2023 RUSH INTO GI:

AN UPDATE IN GASTROENTEROLOGY AND HEPATOLOGY

Non-Alcoholic Fatty Liver Disease & Non-Alcoholic Steatohepatitis

Overview, Risk Populations, and Drug Advancements

Disclosures

- I have no disclosures

Objectives

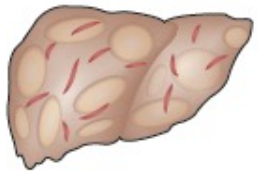
- Review NAFLD and NASH prevalence and disease progression
- Identify best practices for assessing and treating NAFLD and NASH
- Review drug advancements for NASH

Overview

NAFLD & NASH Prevalence

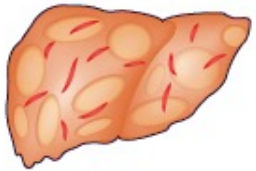
Non-Alcoholic Fatty Liver

NAFLD



Non-Alcoholic Steatohepatitis

NASH



NASH with F3/F4 Fibrosis

83.1 Million

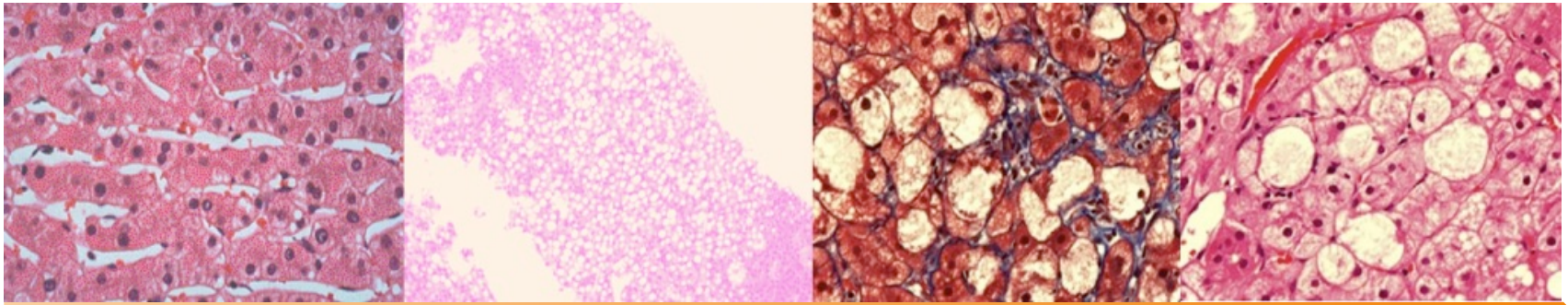
16.5 Million

3.3 Million

Unmet Need

Estes et al. 2017; ACG 2022.

Review of Fatty Liver Histology



Normal

NAFL

- >5% hepatic steatosis
- No evidence of hepatocyte injury (ballooning) or fibrosis

NASH

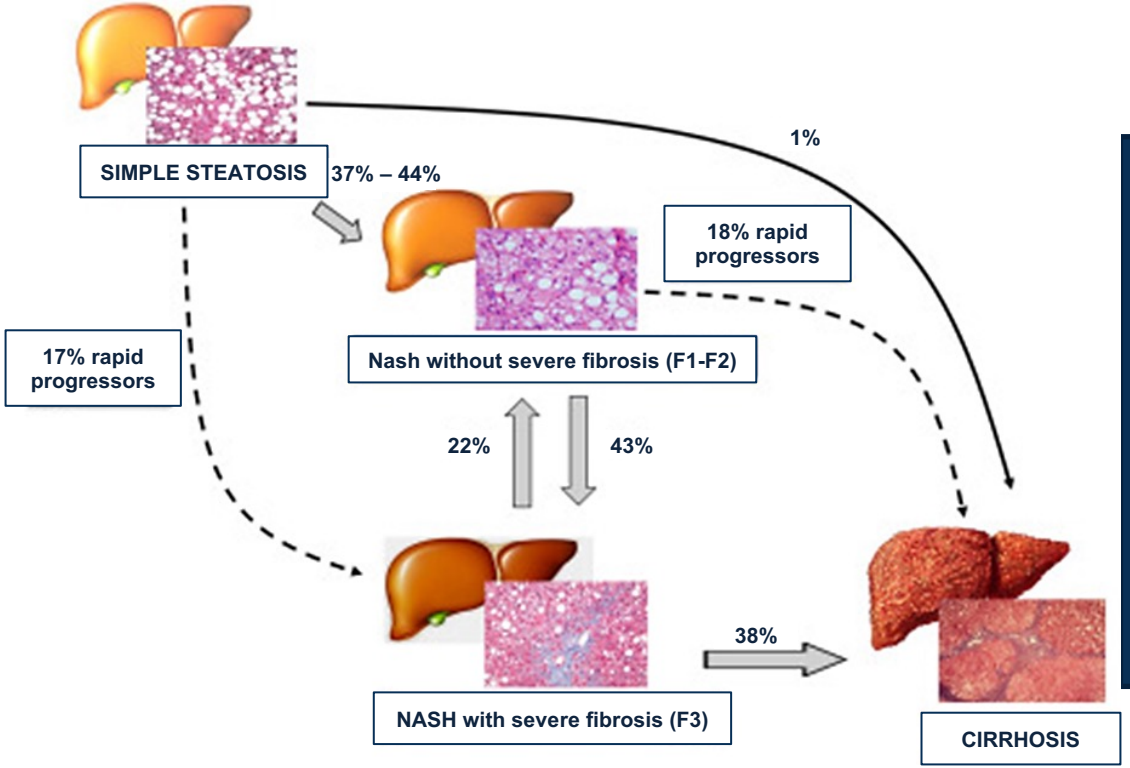
- Progressive type of NAFLD
- >5% hepatic steatosis ± inflammation with hepatocyte injury (ballooning) ± fibrosis

NASH Cirrhosis

Cirrhosis + current or previous histological evidence of steatosis

Chalasani et al. 2018; ACG 2022.

Natural Progression of NAFLD Over 7-14 Years



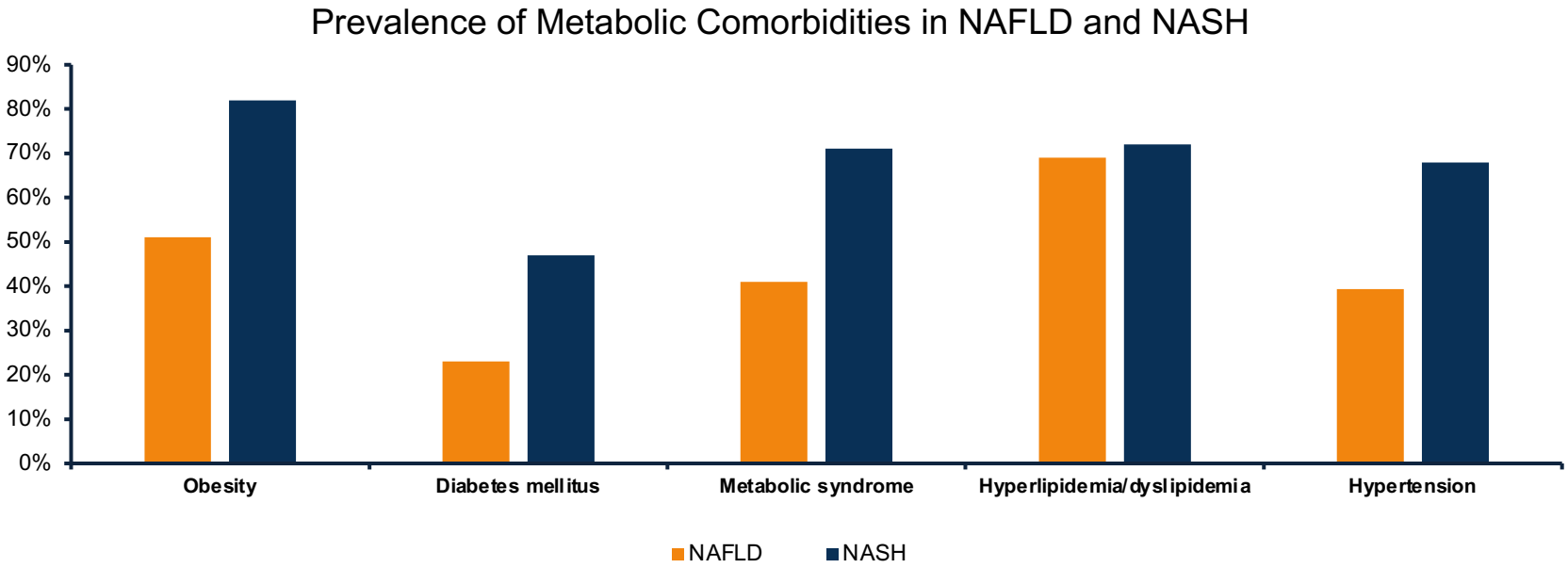
NAFLD is a slowly progressive disease

- 1 fibrosis stage every 14 years in NAFL and every 7 years in NASH
- Doubled by arterial hypertension
- More rapid in about 20% of cases

Marengo et al. 2016.

Identify Risk Population

Prevalence of Metabolic Comorbidities

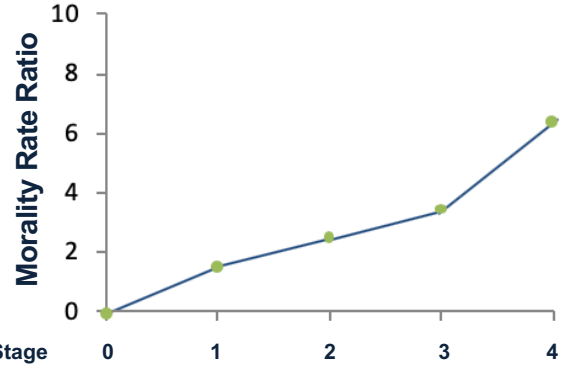


Marchisello et al. 2019; Younossi et al. 2016.

Mortality Increases With Fibrosis in NAFLD

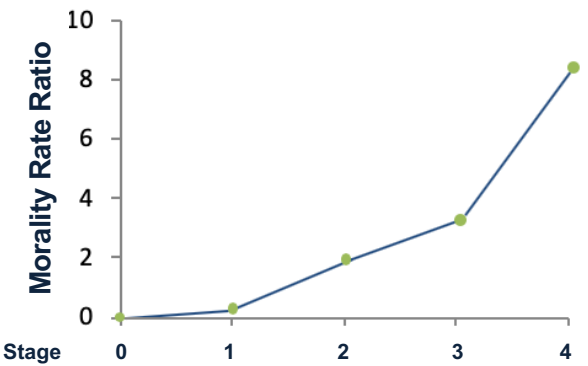
Systematic review and meta-analysis of 5 studies in 1,495 NAFLD patients with 17,452 patient-years follow-up

All-Cause Mortality



Fibrosis Stage	0	1	2	3	4
Mortality Rate Ratio (95% CI)		1.58 (1.19-2.11)	2.52 (1.85-3.42)	3.48 (2.51-4.83)	6.40 (4.11-9.95)
Mortality Rate (per 1,000 PYF)	15.2	17.1	27.9	36.0	45.8

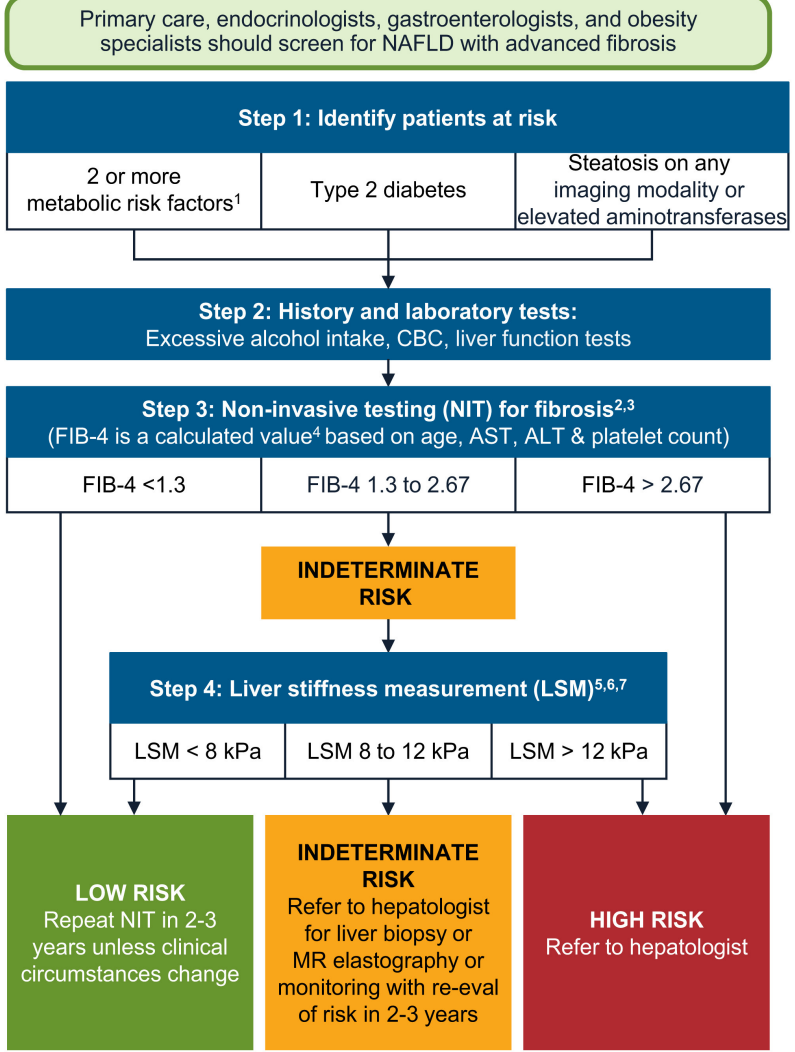
Liver-Related Mortality



Fibrosis Stage	0	1	2	3	4
Mortality Rate Ratio (95% CI)		1.41 (0.17-11.95)	9.57 (1.67-54.93)	16.69 (2.92-95.36)	42.30 (3.51-510.34)
Mortality Rate (per 1,000 PYF)	0.30	0.64	4.26	7.92	23.3

Dulai et al. 2017; ACG 2022.

2021 AGA Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease



Kanwal et al. 2021

Drug Advancements

AASLD Treatment Guidelines

- Management of NAFLD should consist of treating liver disease AND associated metabolic comorbidities
  - Lifestyle modifications with target goal of 5-10% total body weight loss (TBWL)
  - Recommended therapies
    - Vitamin E 800 IU/day
    - Pioglitazone

Chalasani et al. 2018.

Therapy Extends Beyond the Liver

	LOW RISK FIB-4 <1.3 or LSM <8 kPa or liver biopsy F0-F1	**INDETERMINATE RISK** FIB-4 1.3-2.67 and/or LSM 8-12 kPa and liver biopsy not available	**HIGH RISK**[1] FIB-4 >2.67 or LSM >12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4,5,6]	Yes[4,5,6,7]
CVD risk reductions[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

No Therapy Yet

Kanwal et al. 2021.

Footnotes:

1. Patients with F4 or cirrhosis (based on biopsy, LSM values based on vibration controlled transient elastography (VCTE, FibroScan®) or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm^3.
2. All patients require regular physical activity, healthy diet, avoid excess alcohol intake.
3. Weight loss recommended for cardiometabolic benefit and reversal of steatosis. Greater weight loss is often associated with more benefit, such as reversal of steatohepatitis (usually with weight loss ≥7%) or fibrosis (usually with weight loss ≥10%).
4. Individualize based on further work-up and efforts to confirm the diagnosis of NASH. A liver biopsy provides helpful information and should be considered for cases where there is a diagnostic doubt such as patients with indeterminate, unreliable, or conflicting non-invasive assessments of as part of phase 2 or 3 clinical trials.
5. No pharmacological agent is FDA-approved for the treatment of NASH. Patients with T2DM may benefit from some diabetes medications. Such as pioglitazone[80,81,86,87,88] and some GLP-1 RAs[84,85] that have reported histological improvement in RCTs in patients with NASH, either with or without diabetes. Among GLP-1 RAs, semaglutide has the strongest evidence of liver histological benefit[85].
6. Vitamin E improves steatohepatitis in patients with NASH without diabetes[80], with less evidence in patients with T2D[81].
7. Pharmacotherapy in patients with NASH cirrhosis is very limited and should be avoided until more data become available.
8. Statins can be used safely in patients with steatohepatitis and liver fibrosis; to be avoided in decompensated cirrhosis.

Kanwal et al. 2021.

Weight Management in NAFLD

Fibrosis Risk Stratification

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	**Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	**High Risk** FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liraglutide 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HCC = Hepatocellular carcinoma, NASH = Nonalcoholic steatohepatitis

1. Persons with confirmed cirrhosis based on biopsy or high likelihood based on LSM >13.6kPa from vibration controlled transient elastography (FibroScan®), ELF ≥9.8 or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm^3.
2. These goals should only be taken as a broad guidance. NAFLD/NASH may also improve by changes in macronutrient content, exercise and other factors beyond magnitude of weight loss. All high-quality studies available limited to a maximum of 12 month duration.
3. No high-quality evidence for pharmacotherapy in persons with NASH cirrhosis. Treatment should be individualized and used with caution only by liver specialists.
4. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

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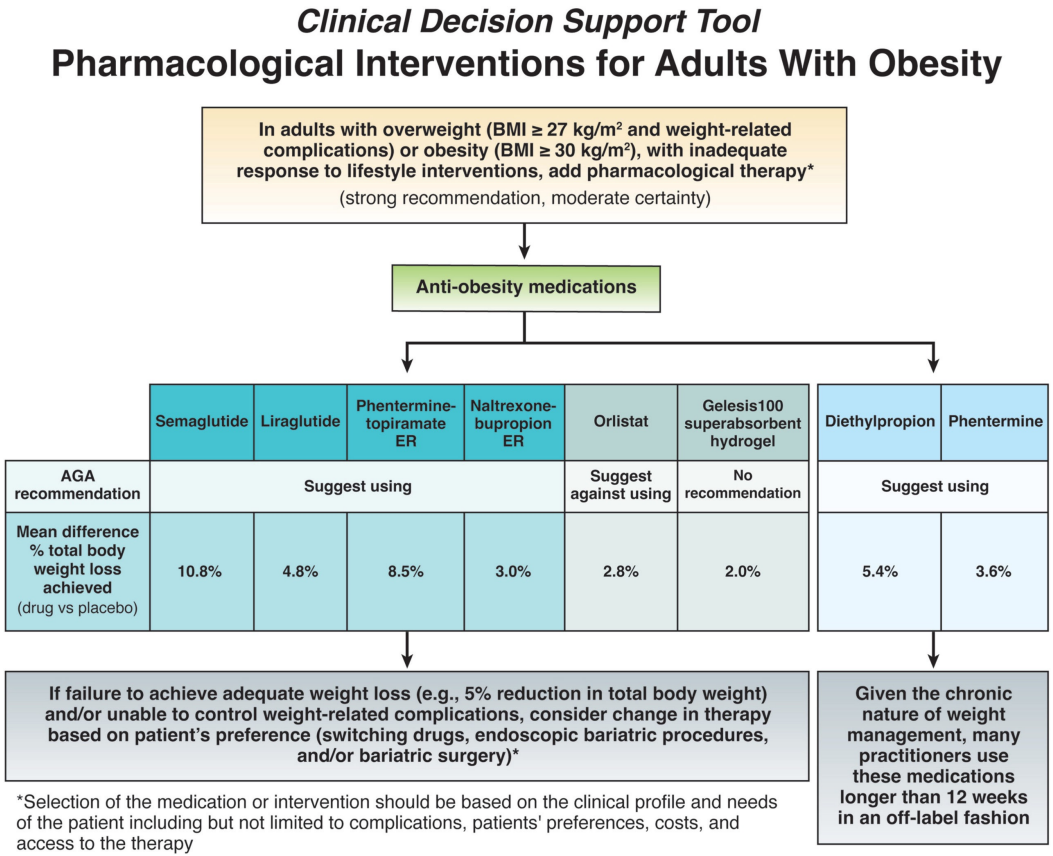
Algorithm Figure 3

Cusi et al. 2022.

AACE.

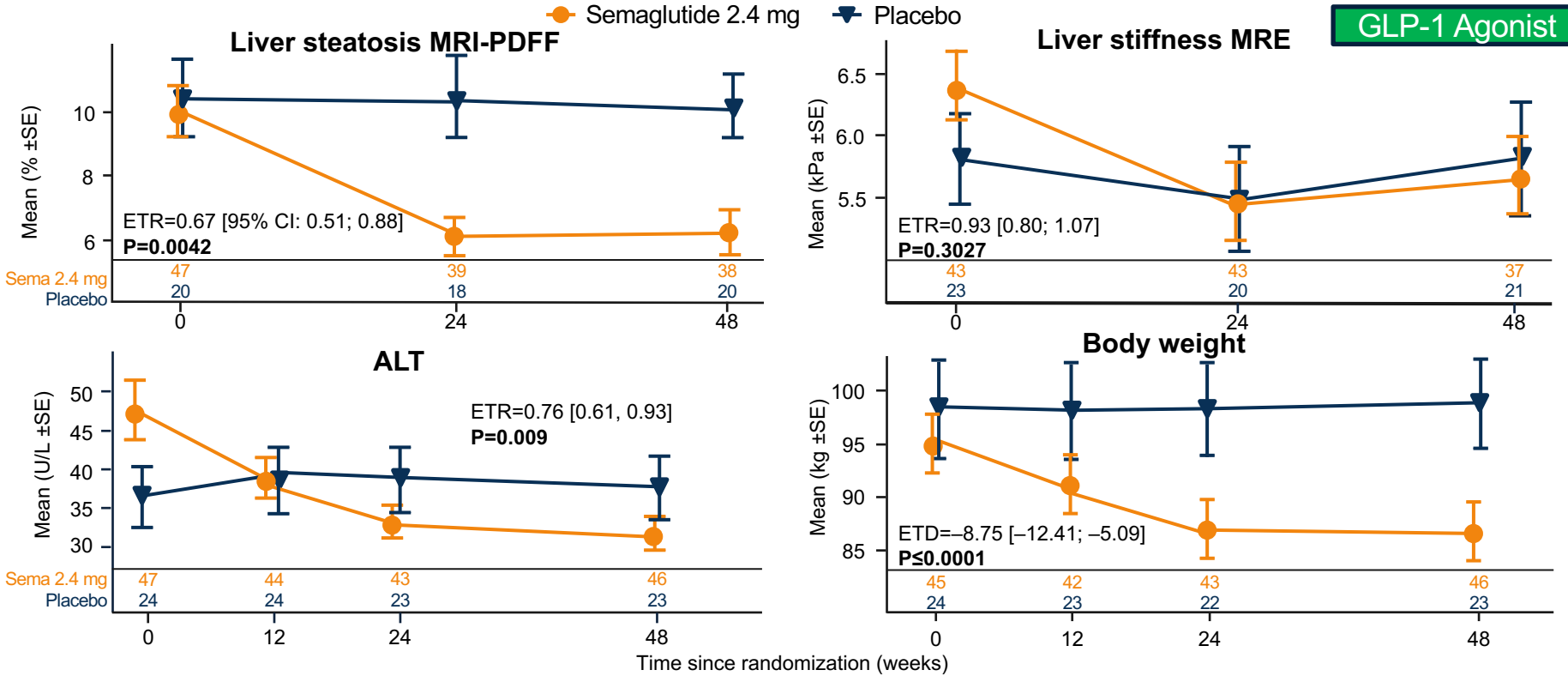
Pharmacotherapy for Weight Loss



Grunvald et al. 2022.

Semaglutide 2.4 mg Once Weekly Improved Liver and Metabolic Parameters, and Was Well Tolerated, in Patients With Non-Alcoholic Steatohepatitis-Related Cirrhosis: A Randomized, Placebo-Controlled Phase 2 Trial

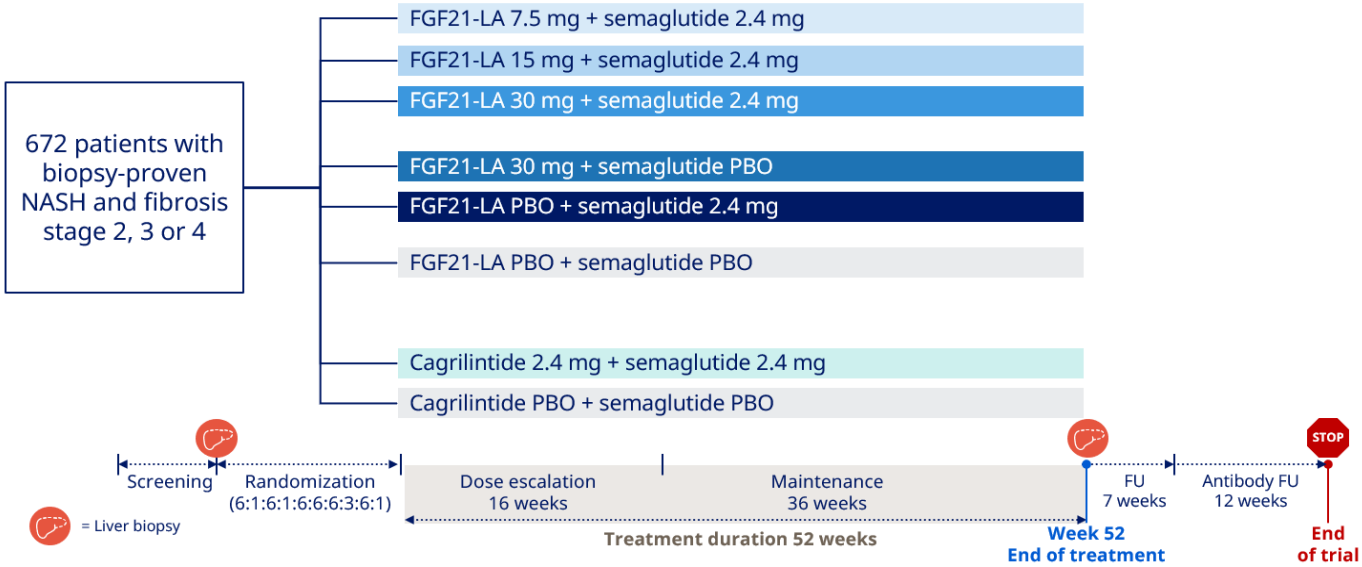
GLP-1 Agonist



ETD, estimated treatment difference; ETR, estimated treatment ratio.

Loomba R et al. *EASL*. 2022. #LB001. Sponsored by Novo Nordisk.

On-Going Phase 2 Study Design: Semaglutide + FGF21 or Cagrilintide in NASH (F2-F4)



Primary Endpoint:

- Improvement in liver fibrosis with no worsening of NASH from baseline to Week 52

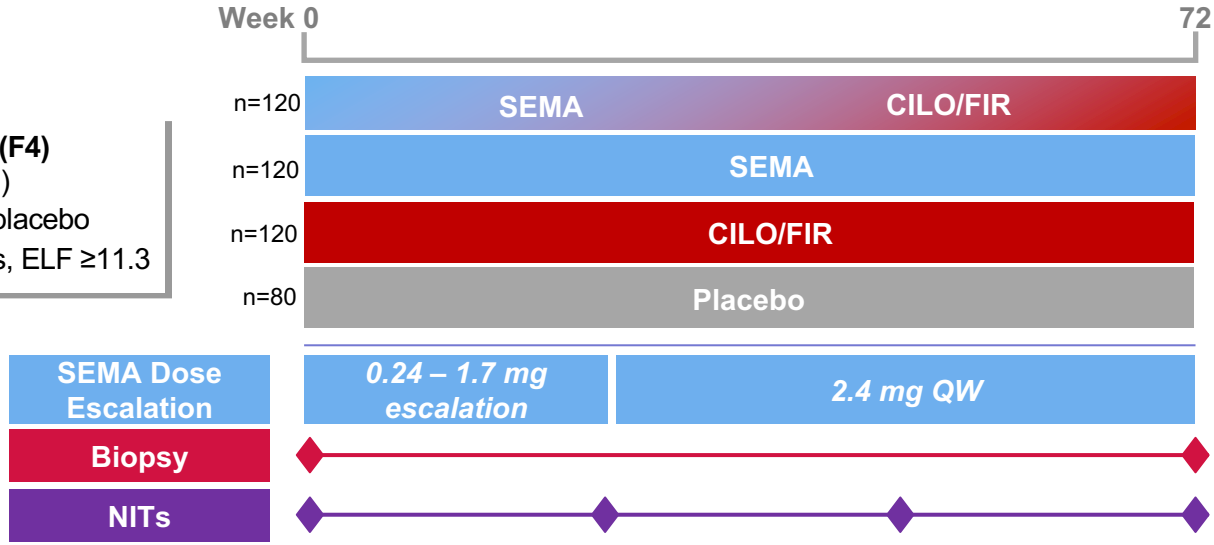
Secondary Endpoints:

- Changes in liver histology, liver enzymes, metabolic laboratory values
- Change in body weight

https://www.clinicaltrials.gov/ct2/show/NCT05016882?term=NCT05016882&draw=2&rank=1
Sponsored by Novo Nordisk.

Phase 2b Study Design: Semaglutide (SEMA)+ Cilofexor (CILO) + Firsocostat (FIR)

Cirrhosis (F4)
(N=440)
3:2 active vs placebo
Stratify by diabetes, ELF ≥11.3



Endpoints

- Histology (+Path AI)
- NITs (e.g. ELF, FibroScan)

- Co-primary endpoints (SEMA+CILO/FIR vs placebo)
  - NASH resolution
  - Fibrosis improvement (≥1-stage) without worsening of NASH

https://clinicaltrials.gov/ct2/show/NCT04971785?term=cilofexor&cond=Nash&draw=2&rank=1
Sponsored by Gilead.

Phase 3 Regenerate Study: Obeticholic Acid (Oca)

Intercept

FXR Agonist

Intercept Announces Positive Data in Fibrosis due to NASH from a New Analysis of its Phase 3 REGENERATE Study of Obeticholic Acid (OCA)

July 7, 2022

OCA 25 mg met the agreed primary endpoint of improvement in liver fibrosis without worsening of NASH at 18 months (p<0.0001), consistent with the original REGENERATE analysis

OCA 25 mg demonstrated double the response rate in reduction of liver fibrosis without worsening of NASH vs. placebo

	Placebo n=311	OCA 10 mg n=312	OCA 25 mg n=308
At least one stage of fibrosis improvement with no worsening of NASH*	9.6%	**14.1%** p=NS	**22.4%** p<0.0001
Resolution of NASH‡ with no worsening of liver fibrosis	3.5%	6.1% p=NS	6.5% p=NS

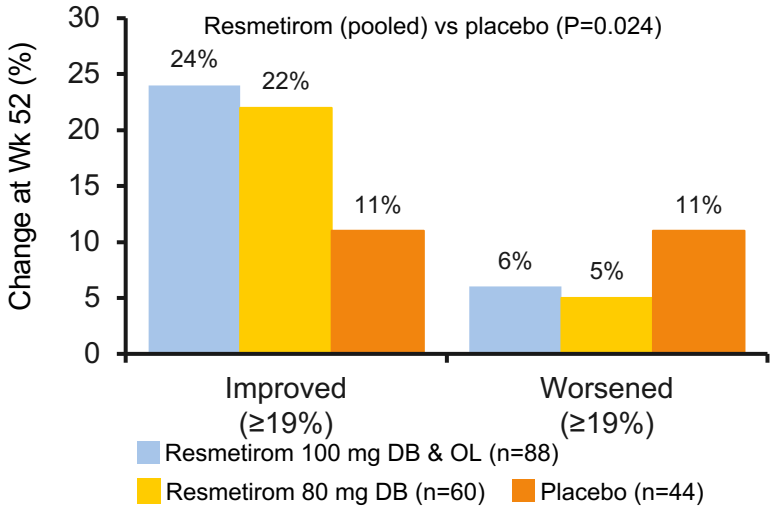
https://ir.interceptpharma.com/news-releases/news-release-details intercept-announces-positive-data-fibrosis-due-nash-new-analysis

Sponsored by Intercept.

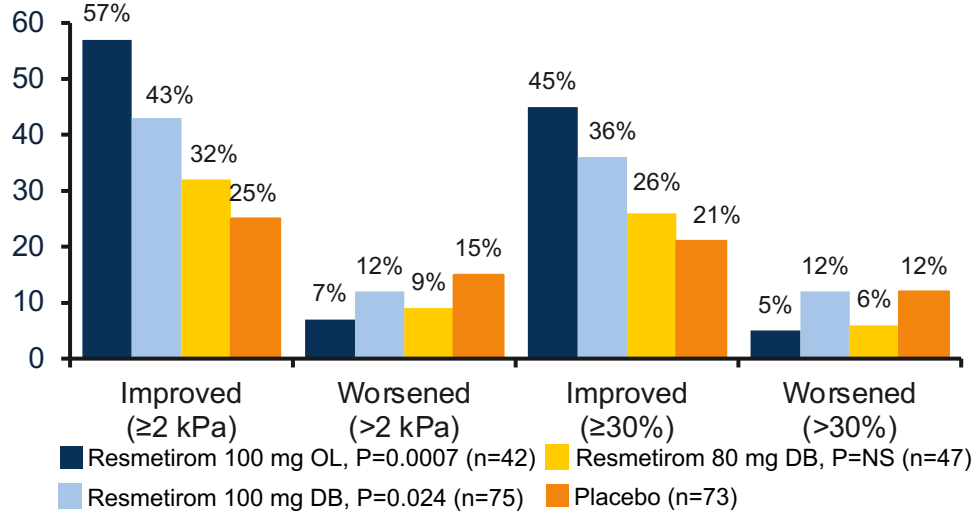
MAESTRO-NAFLD-1 a 52-Week Double-Blind, Placebo-Controlled Phase 3 Clinical Trial of Resmetirom in Patients With NAFLD

TSH B Agonist

MRE change at Week 52: baseline LSM ≥2.9 kPa



FibroScan change at Week 52, baseline VCTE ≥7.2 kPa



- Resmetirom was safe and well tolerated
- Safety and efficacy are in line with expectations from Phase 2 liver biopsy study
- Key secondary endpoints were achieved, despite COVID pandemic
- MAESTRO-NAFLD-1 demonstrates resmetirom has application in a 'real-world' biopsy-free future

Harrison S et al. *EASL*. 2022. #LB005. Sponsored by Madrigal Pharmaceuticals.

Key Take Aways

- NAFLD is present in more than 30% of Americans
- NASH is a histologic diagnosis
- Fibrosis is associated with liver related morbidity and mortality
- Lifestyle intervention remains the cornerstone of therapy
- There are no approved pharmacologic therapies for NASH
  - Rich pipeline of drugs
  - Medications approved for weight loss may aid in improving overall health outcomes including liver disease

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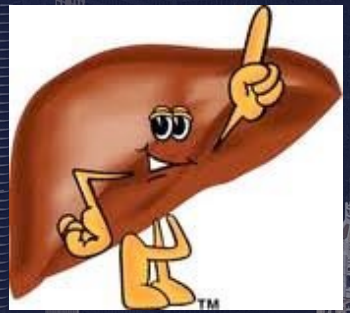
Thank You!

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