Treatment Updates in MASH

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Lifestyle Modifications Remain the Backbone of Therapy

Lifestyle Recommendations are Very Important

Caloric intake reduction

≥30% or

~750-1,000 kcal/day improved insulin resistance and hepatic steatosis

*Limit consumption of fructose-enriched beverages

Weight loss

of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

Exercise

alone may reduce steatosis, but effect on other histologic features unknown

No heavy alcohol consumption

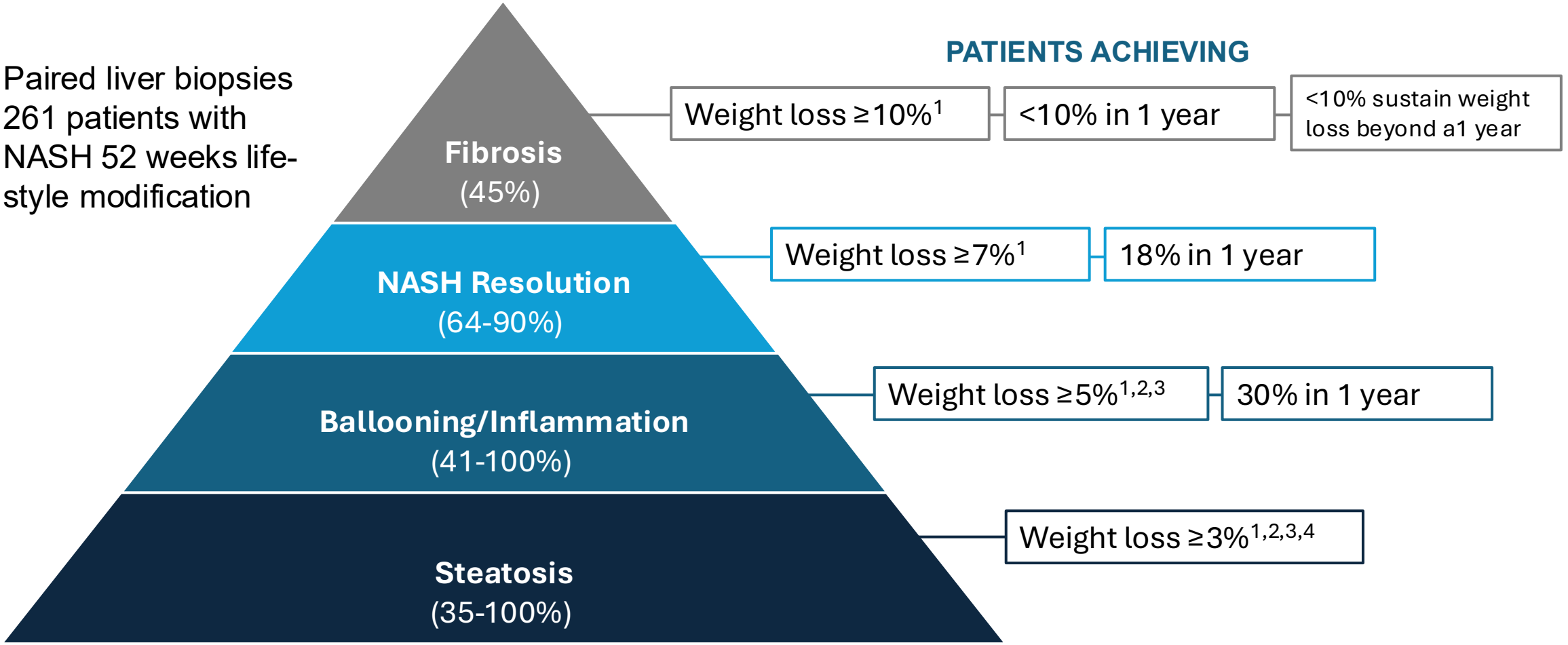
Insufficient data to guide recommendations regarding nonheavy alcohol consumption

**Drink ≥2 cups of caffeinated coffee daily

Chalasani N et al. *Hepatology*. 2018; 67(1):328-357; Diehl AM, Day C. *New Engl J Med.* 2017; 377:2063-72.

Weight Loss Through Life-Style Modifications Reduces MASH

Paired liver biopsies
261 patients with NASH 52 weeks life-style modification



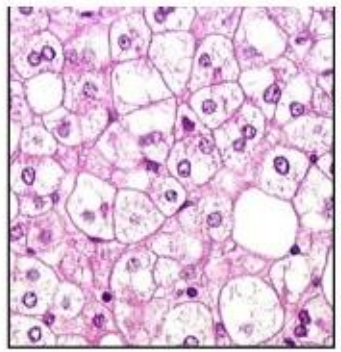
1. Vilar-Gomez. *Gastroenterology.* 2015; 2. Promrat. *Hepatology.* 2010; 3. Harrison. *Hepatology.* 2009; 4. Wong. *J Hepatol.* 2013.
*Depending on degree of weight loss.

FDA Approved Therapies for MASH

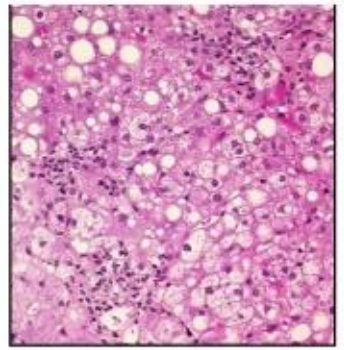
FDA Endpoints for Drug Approval: Evaluate at Week 24 versus Baseline

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

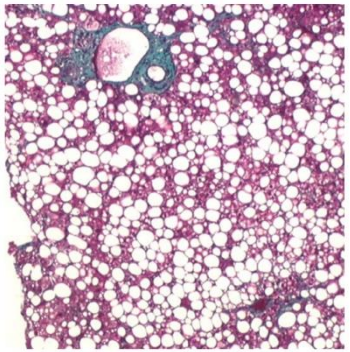
Improvement (reduction) in fibrosis of at least one stage **without** worsening of **MASH** (increased ballooning, inflammation, or steatosis)



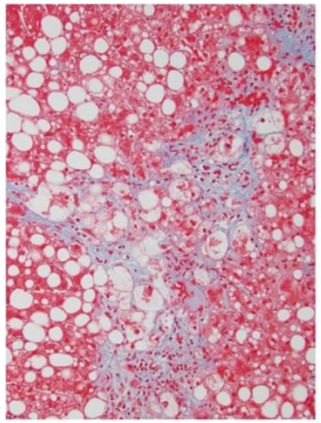
Ballooning



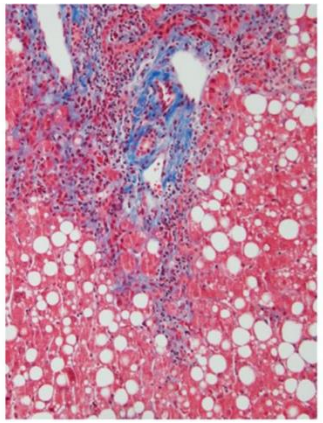
Inflammation



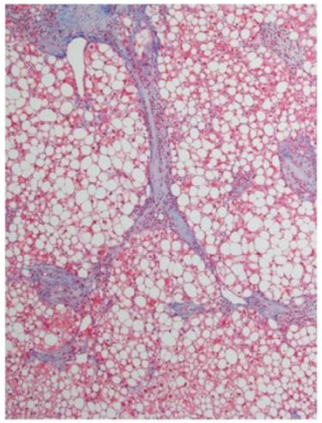
Steatosis



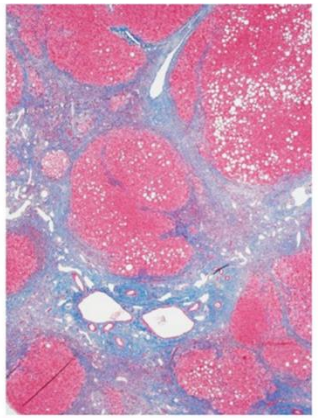
Perisinusoidal
1



Periportal
2



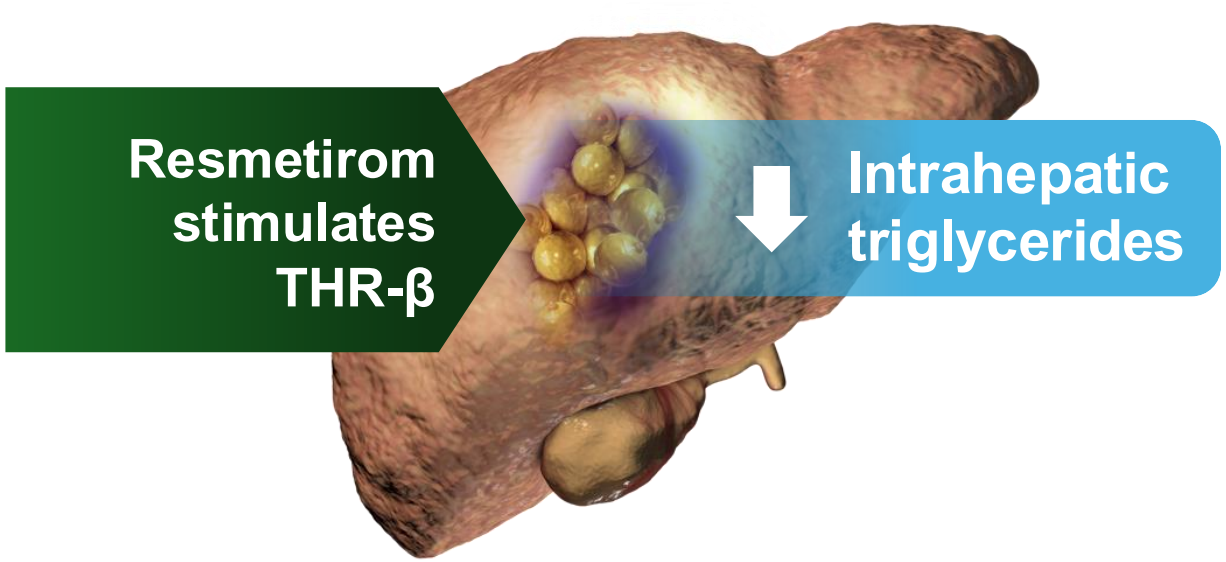
Bridging
3



Cirrhosis
4

First FDA Approved Medication for MASH: Resmetirom

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)

Reduces hepatic steatosis

- Stimulates lipophagy
- Stimulates mitochondrial biogenesis
- Inhibits lipogenesis

May interfere with fibrogenesis by inhibiting TGF-β signaling

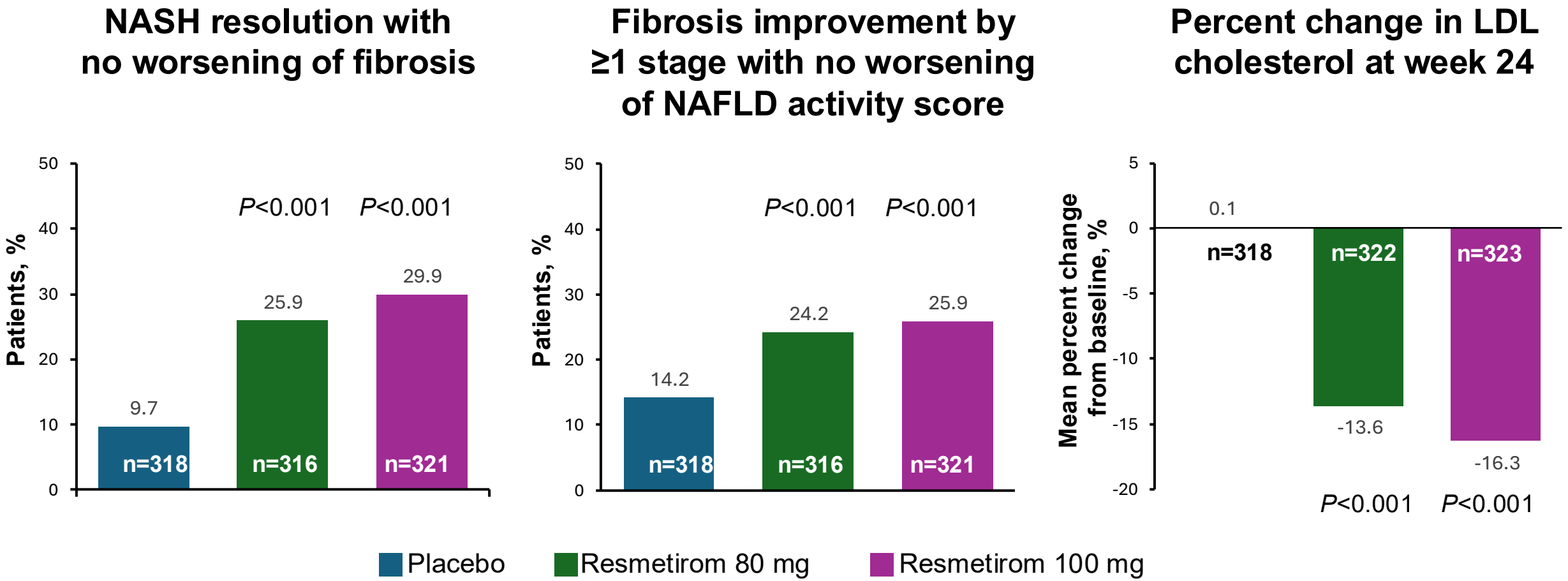
1. Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509; 2. Rezdiffra (resmetirom) [prescribing information]. Madrigal Pharmaceuticals, Inc.; West Conshohocken, PA; 2024.

Resmetirom: Phase 3 Study Design

- Patient population
  - 966 patients
  - Fibrosis stage: 5.1% F1b, 33% F2, 61.9% F3 (cirrhotics excluded)
  - Hypertension: 78.1%
  - Dyslipidemia: 71.3%
  - T2DM: 67%
  - Statin use: 48.9%
  - GLP-1 receptor agonist use: 14.3%

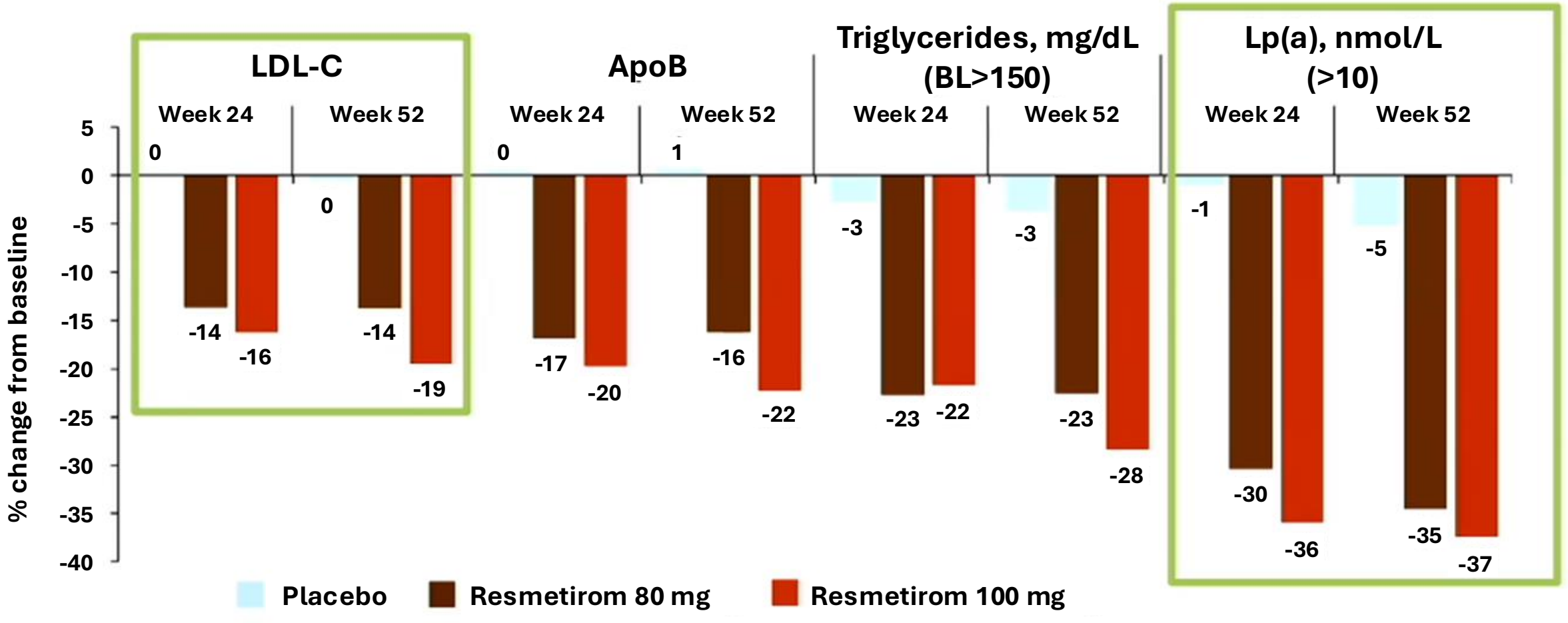
Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509.

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



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

Resmetirom: Favorable Atherogenic Lipid Profile



Harrison S et al. *NEJM*. 2024.

Resmetirom: Phase 3 Safety Summary

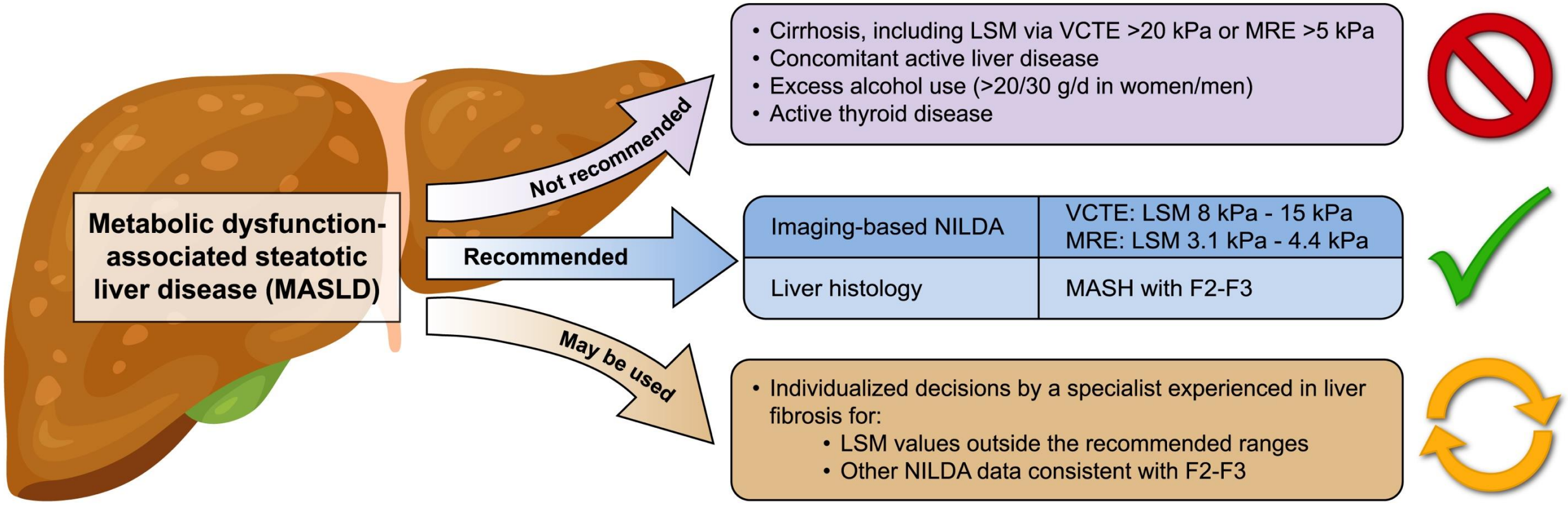
Adverse events >10% of patients in any group

	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.

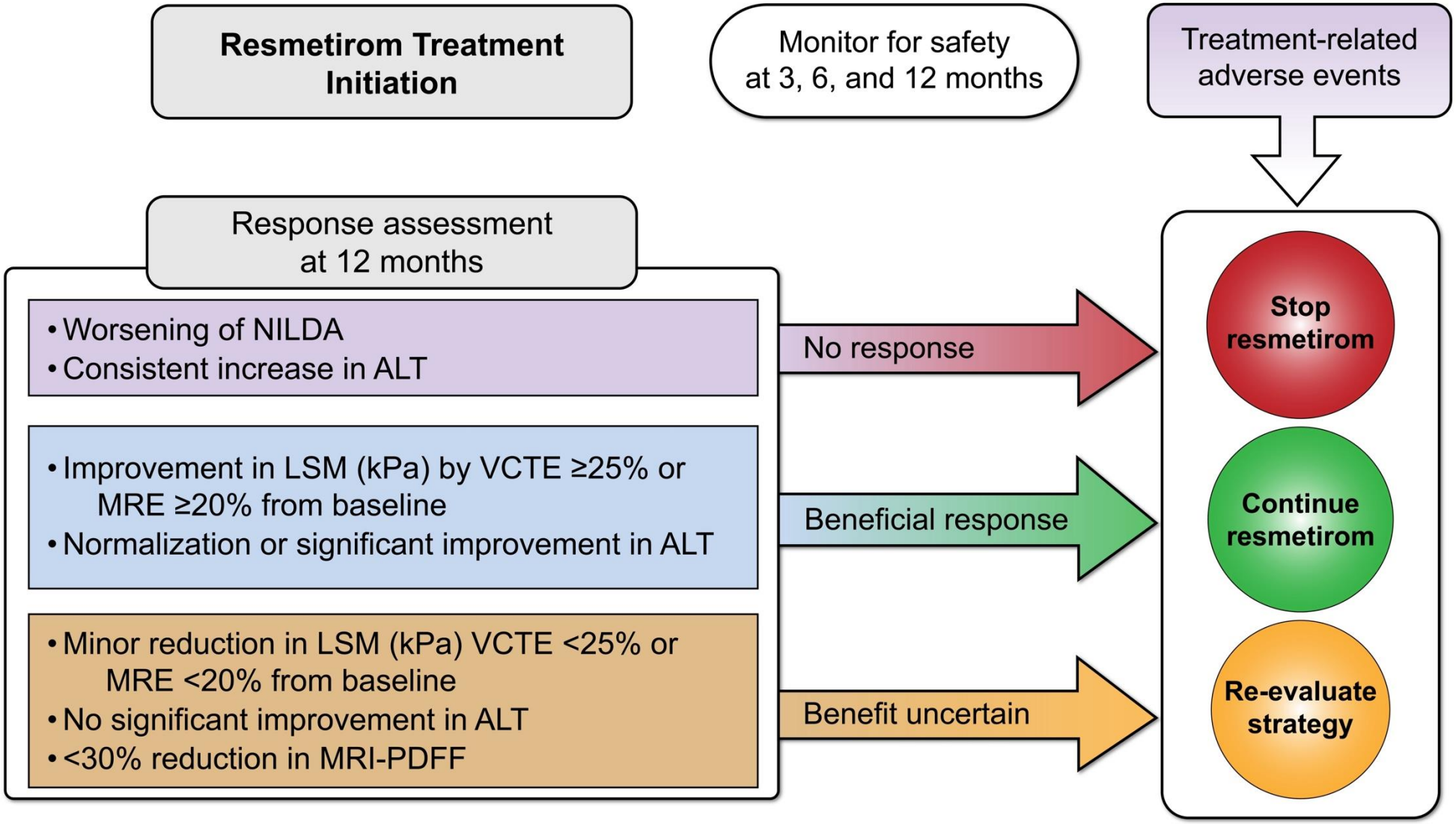
Resmetirom: Determining Who is Eligible for Treatment



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

Resmetirom: Assessing for Safety and Response



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Resmetirom: Safety Assessments

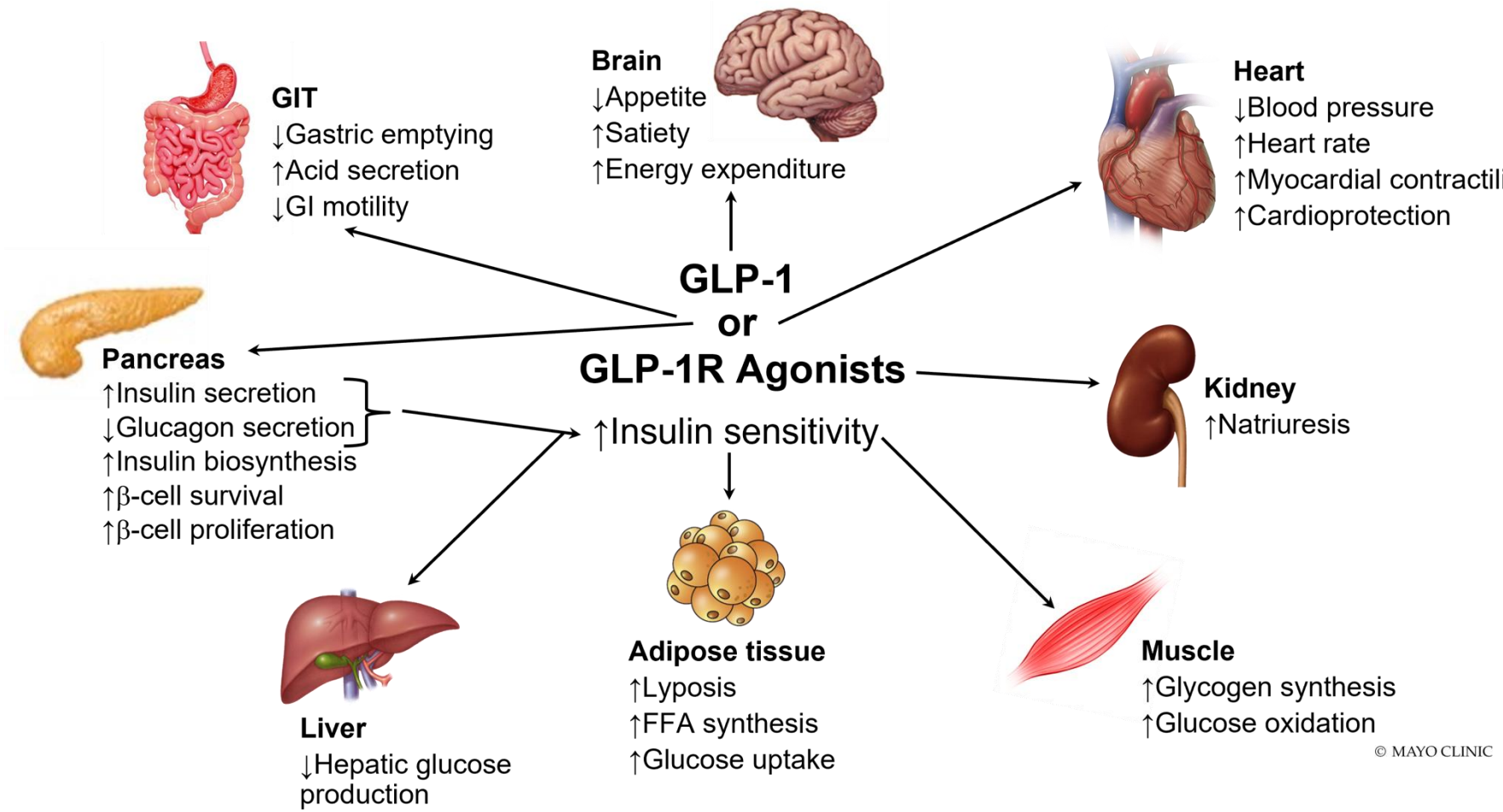
	Safety/Efficacy assessments	Safety assessments		Efficacy assessments	
Timeframe	**Hepatic function panel**	**Thyroid function**	**Lipid profile**	**Noninvasive measurement of liver stiffness**	**MRI-PDFF**
Before treatment initiation	✓	✓	✓	✓	Consider
3 months	✓				
6 months	✓	✓	✓		
12 months	✓	✓	✓	Repeat 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

Second FDA Approved Medication for MASH: Semaglutide

Glucagon-like Peptide-1 Receptor Agonists: Semaglutide



1. Campbell, Drucker. *Cell Metab*. 2013;17:819–37; 2. Baggio, Drucker. *J Clin Invest*. 2014;124:4223–6; 3. Flint et al. *J Clin Invest*. 1998;101:515–20;
4. Blundell et al. *Diabetes Obes Metab*. 2017;19:1242–51; 5. Tong, D'Alessio. *Diabetes*. 2014;63:407–9; 6. Armstrong et al. *J Hepatol*. 2016;64:399–408;
7. Armstrong et al. *Lancet*. 2016;387:679–90; 8. MacDonald et al. *Diabetes*. 2002;51(Suppl 3):S434–42; 9. Drucker. *Cell Metab*. 2016;24:15–30.

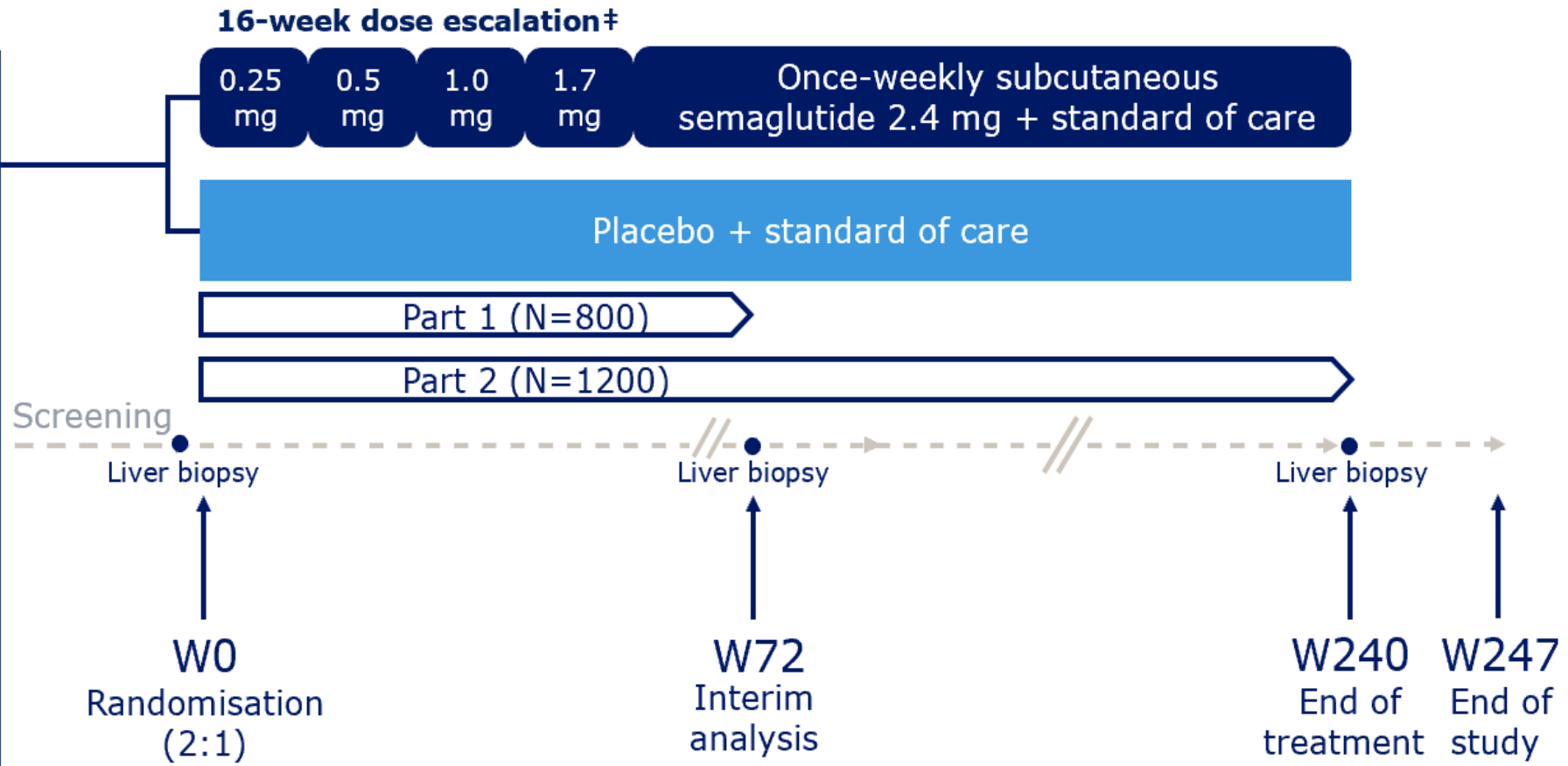
Semaglutide: Phase 3 Trial Design (ESSENCE)

Key inclusion criteria

- Age ≥18 years old
- Histological evidence of fibrosis stage 2 or 3*
- NAS ≥4†

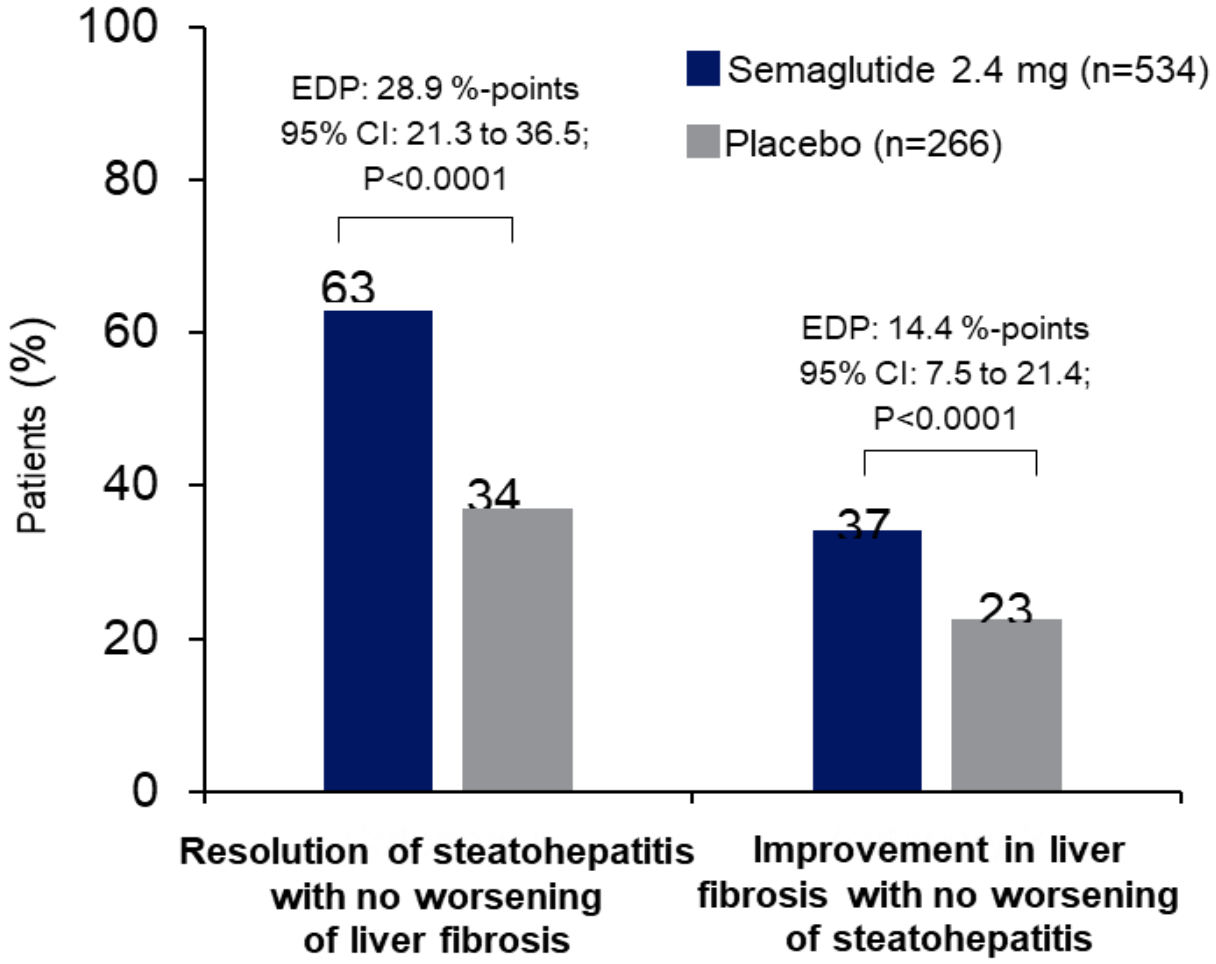
Key exclusion criteria

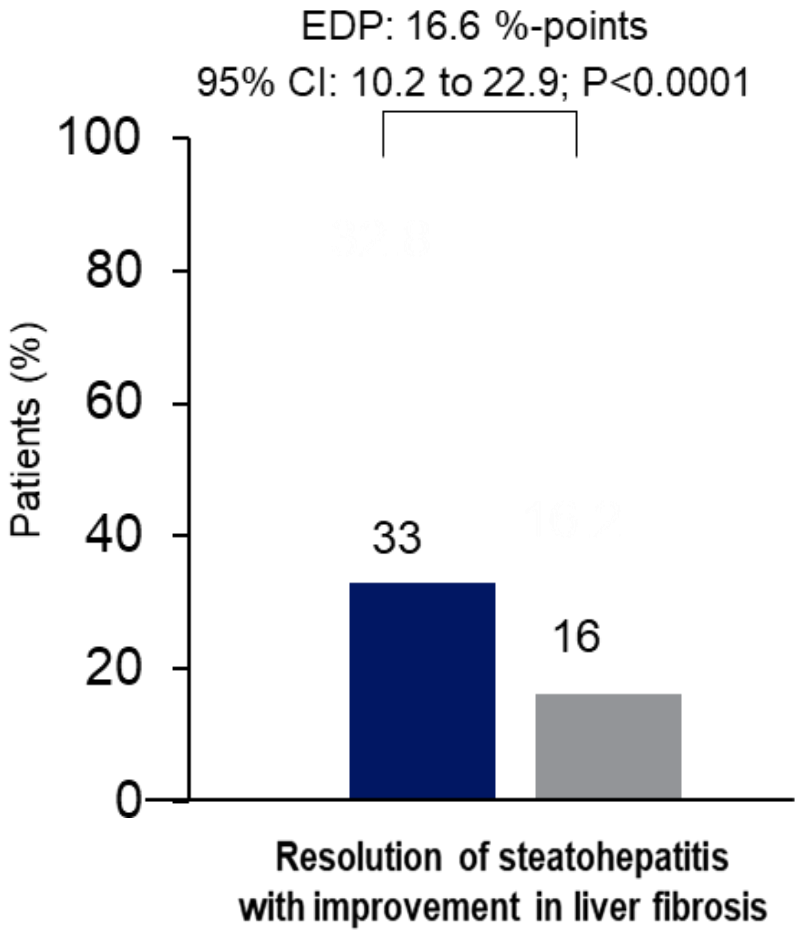
- Chronic liver diseases other than MASLD
- Known or suspected excessive consumption of alcohol (>20 g/day for women or >30 g/day for men)
- Treatment with GLP-1RAs or unstable use of other glucose-lowering, lipid-lowering or weight loss medications within 90-days prior to screening



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

ESSENCE: Primary Endpoint Among Patients With MASH Treated With Semaglutide for 72 Weeks



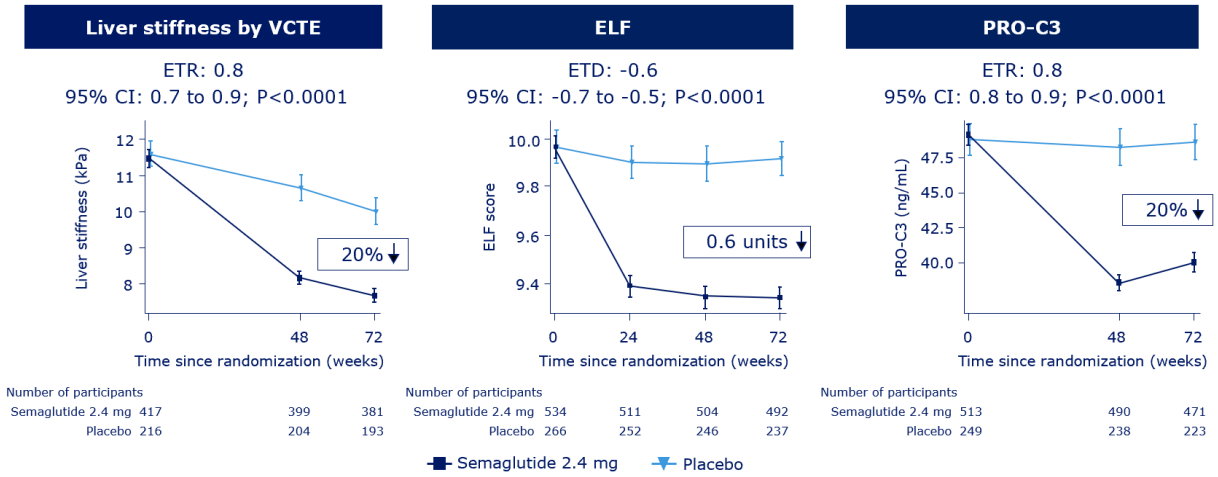


EDP, estimated difference in responder proportions.

Newsome P et al. *AASLD*. 2024. Late-breaking abstract #5018. Sponsored by Novo Nordisk.

Phase 3 Semaglutide: NITs and Safety

Non-Invasive Markers Over Time



Semaglutide use resulted in statistical improvement in VCTE (kPa), ELF and PRO-C3 compared to placebo.

Safety Profile

	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)

Semaglutide related adverse events are mainly GI in nature

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

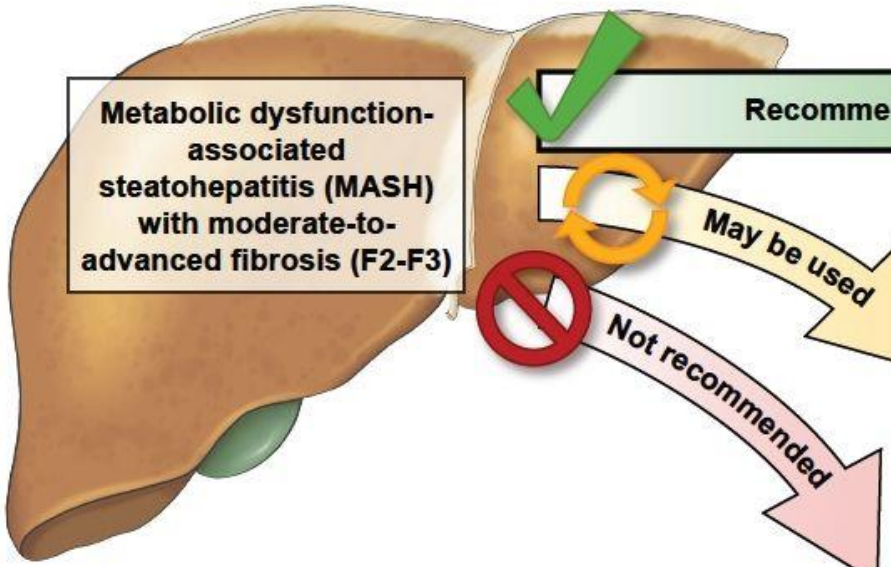
Semaglutide AEs and Safety

Based on the ESSENCE trial (*NEJM* 2025):

- **Common Side Effects:** Primarily gastrointestinal issues, including nausea (36%), diarrhea (27%), and vomiting (19%), which were mostly mild and manageable.
- **Serious Events:** Rates of serious adverse events were balanced between groups (13.4% for both), with low discontinuation rates (2.6%) due to side effects.
- **Key Risks:** A slight increase in gallbladder disorders was noted, but there were no new safety signals or evidence of drug-induced liver injury.

Sanyal AJ, Newsome PN, Kliers I et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *N Engl J Med.* 2025; 392(21):2089-2099. doi:10.1056/NEJMoa2413258.

Semaglutide: Determining Who is Eligible for Treatment



Metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis (F2-F3)

Recommended

Imaging-based NIT	VCTE: LSM 8 - 15 kPa[a] MRE: LSM 3.1 - 4.4 kPa[a]
Blood-based NIT	ELF 9.2 - 10.5
Liver histology	MASH with F2-F3[b]

May be used

- LSM values outside the recommended ranges[c]
  - VCTE: LSM 15-20 kPa
  - MRE: LSM 4.4-5 kPa
  - ELF: 10.5-11.3
- Other NIT data consistent with F2-F3

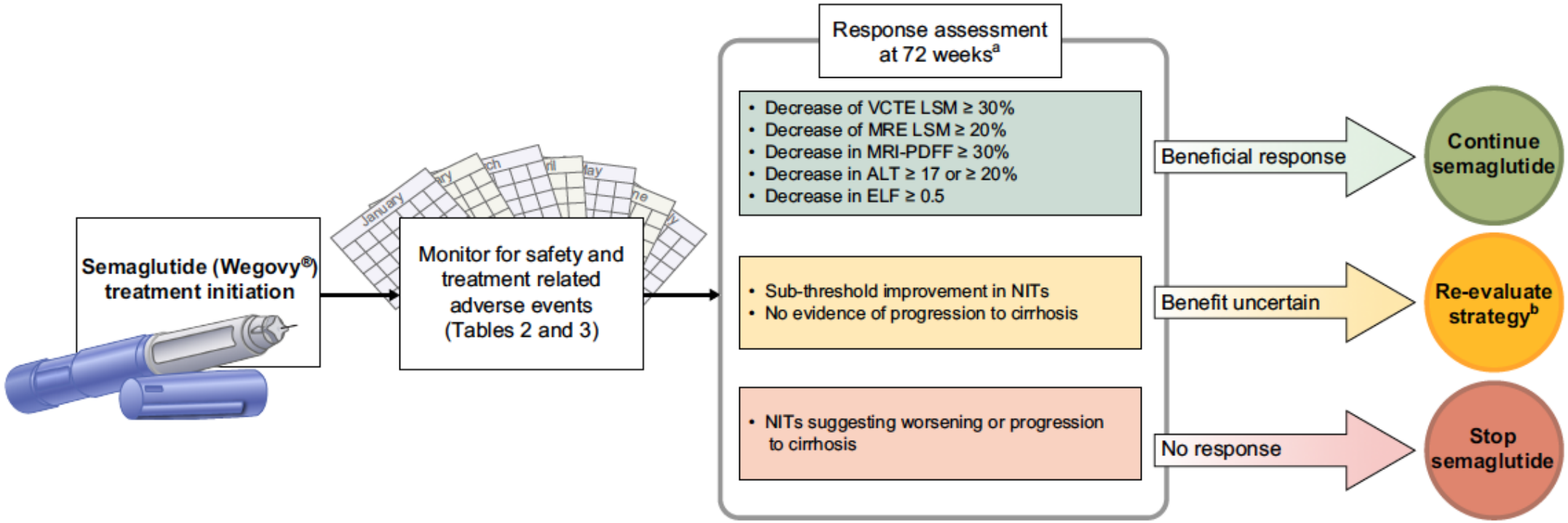
Not recommended

- Cirrhosis, including LSM via VCTE >20 kPa, MRE >5 kPa, or ELF score >11.3
- Concomitant active liver disease
- Pregnancy, personal or family history of medullary thyroid carcinoma (MTC), patients with multiple endocrine neoplasia syndrome type 2 (MEN2), or history of pancreatitis

[a] Modified from the AASLD NILDA guidelines.[5]
[b] Liver biopsy is not routinely recommended for the diagnosis and staging of MASH with F2-3
[c] Refer to "Whom to treat" for details
VCTE – Vibration-controlled transient elastography; MRE – Magnetic resonance elastography; ELF – Enhanced liver fibrosis; LSM – Liver stiffness measurement; NIT – Non-invasive test.

Bansal M et al. *Hepatology*. 2025.

Semaglutide: Assessing Safety and Response



[a] Assess based on the same imaging-based or blood-based markers used to determine treatment eligibility.
[b] Options may include re-optimizing lifestyle interventions and considering other therapy, with or without stopping semaglutide.

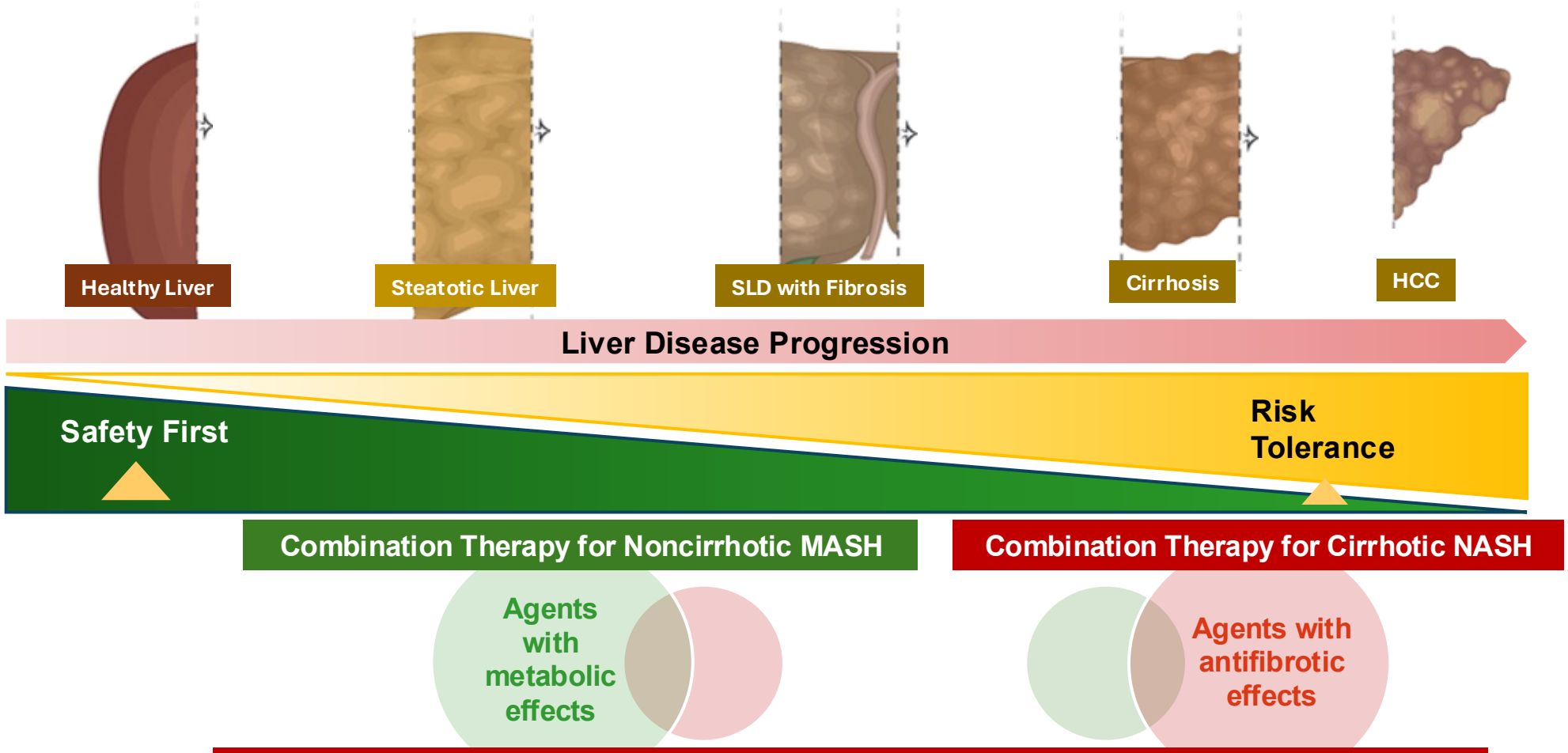
Bansal M et al. *Hepatology*. 2025.

Semaglutide: Safety Assessments

Timeframe	Safety assessments		Efficacy assessments		
	Symptoms	Diagnostic tests	Hepatic function panel	Non-invasive measurement of fibrosis	Non-invasive measurement of steatosis
Before treatment initiation	Active suicidal thoughts	• Evaluation for thyroid nodules • Consider retinal exam prior to GLP-1 RA therapy in patients with T2DM if not performed in past 12 months	X	X	X
On treatment monitoring	Nausea, vomiting, diarrhea, constipation, abdominal pain, depression or suicidal thoughts	As clinically indicated: • Pregnancy test • Hepatic function panel • RUQUS for symptomatic gallstone disease			
72 Weeks		Retinal exam as per society guidelines	X	X	X

Bansal M et al. *Hepatology*. 2025.

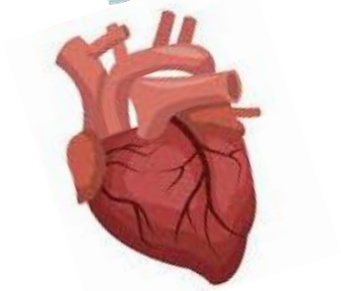
Clinical Trials of New Medications Future Combination Therapy for MASH



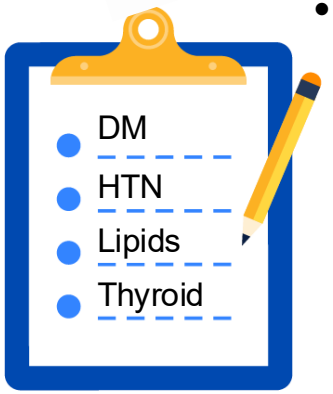
Although Phase 2 clinical trials of different agents suggest high efficacy, only phase 3 clinical trial data with appropriate endpoints can be used to assure efficacy

Integrated Approach to Care of MASLD/MASH Patients

- **Multidisciplinary: hepatologist, endocrinologist, nutritionist**
  - Also psychologist, clinical pharmacist, physical therapist



- **Cardiovascular risk reduction is essential**
  - Manage dyslipidemia, diabetes, hypertension, smoking cessation, antiplatelet therapy



- **Screen and treat other comorbid conditions**
  - Obstructive sleep apnea, PCOS, degenerative joint disease

- **Integrative Weight Loss Centers**
  - Lifestyle interventions for all, obesity pharmacotherapy and/or endoscopic or bariatric surgery when appropriate

- **Individualized Pharmacotherapy for Pre-Diabetes and Diabetes**
  - Optimal glycemic control

- **Prevention strategies for those with advanced hepatic fibrosis**
  - Vaccination, screening and surveillance (varices / HCC).

Summary

- Reversal of MASH and improvement of fibrosis is feasible with both resmetirom and semaglutide.
  - Effectively use NITs to assess treatment response
- Resmetirom and semaglutide only approved for MASH w/ F2-F3 and not yet approved for MASH-related cirrhosis.
- Large % of non-responders with FDA-approved medications underscores need for additional therapies, including combination pharmacotherapies.
- Effectively target / treat each complication of metabolic syndrome, including MASH.