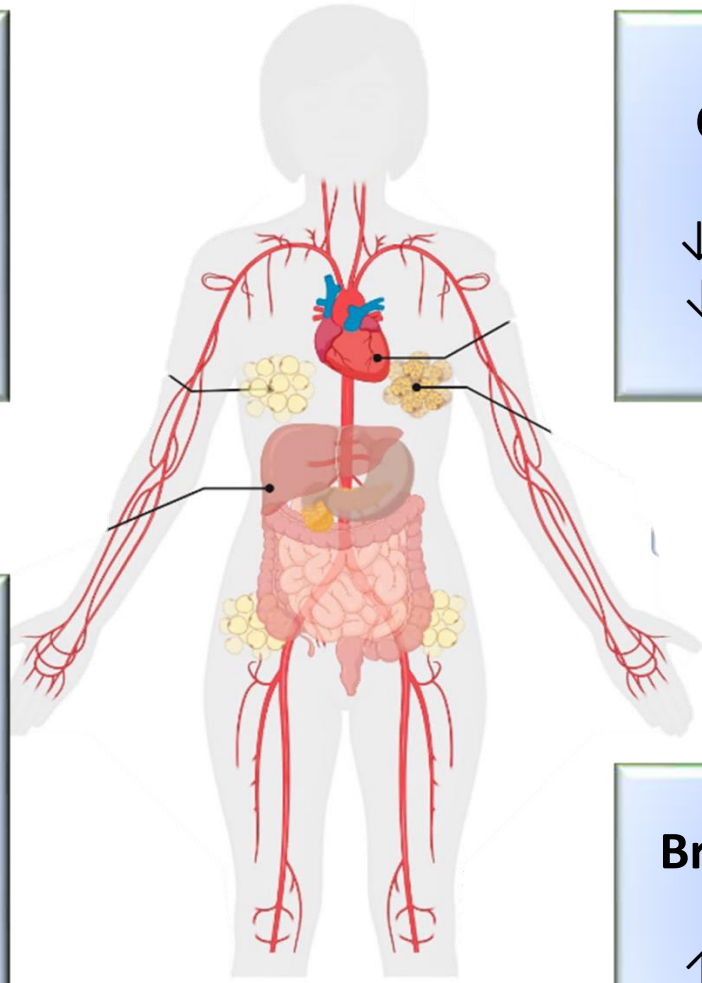
Adipose Tissue



Liver

White adipocytes
↑ Glucose uptake
↑Lipolysis
↑β oxidation
↑Fatty acid storage

Liver
↑Gluconeogenesis
↑Ketogenesis
↑Lipid oxidation
↑Lipolysis
↑ Insulin Sensitivity



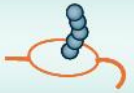
Cardiovascular
↓ Inflammation
↓ Oxidative stress
↓ Atherosclerosis

Brown adipocytes
↑ Energy waste
↑ Thermogenesis

Falamarzi K, Front Med (Lausanne). 2022 Nov 15;9:967375.

Fibroblast Growth Factor 21 (FGF-21) Agonists

*Now called efimosfermin

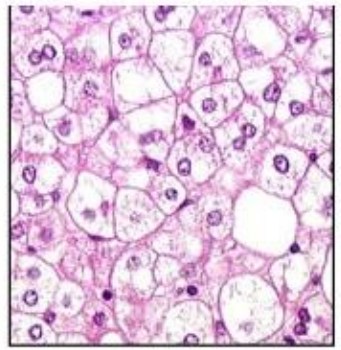
	Efruxifermin (AKR-001)	Pegozafermin (BIO89-100)	BOS-580 (LLF580)
Structure			
Molecular weight (per mol FGF21)	92 kDa (4 kDa)	40 kDa (40 kDa)	90-95 kDa (45-48 kDa)
***In vitro* FGFR agonism**	1c/2c/3c	1c/2c/3c	1c/2c/3c
Apparent target tissue(s)	Liver, adipose, pancreas	Liver, adipose, pancreas	Liver, adipose, pancreas
$T_{1/2}$ anolog (intact C-term) *	3-3.5 days	2.5-4 days	21 days
Pharmaceutical company	Akero Therapeutics	89 Bio	Boston Pharmaceuticals
Clinical development status	Phase 3	Phase 3	Phase 2
Drug administration	Subcutaneous injection Once weekly	Subcutaneous injection Once weekly or every 2 weeks	Subcutaneous injection Once monthly

Harrison SA et al. *J Hepatol.* 2024; 81: 562-576

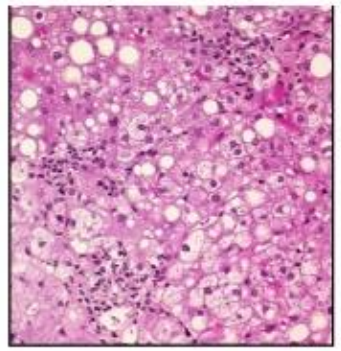
FDA Endpoints for Drug Approval
Evaluate at Week 24 versus baseline

MASH resolution (Total absence of ballooning/absent or mild inflammation)
Without worsening of **fibrosis** (increase of ≥1 stage)

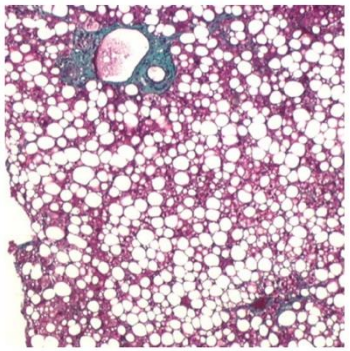
Improvement (reduction) in fibrosis of at least one stage,
Without worsening of **MASH** (Increased ballooning, inflammation, or steatosis)



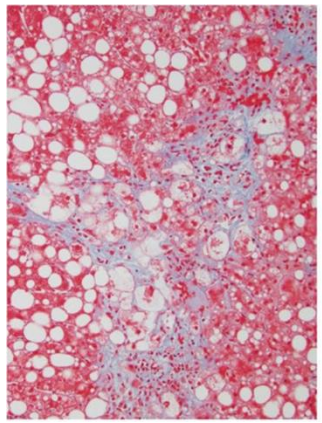
Ballooning



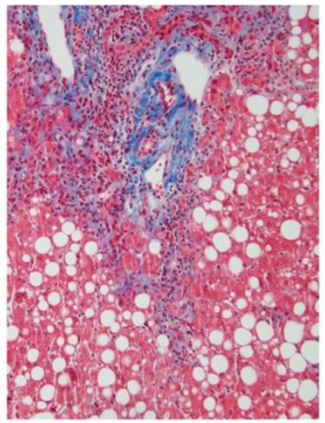
Inflammation



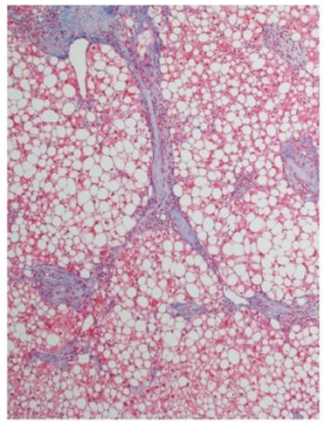
Steatosis



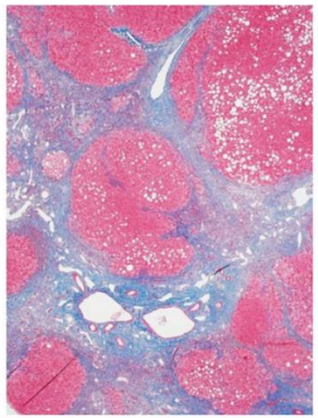
Perisinusoidal
1



Periportal
2

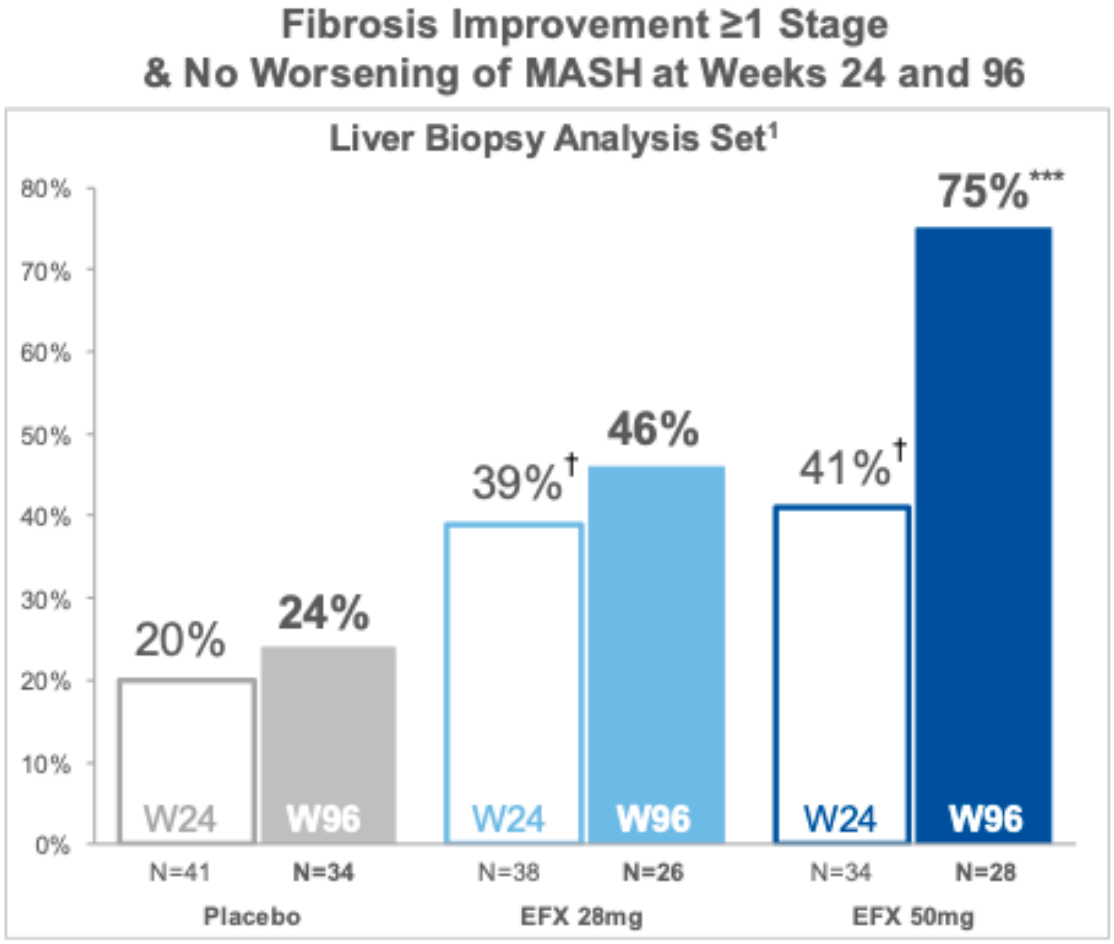


Bridging
3



Cirrhosis
4

Efruxifermin: Substantial Improvement in Fibrosis Between Weeks 24 and 96 in EFX Group



[1] All participants with baseline and specified timepoint
†p<0.05, versus placebo at W24; *** p<0.001, versus placebo at W96 (Cochran-Mantel-Haenszel Test [CMH])

Week 96 ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
19%	30%	49%**

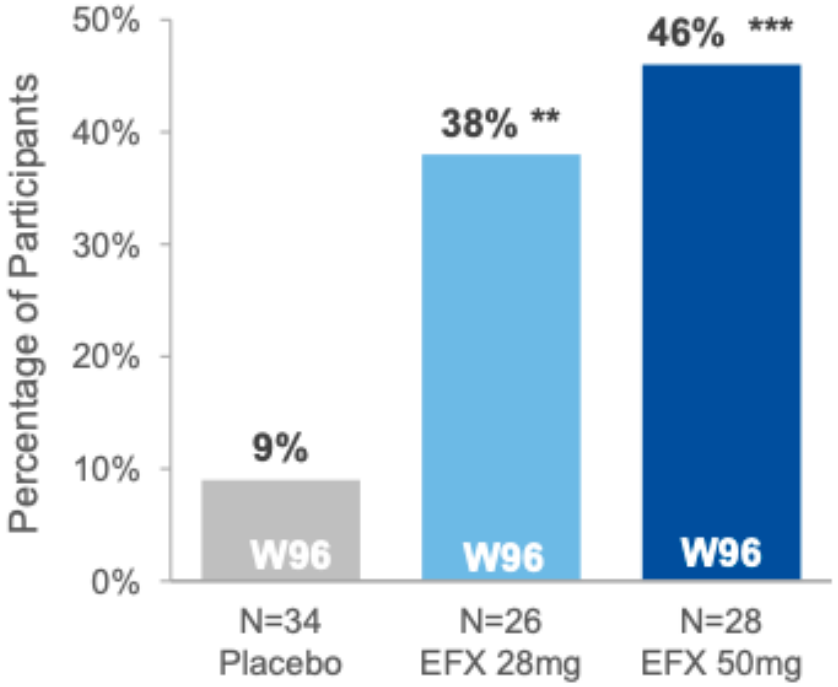
[2] Source data: Modified Full Analysis Set (ITT); All missing biopsies are imputed as a non-responder
**p<0.01 versus placebo (CMH)

Biopsy Reading Method: Biopsies were independently scored by two NASH-CRN trained pathologists, blinded to participant, treatment, and sequence. A third pathologist was available to adjudicate in absence of consensus.

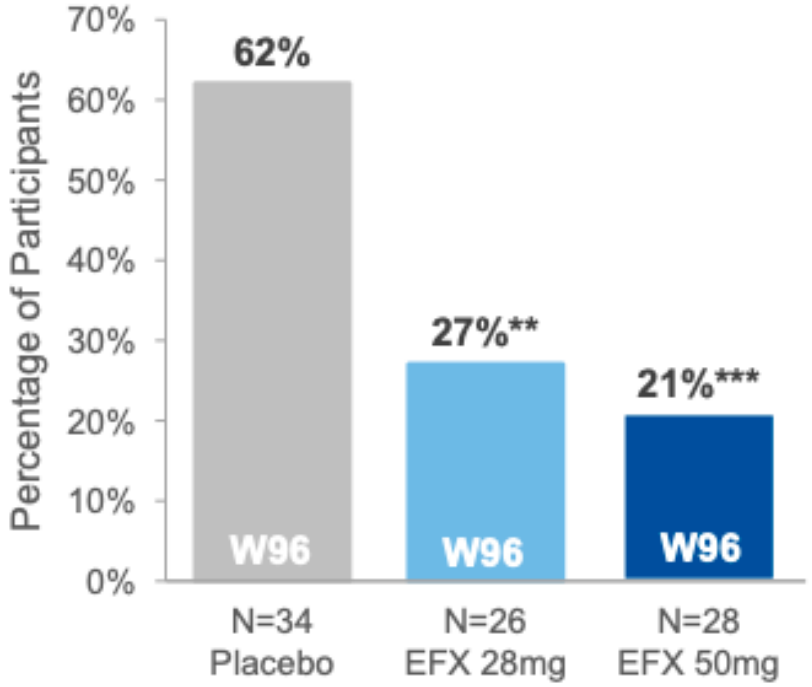
Noureddin M et al., The Liver Meeting 2024, Abstract 0158

Efruxifermin: Disease Reversal After 96 Weeks

A. Proportion of participants no longer at-risk MASH[1] at Week 96 through resolution of *all* components



B. Proportion of participants who still had all components of "at-risk MASH" at Week 96



At-risk MASH defined as:

- Definite MASH (≥ 1 point in each of NAS components)
- F≥2 **and**
- NAS ≥4

*[1] All participants were at-risk MASH at baseline. Participants that resolved only one or two of the at-risk MASH criteria are not shown. MASH Resolution: defined as a NAS of 0-1 for inflammation, 0 for ballooning, and any value for steatosis. **p<0.01, ***p<0.001 versus placebo (CMH)*

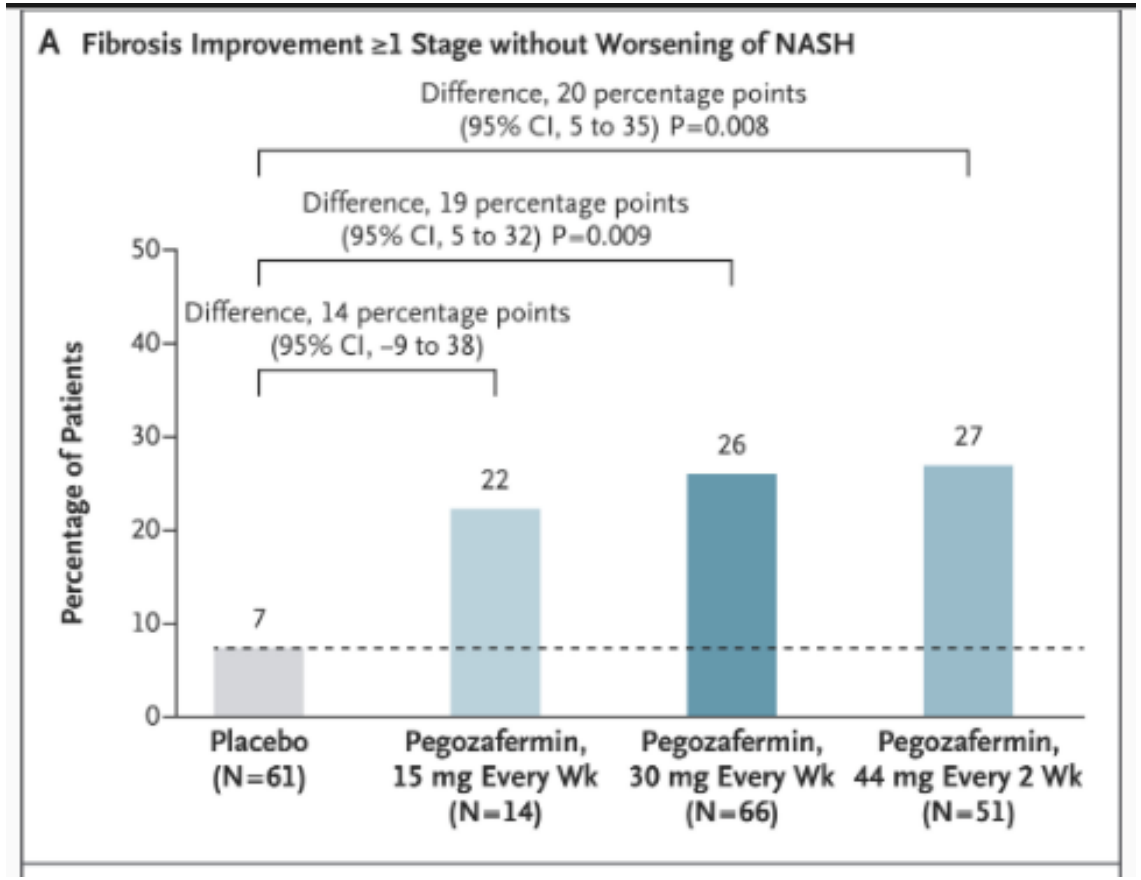
Noureddin M et al., The Liver Meeting 2024, Abstract 5021

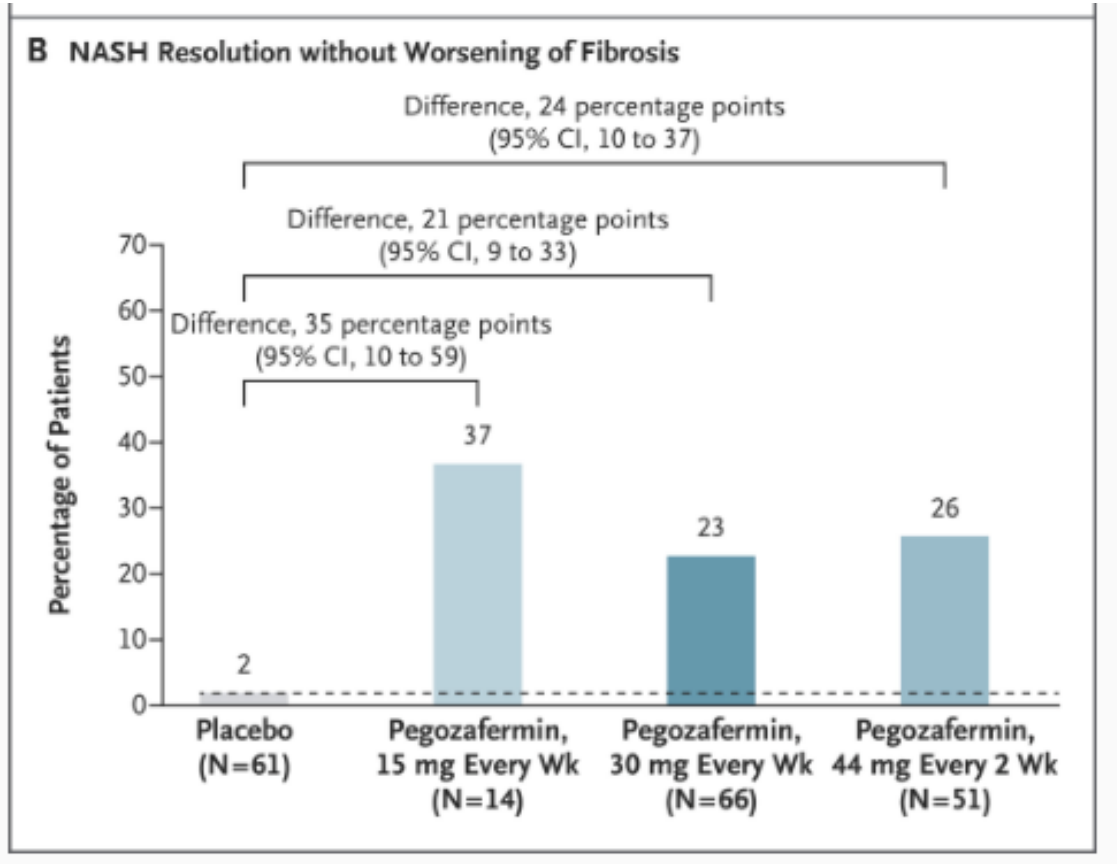
JUST IN….Reversal of Compensated Cirrhosis (F4) Due to MASH at Week 96

- Among patients with baseline and week 96 biopsies (n=134), 39% of patients treated with 50 mg EFX (n=46) (p=0.009) experienced reversal of cirrhosis with no worsening of MASH, compared to 15% for placebo (n=47).
- The study underscores the benefit of longer EFX treatment for patients with compensated cirrhosis (F4).
- Subgroup analyses demonstrated that the observed reversal of cirrhosis was not attributable to GLP-1 therapy.

Akero Press Release, January 28, 2025

Pegozafermin: Statistical Improvement in Both Endpoints at Week 24





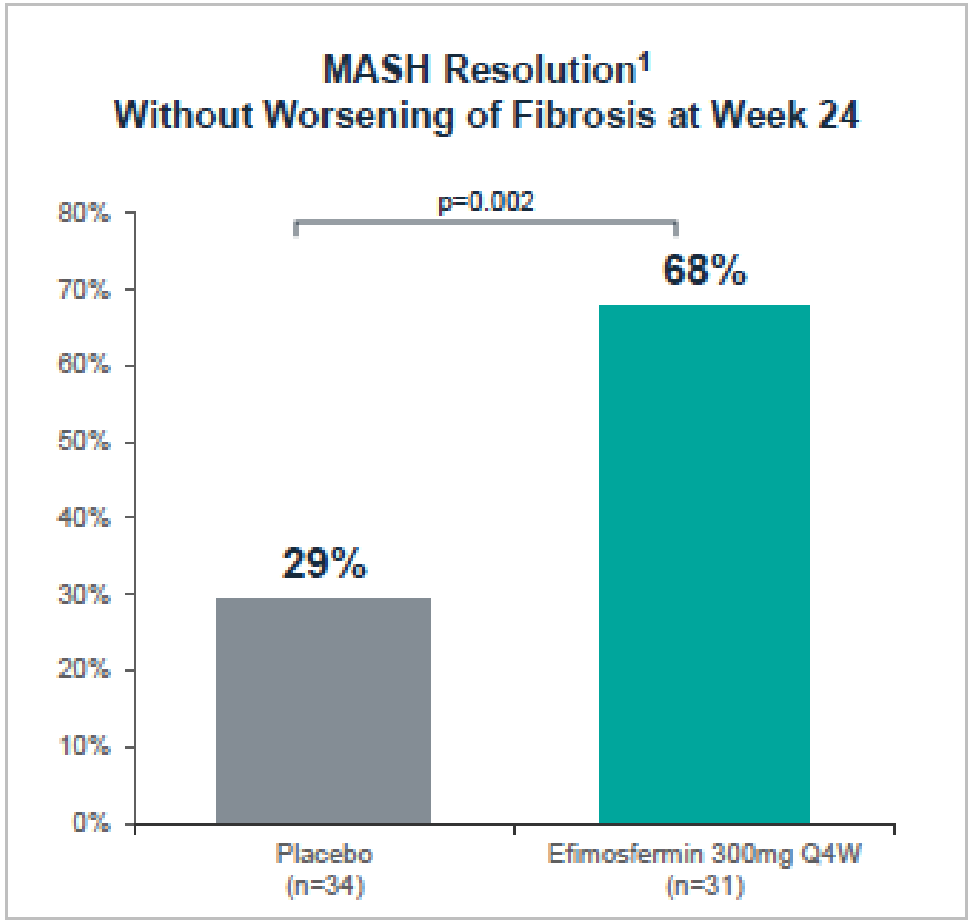
Loomba R et al, *N Engl J Med* 2023; 389:998-1008

Pegozafermin: 48 Week Treatment Results in Sustained Improvement Over Multiple NITs

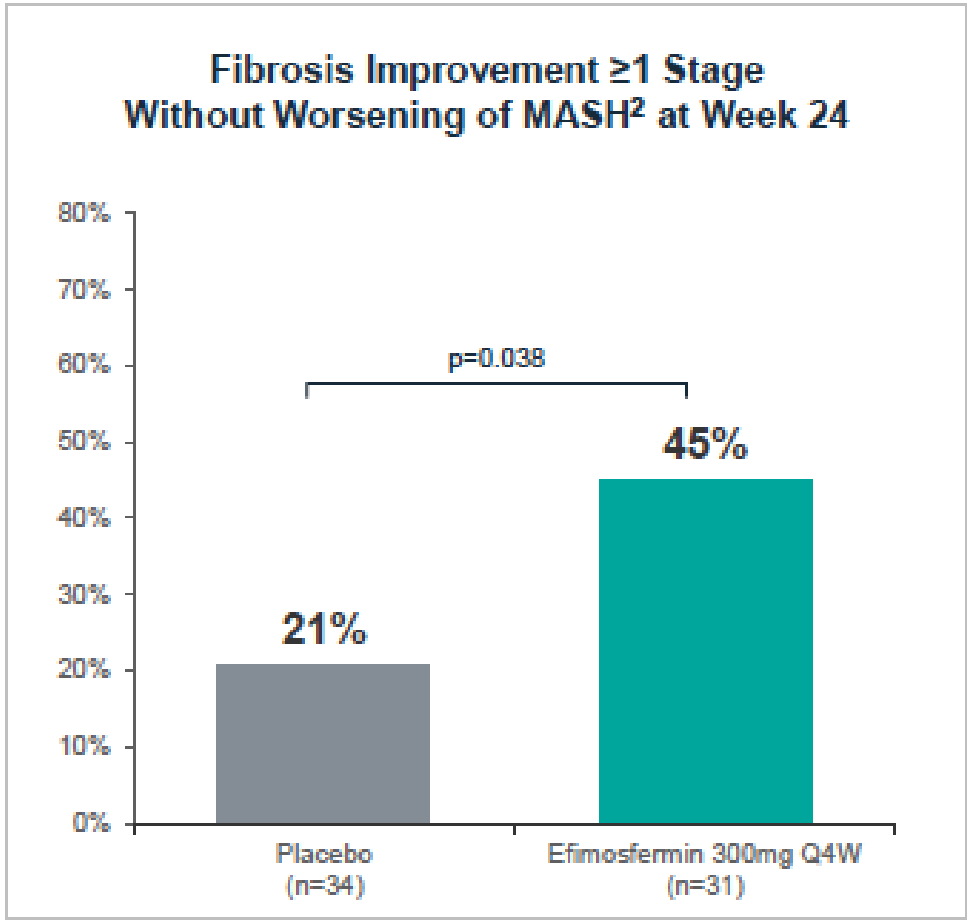
	Placebo Week 24 (n=42)	Placebo Week 48 (n=35)	30mg QW Week 24 (n=66)	30mg QW Week 48 (n=50)	44mg Q2W Week 24 (n=51)	44mg Q2W Week 48 (n=45)
MRI-PDFF	-6%	-11%	-56%	-60%	-60%	-47%
ALT	0%	-11%	-42%	-42%	-32%	-35%
AST	-2%	-4%	-39%	-39%	-34%	-36%
Pro-C3	+6%	+2%	-18%	-15%	-17%	-14%
FAST	-3%	-1%	-56%	-59%	-57%	-51%
VCTE (kPa)	-0.1	-0.8	-2.8	-2.9	-1.5	-1.3
ELF score	+0.2	+0.1	-0.3	-0.3	-0.3	-0.4

Loomba R et al., EASL May 2024; Oral Presentation, Abstract 943.

Efimosfermin Once-monthly Achieved Statistically Significant MASH Resolution and Fibrosis Improvement at Week 24



[1] NAS score of 0 for ballooning and 0-1 for inflammation



[2] Improvement in liver fibrosis ≥1 stage and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis)

Nourredin M et al., AASLD November 2024; Late–breaker oral presentation, Abstract 5017.

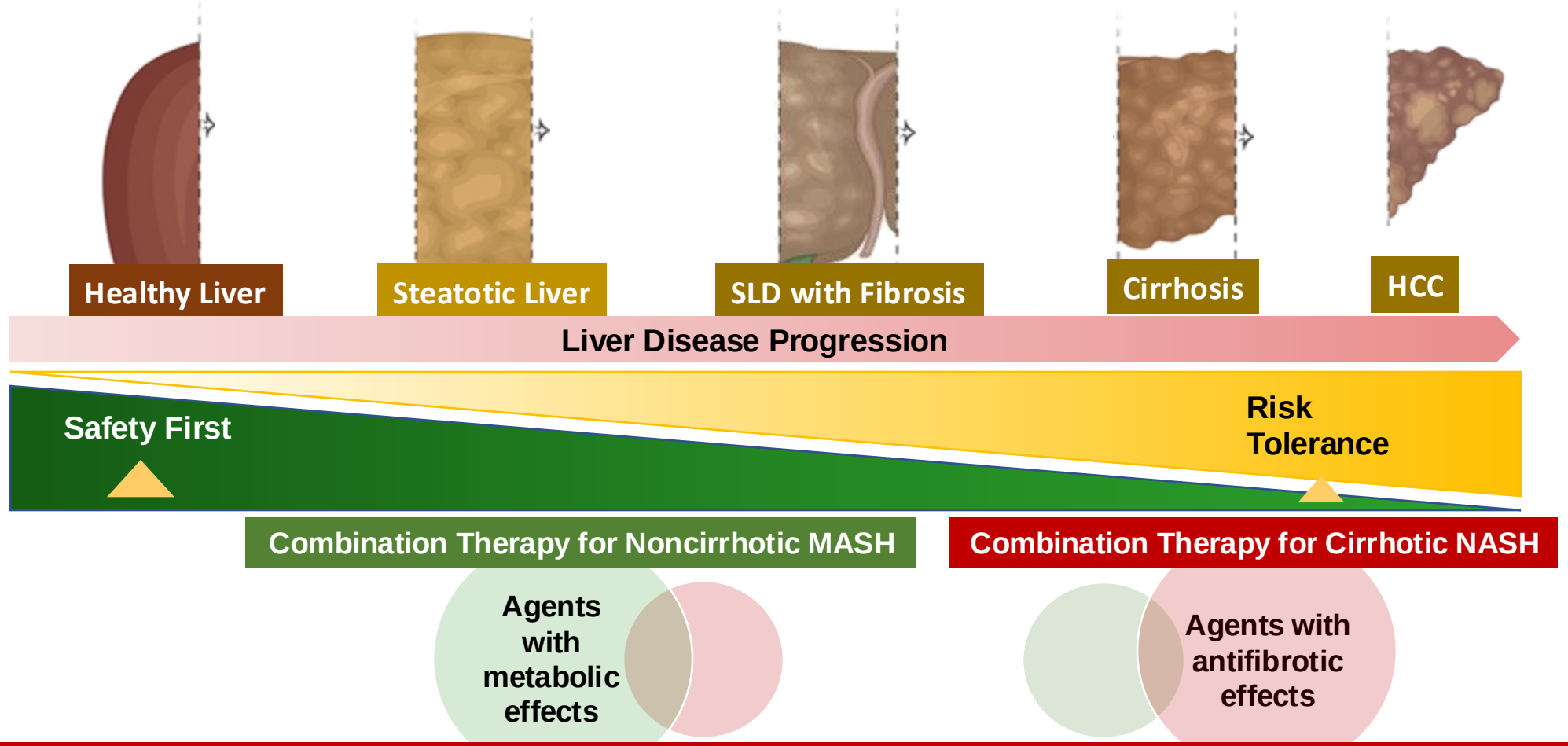
New Therapies for MASH

Therapy	THR B Agonist	GLP-1 Agonists	FGF-21 Agonists
Presence on the market	Since March 2024	June 2021 **(Not Approved for MASH)**	Pending
Indication	MASLD	Overweight +/- comorbidities	MASLD
Mechanism of action	Mainly Hepatic: ↓ intracellular fat/fibrogenesis	Hepatic and extrahepatic: ↓ intracellular fat, ↓fibrosis	Hepatic and extrahepatic ↓ intracellular fat
Side Effects	GI symptoms	GI symptoms	GI symptoms

THR B + GLP-1 Agonists

GLP 1 Agonists + FGF-21

Clinical Trials of New Medications: Future Combination Therapy for MASH



Although Phase 2 clinical trials of different agents suggest high efficacy, only Phase 3 clinical trial data with appropriate endpoints can be used to confirm efficacy.