# Therapeutic Agent Development in MASH in 2024:

# On the cusp or on the brink?

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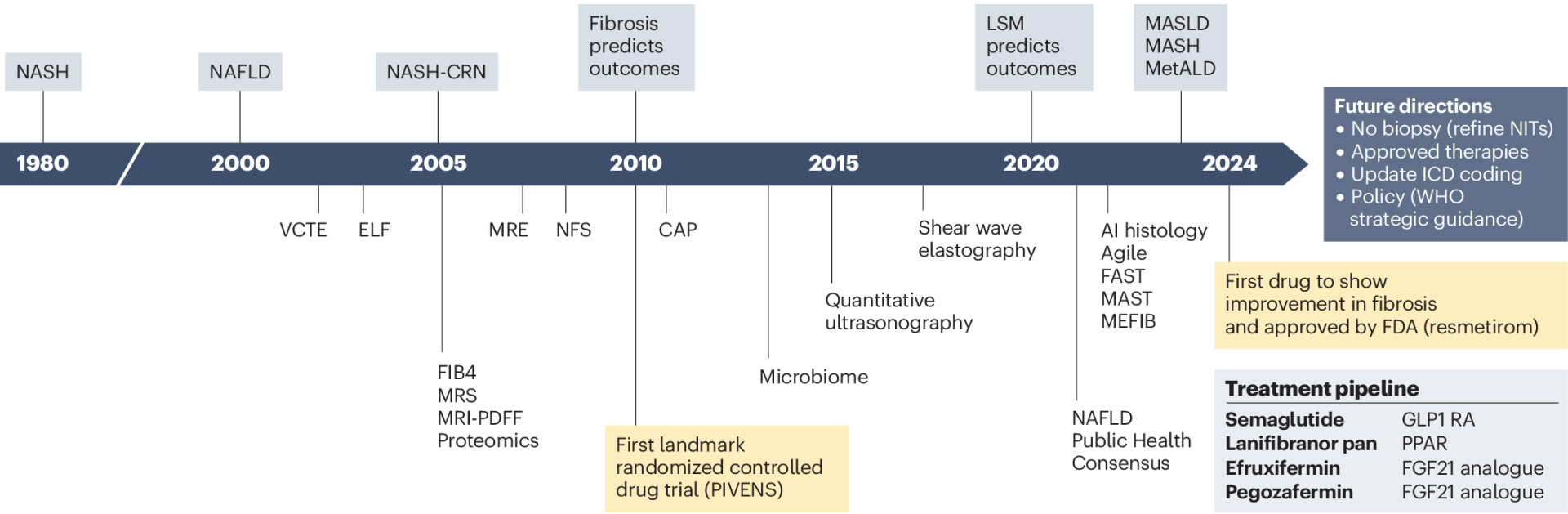
Professor of Medicine
University of Chicago

**Consulting past 24 months:**

- Alnylam, Amgen, AMRA, BMS, Boehringer Ingelheim, Cytodyn, Enanta, Galecto, Merck, Akero, Theratechnologies, Intercept Pharmaceuticals, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Fractyl, Siemens, Thetis, Terns, Sagimet, 89Bio and Novartis

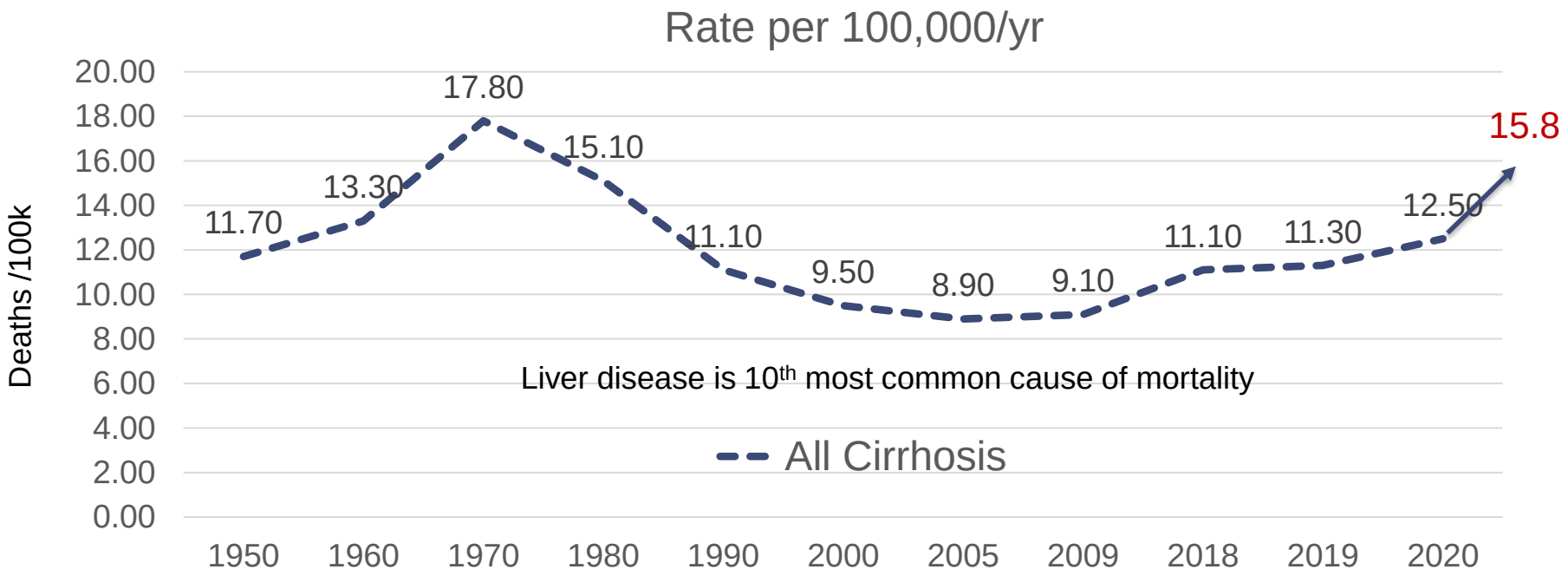
# Timeline of MASLD and MASH




Allen, A.M., *et al.* Envisioning how to advance the MASH field.
*Nat Rev Gastroenterol Hepatol* (2024). https://doi.org/10.1038/s41575-024-00938-9

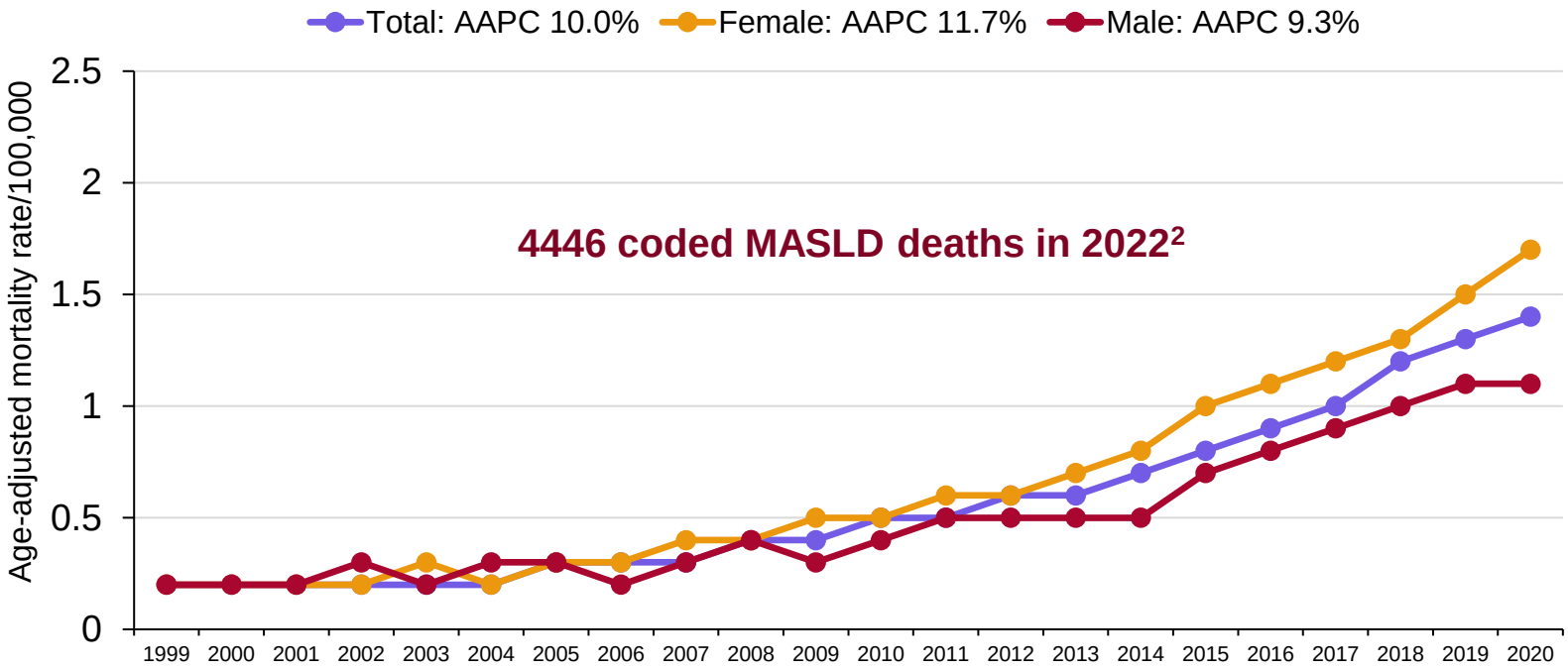
# Epidemiology

# CDC Reported Mortality Rates for Any Cirrhosis 1950-2020




NIH NIAA National Institute on Alcohol Abuse and Alcoholism Division of Epidemiology and Prevention
Research Alcohol Epidemiologic Data System Surveillance Report #120
Apparent Per Capita Alcohol Consumption: National, State, And Regional Trends, 1977–2021.

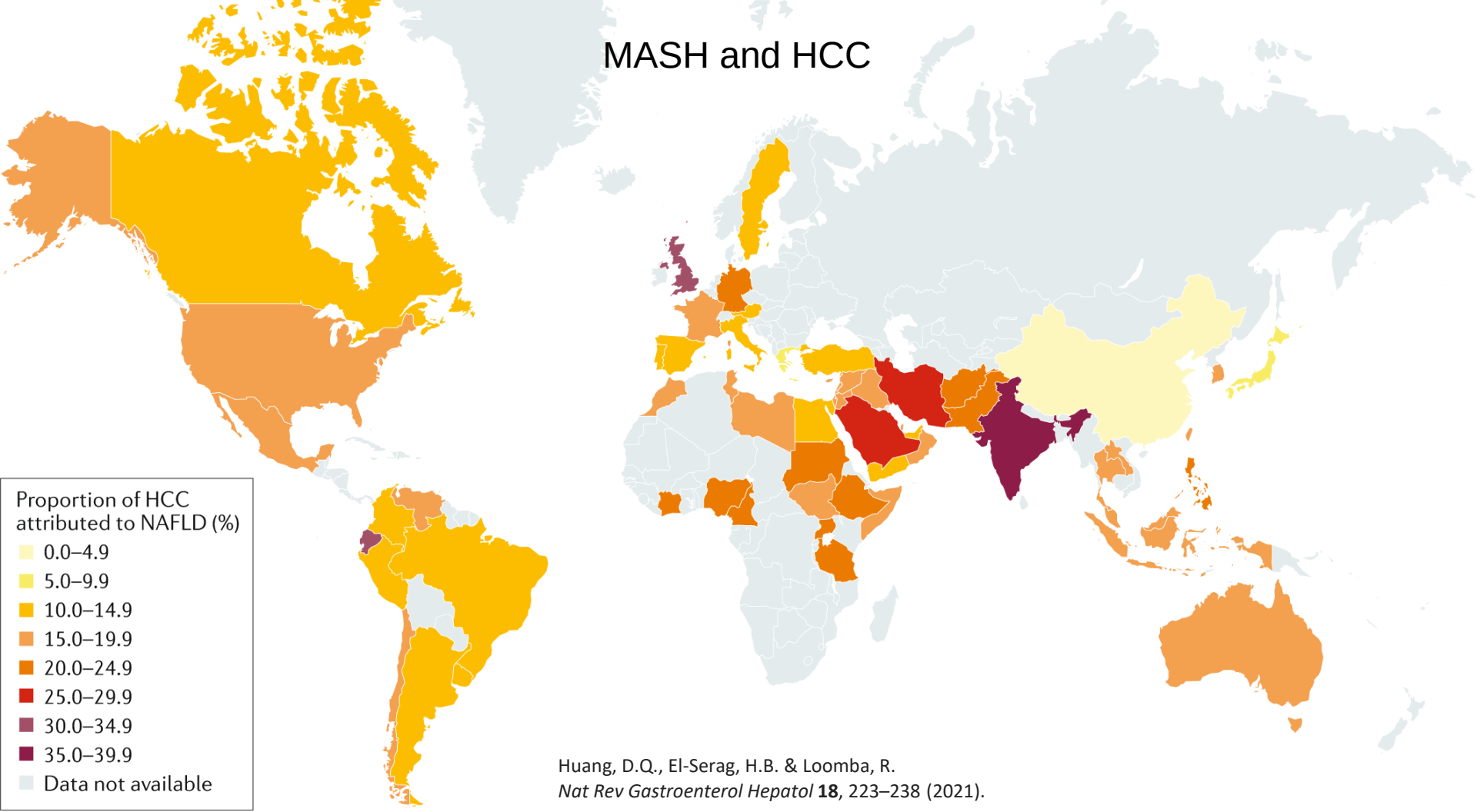
# CDC Reported Mortality Rates for MASLD/MASH




AAPC, average annual percentage change; CDC, Centers for Disease Control and Prevention; MASLD, metabolic dysfunction-associated steatotic liver disease.

1. Ilyas F, Ali H, Patel P, Sarfraz S, Basuli D, Giammarino A, Kumar Satapathy S. Increasing nonalcoholic fatty liver disease-related mortality rates in the United States from 1999 to 2022. Hepatol Commun. 2023;7:e00207. 2. Ilyas F, Ali H, Patel P, Sarfraz S, Basuli D, Giammarino A, Kumar Satapathy S. Increasing nonalcoholic fatty liver disease-related mortality rates in the United States from 1999 to 2022. Hepatol Commun. 2023;7:e00207

# MASH and HCC



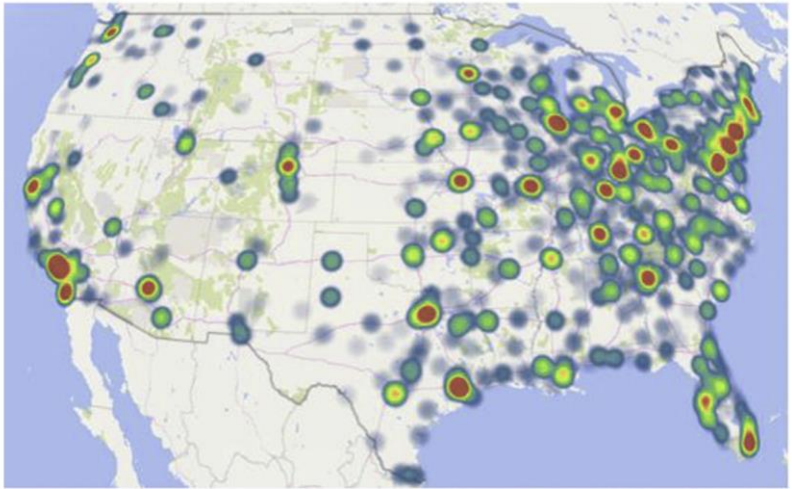

Huang, D.Q., El-Serag, H.B. & Loomba, R.
*Nat Rev Gastroenterol Hepatol* **18**, 223–238 (2021).

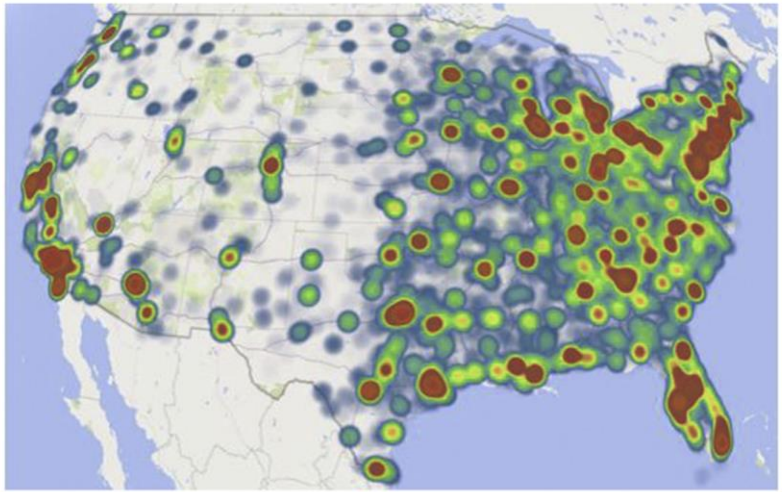
# NASH Prevalence by ICD-10 Codes

Verbatim
N=~200,000

"Proprietary data sources from IQVIA"

Implied
>16,000,000





<6/site >1500

61% PCP
**15% GI / Hepatologist**
<5% Endo / Diabetologist
~20% All other

97% PCP
<5% Endo / Diabetologist
**<1% GI / Hepatologist**
<1% All other

DeLegge et al. *Gastro Clinics* 49, 1, 123-140, 2020.

# Characteristics of MASH patient with vs. without cirrhosis

Of approximately **16 million** adults captured within CDM, 28,576 (0.18%) adults had MASH

- Of those, 9,157 (32%) had cirrhosis at index
- Based on cross sectional analyses,[1] >2,240,000 (14%) of patients in CDM will have MASH
  - 1.28% of patients (1:78) with MASH are diagnosed.

| | With cirrhosis (n=9,157) | Without cirrhosis (n=19,419) |
|---|---|---|
| Follow-up per person, years, mean (SD) | 2.5 (1.6) | 3.2 (1.5)* |
| Age at index, years, mean (SD) | 67.1 (10.8) | 59.8 (13.4)* |
| Categorical age at index, years, n (%) | | |
| ≥65 years | 6,191 (67.6) | 8,791 (45.3) |
| Female sex, n (%) | 5,999 (65.5) | 11,431 (58.9)^ |
| Comorbidities of interest, n (%) | | |
| CVD | 7,790 (85.1) | 13,108 (67.5)* |
| T2DM | 5,209 (56.9) | 5,899 (30.4)* |
| Obesity | 4,820 (52.6) | 9,734 (50.1)* |
| Categorical FIB-4, n (%) | | |
| Low risk (FIB-4 < 1.0) | **291 (8.7)** | 2,210 (31.4) |
| Intermediate risk (1.0 ≤ FIB-4 ≤3.25) | 1,579 (47.0) | 4,391 (62.1) |
| High risk (FIB-4 > 3.25) | 1,487 (44.3) | 447 (6.3) |
| FIB-4 Unavailable (%) | 5,800 (63.3) | 12,371 (63.7) |

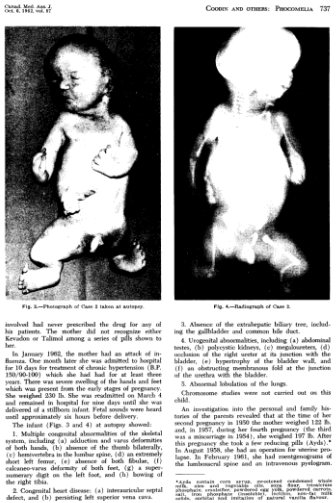
CDM, Clinformatics Data Mart; CVD, cardiovascular disease; FIB-4, Fibrosis-4; NASH, nonalcoholic steatohepatitis; SD, standard deviation; T2DM, type 2 diabetes mellitus. *P<0.01 when using two-tailed Student's T-Test to compare the means between cohorts with vs without cirrhosis. ^P<0.01 when using chi-squared test to compare the distribution categorical characteristics between the cohorts with vs. without cirrhosis.

[1]Harrison et al., *J Hepatol*. 2021 Aug;75(2):284-291. Epub 2021 Mar 18. PMID: 33746083.

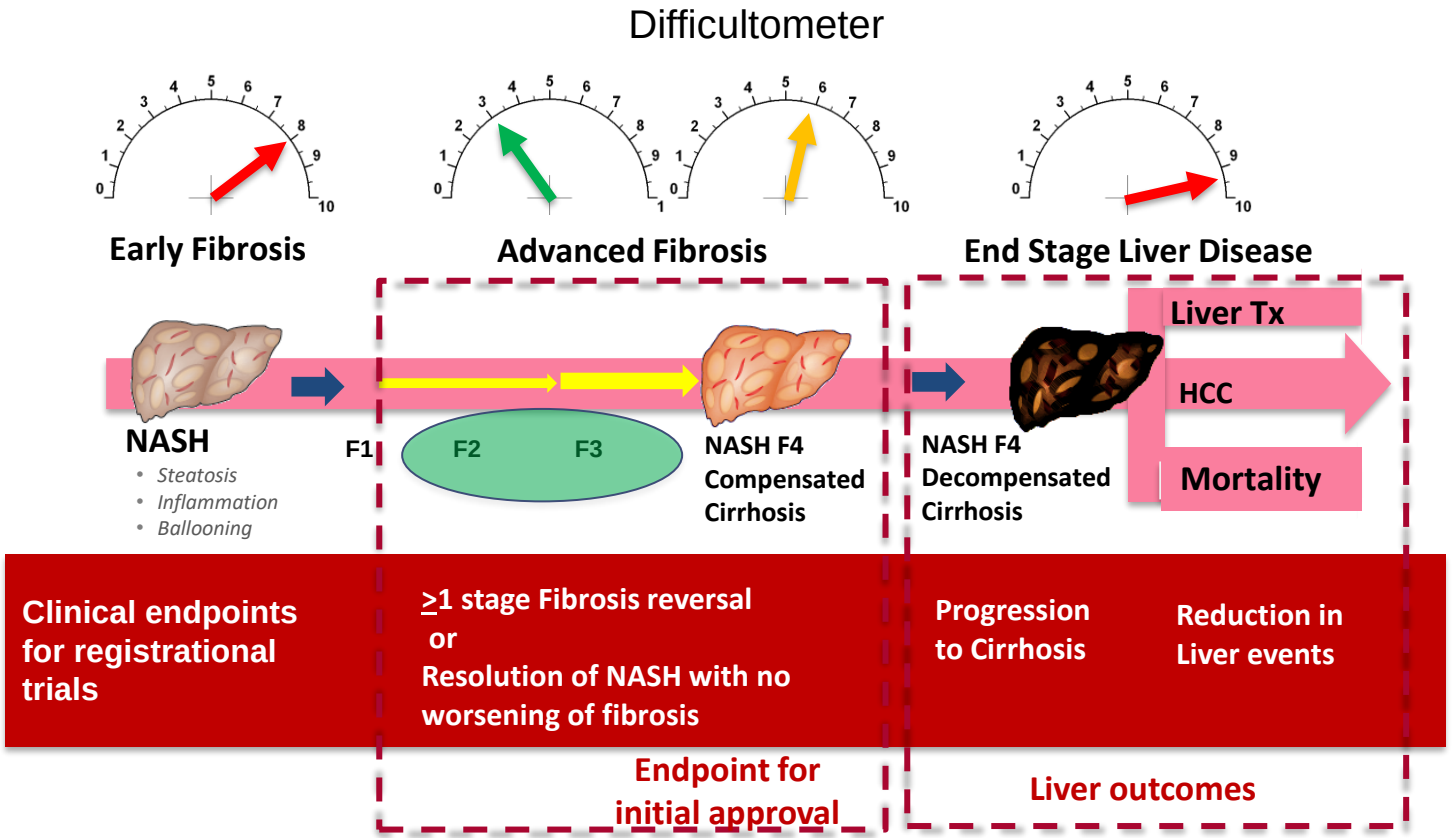
# Therapeutics

# The long shadow of phocomelia

- Frances Oldham Kelsey
  - 1934 BSc, MSc, McGill
  - 1938 PhD, University of Chicago
  - 1950 MD, University of Chicago
- 1960 joined FDA
  - Assigned review of thalidomide
  - Already approved in dozens of countries
  - Denied approval on basis of lack of evidence of safety
- 1962 President's Award for Distinguished Civilian Service
- Head Investigational Drug Branch
- Head Division Scientific Investigations



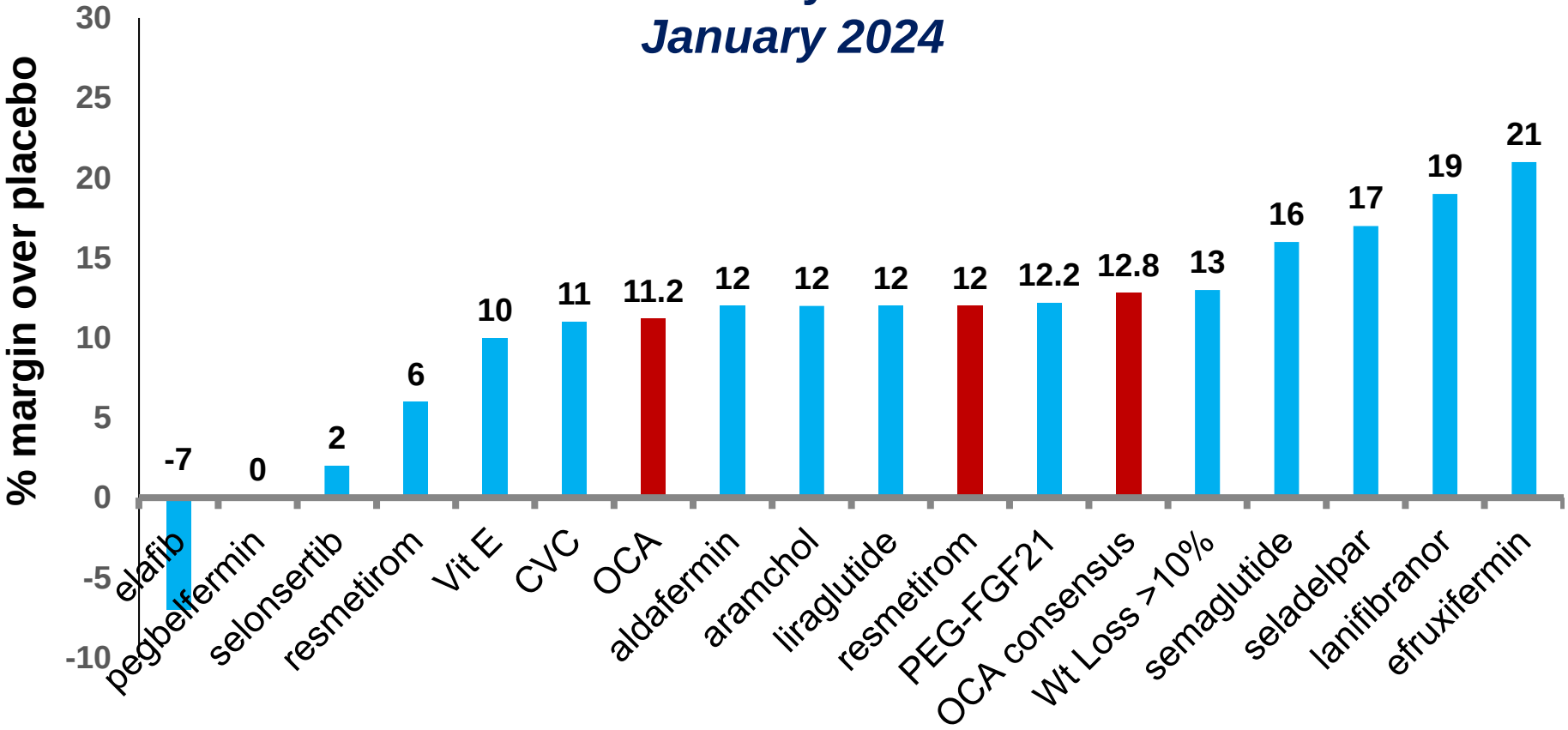
# Regulatory pathway for NASH treatments




Adapted from: Younossi et al. Hepatology 2015; Sanyal et al. Hepatology 2006

# MASH Therapeutic Agents in Late-Stage Development – Fibrosis Efficacy over Placebo

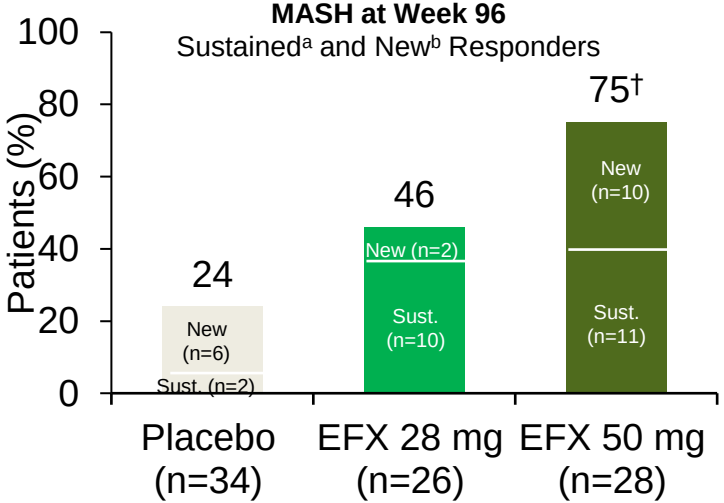
***January 2024***



# HARMONY: Safety of efruxifermin for 96 weeks among patients with MASH F2–F3 fibrosis

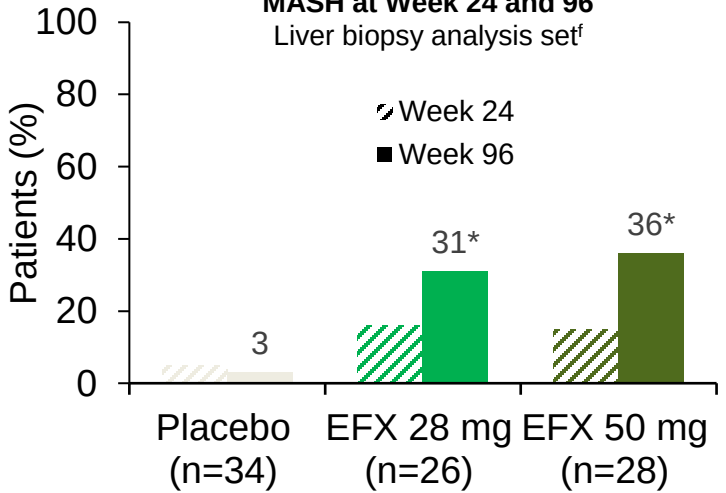
**≥1-stage improvement in fibrosis and no worsening of MASH at Week 96**

Sustained[a] and New[b] Responders




**2-stage improvement in fibrosis and no worsening of MASH at Week 24 and 96**

Liver biopsy analysis set[f]




*P<0.01, †P<0.001 vs placebo (CMH)

[a]Responder at Weeks 24 and 96; [b]Responder at Week 96; [c]Among Week 24 Non-Responders with Week 96 biopsies; [d]Not analyzed for statistical significance; [e]Among Week 24 Responders with Week 96 biopsies; [f]All patients with baseline and Week 24 or 96 biopsies; [g]Patients with missing biopsies are imputed as nonresponders

Ratziu V, et al. EASL ILC 2024. LBO-002. Sponsored by Akero Therapeutics

# HARMONY: Safety of efruxifermin for 96 weeks among patients with MASH F2–F3 fibrosis

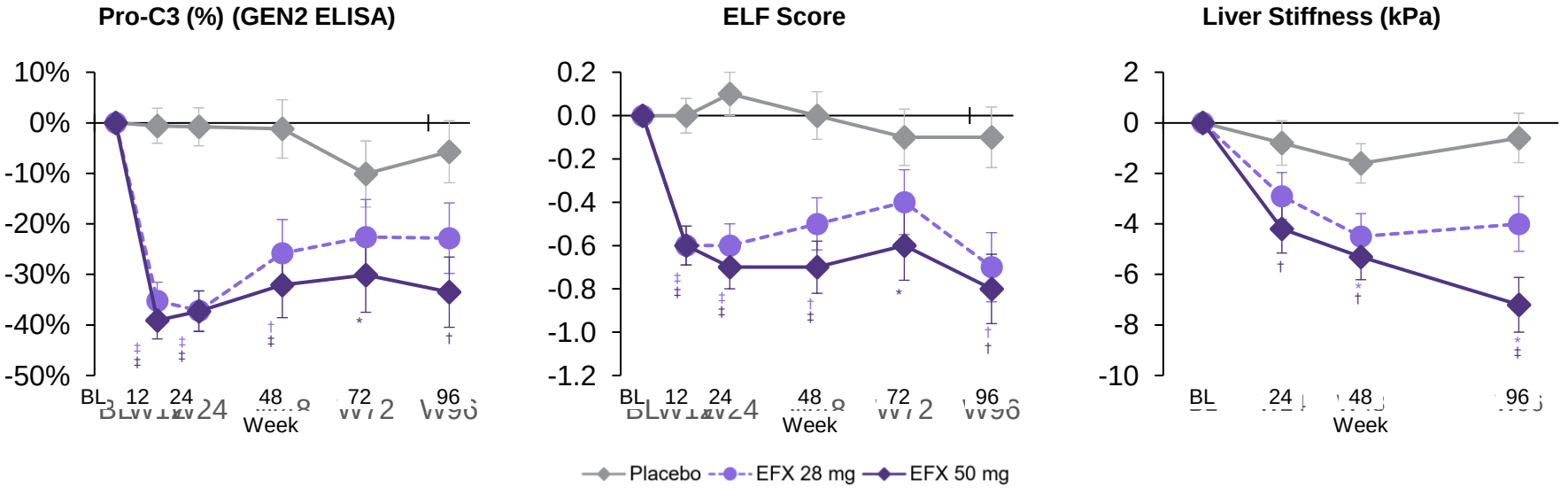
| Data are n (%) | Placebo (n=43) | EFX 28 mg (n=40) | EFX 50 mg (n=43) |
|---|---|---|---|
| Leading to death | 0 | 0 | 0 |
| SAEs | 4 (9%) | 4 (10%) | 7 (16%) |
| Leading to discontinuation | 0 | 4 (10%) | 5 (12%) |
| Most frequent (≥15%) drug–related TEAEs | | | |
| Diarrhea | 7 (16%) | 16 (40%) | 16 (37%) |
| Nausea | 5 (12%) | 12 (30%) | 14 (33%) |
| Increased appetite | 3 (7%) | 7 (18%) | 10 (23%) |
| Injection site erythema | 6 (14%) | 8 (20%) | 7 (16%) |
| Injection site bruising | 2 (5%) | 6 (15%) | 3 (7%) |

- Markers of liver function and hemostasis remained stable, including MELD, and CP score
- No reported events of DILI
- Blood pressure unchanged after 96 weeks of EFX Treatment
- No significant changes in BMD after 48 weeks
- Statistically significant, modest reductions in BMD after 96 weeks

Ratziu V, et al. EASL ILC 2024. LBO-002. Sponsored by Akero Therapeutics

# HARMONY: Safety of efruxifermin for 96 weeks among patients with MASH F2–F3 fibrosis

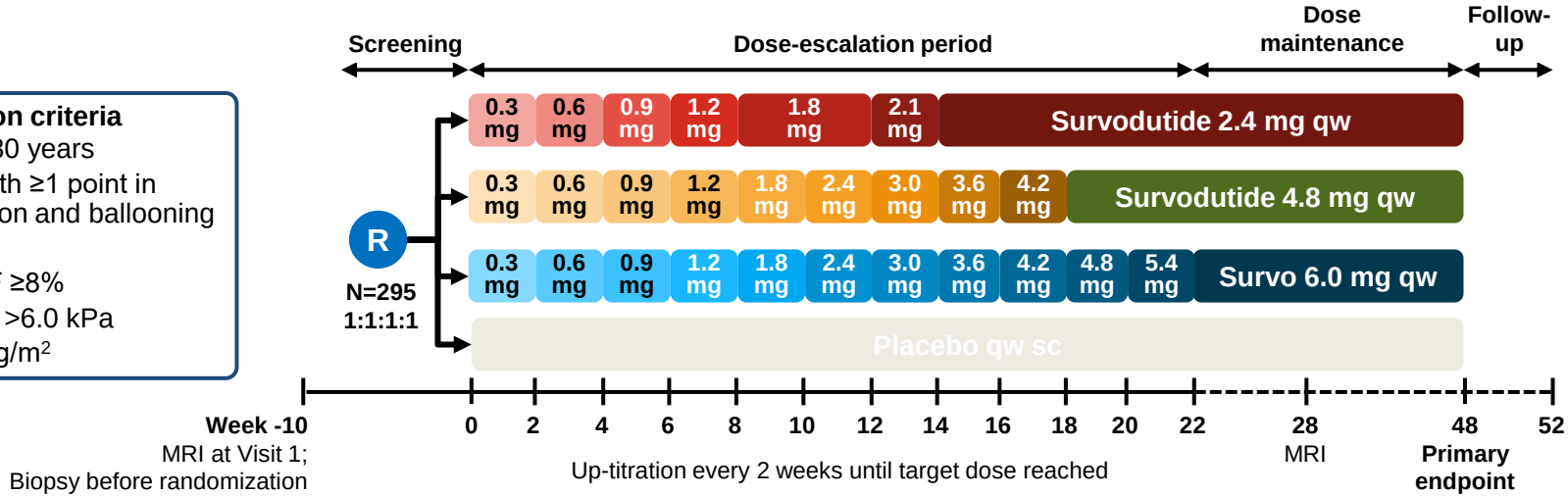
**LS Mean change from baseline to Week 96**




Ratziu V, et al. EASL ILC 2024. LBO-002. Sponsored by Akero Therapeutics

# Phase 2 randomized double-blind, placebo-controlled trial of survodutide (glucagon and GLP-1 receptor dual agonist) for patients with MASH and fibrosis

**Key inclusion criteria**
- Aged 18–80 years
- NAS ≥4 with ≥1 point in inflammation and ballooning
- F1–3
- MRI-PDFF ≥8%
- FibroScan >6.0 kPa
- BMI ≥25 kg/m$^2$



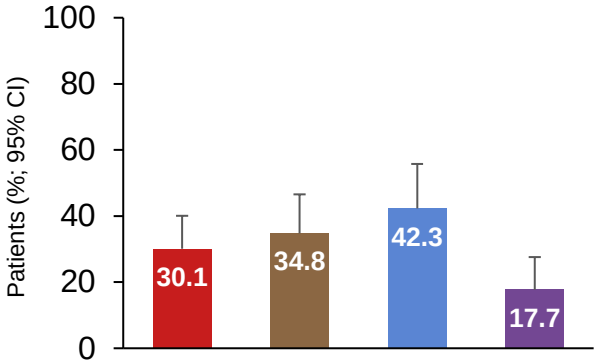

**Primary endpoint:**
- Histological improvement of MASH without worsening of fibrosis at Week 48

Survodutide **activity 8-fold higher for GLP-1R than GCGR**

Sanyal et al., ILC LB GS-006, 2024.

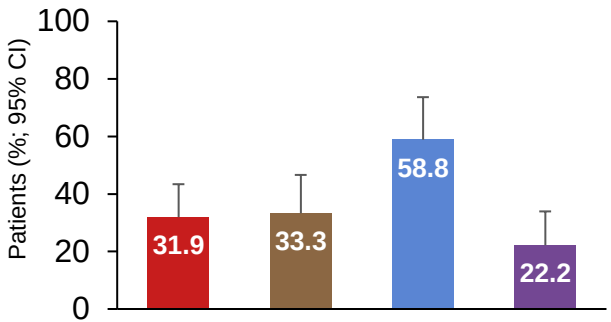
# Phase 2 trial: Improvement in liver fibrosis with no worsening of MASH among patients with MASH and fibrosis treated with survodutide for 48 weeks

**Actual treatment: Improvement in liver fibrosis with no worsening in MASH[a] (F1–F3 population)**



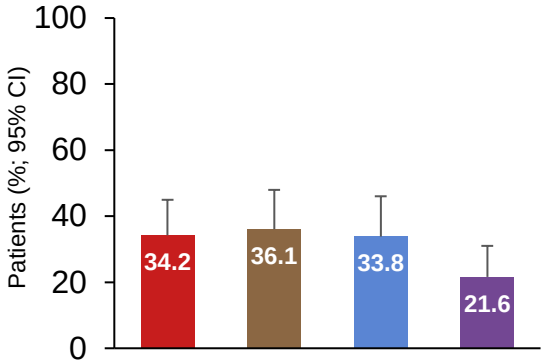

| | Survo 2.4 mg (n=93) | Survo 4.8 mg (n=69) | Survo 6.0 mg (n=52) | Placebo (n=79) |
|---|---|---|---|---|
| Paired biopsy results[c]: | 50.0% | 45.3% | 50.0% | 21.1% |
| Nominal P-values: | 0.0587 | 0.0181 | 0.0011 | |

**Actual treatment: Improvement in liver fibrosis with no worsening in MASH[a] (F2/F3 population)**




| | Survo 2.4 mg (n=72) | Survo 4.8 mg (n=54) | Survo 6.0 mg (n=34) | Placebo (n=63) |
|---|---|---|---|---|
| Paired biopsy results[c]: | 56.1% | 40.9% | 64.5% | 25.9% |
| Nominal P-values: | 0.2173 | 0.1909 | 0.0004 | |

**≥1-stage decrease in fibrosis Sanyal et al. NEJM 2024**




Sanyal et al., ILC LB GS-006, 2024.

# Phase 2 trial: Survodutide for MASH for 48 weeks

| AE, n (%) | Survo 2.4 mg (n=73) | Survo 4.8 mg (n=72) | Survo 6.0 mg (n=74) | Total survo (n=219) | Placebo (n=74) |
|---|---|---|---|---|---|
| Any AE | 71 (97.3) | 67 (93.1) | 70 (94.6) | 208 (95.0) | 68 (91.9) |
| **AE according to preferred term (≥20% in any treatment group)** | | | | | |
| Nausea | 46 (63.0) | 49 (68.1) | 49 (66.2) | 144 (65.8) | 17 (23.0) |
| Diarrhea | 30 (41.1) | 40 (55.6) | 37 (50.0) | 107 (48.9) | 17 (23.0) |
| Vomiting | 27 (37.0) | 33 (45.8) | 29 (39.2) | 89 (40.6) | 3 (4.1) |
| Constipation | 15 (20.5) | 12 (16.7) | 19 (25.7) | 46 (21.0) | 11 (14.9) |
| COVID-19 | 18 (24.7) | 16 (22.2) | 7 (9.5) | 41 (18.7) | 14 (18.9) |
| Headache | 13 (17.8) | 16 (22.2) | 11 (14.9) | 40 (18.3) | 12 (16.2) |
| Decreased appetite | 16 (21.9) | 9 (12.5) | 13 (17.6) | 38 (17.4) | 7 (9.5) |
| Fatigue | 15 (20.5) | 11 (15.3) | 11 (14.9) | 37 (16.9) | 6 (8.1) |
| Dyspepsia | 7 (9.6) | 9 (12.5) | 15 (20.3) | 31 (14.2) | 3 (4.1) |
| Investigator-defined drug-related AE | 60 (82.2) | 59 (81.9) | 60 (81.1) | 179 (81.7) | 36 (48.6) |
| AE leading to discontinuation of trial medication[a] | **12 (16.4)** | **15 (20.8)** | **17 (23.0)** | **44 (20.1)** | **2 (2.7)** |
| Discontinuation due to gastrointestinal AE | 10 (13.7) | 13 (18.1) | 12 (16.2) | 35 (16.0) | 1 (1.4) |
| SAE | 4 (5.5) | 7 (9.7) | 6 (8.1) | 17 (7.8) | 5 (6.8) |
| Drug-related serious AE | 1 (1.4) | 0 (0) | 0 (0) | 1 (0.5) | 0 (0) |

[a]Most trial discontinuations occurred during the rapid dose-escalation phase

**Safety from the Phase 2 trial of semaglutide**

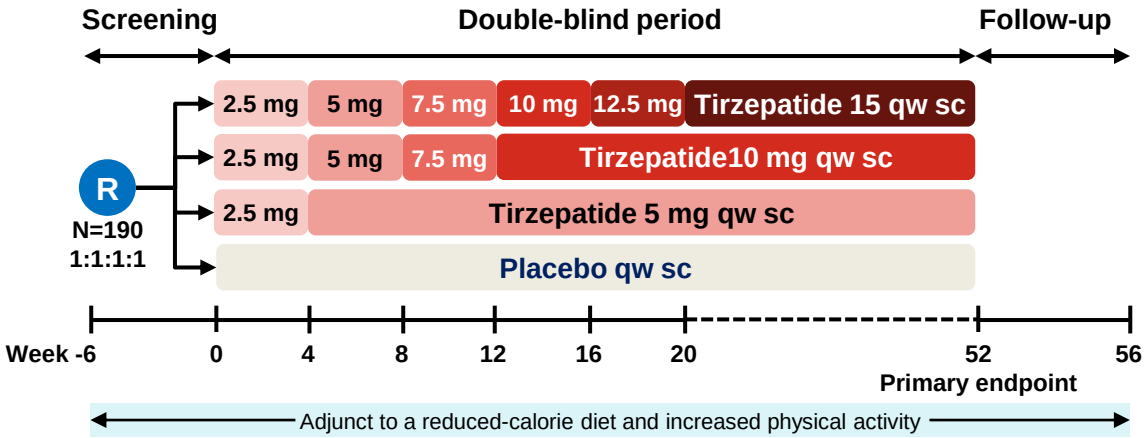
| AE, n (%) | Sema 0.1 (n=73) | Sema 0.2 (n=78) | Sema 0.4 (n=81) | Placebo (n=80) |
|---|---|---|---|---|
| Any AE | 72 (90) | 76 (97) | 76 (94) | 67 (84) |
| AEs from GI disorders | 51 (64) | 60 (77) | 55 (68) | 36 (45) |
| AE according to preferred term | | | | |
| Nausea | 24 (30) | 29 (37) | 34 (42) | 9 (11) |
| Diarrhea | 23 (29) | 22 (28) | 16 (20) | 11 (14) |
| Vomiting | 14 (18) | 17 (22) | 12 (15) | 2 (2) |
| Constipation | 13 (16) | 17 (22) | 18 (22) | 10 (12) |
| Decreased appetite | 16 (20) | 18 (23) | 18 (22) | 4 (5) |

Newsome PN, et al. NEJM 2021

Sanyal et al., ILC LB GS-006, 2024.

# SYNERGY-NASH: Phase 2 randomized, double-blind, placebo-controlled trial of tirzepatide (GLP-1/GIP dual agonist) for patients with MASH and F2–F3 fibrosis

**Key inclusion criteria**
- Aged 18-80 years
- BMI ≥27 kg/m$^2$ and ≤50 kg/m$^2$ with or without T2DM
- Diagnosis of MASH, F2–3 fibrosis and NAS of ≥4 with ≥1 point for steatosis, ballooning, and lobular inflammation




**Primary endpoint:** Resolution of MASH and no worsening of fibrosis at Week 52

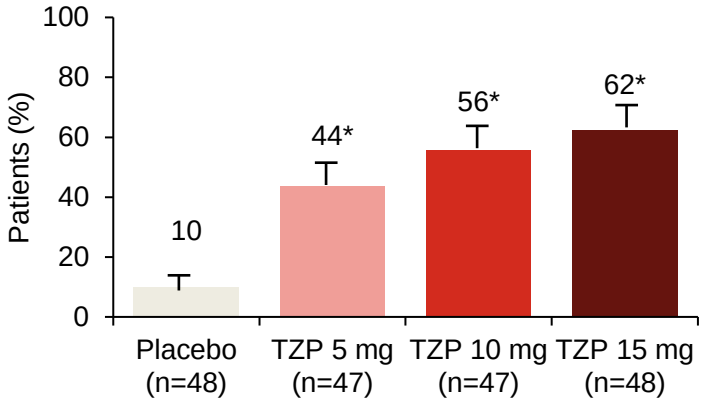
**Other efficacy endpoints at Week 52:**
- ≥1 stage decrease in fibrosis and no worsening of MASH
- ≥2 point decrease in NAS, with ≥ 1 point decrease in at least 2 NAS components
- Change from baseline in MRI-PDFF, VCTE LSM, ELF, Pro-C3

Loomba R, et al. EASL ILC 2024. LBO-001. Sponsored by Eli Lilly and Company

# SYNERGY-NASH: Phase 2 randomized, double-blind, placebo-controlled trial of tirzepatide (GLP-1/GIP dual agonist) for patients with MASH and F2–F3 fibrosis

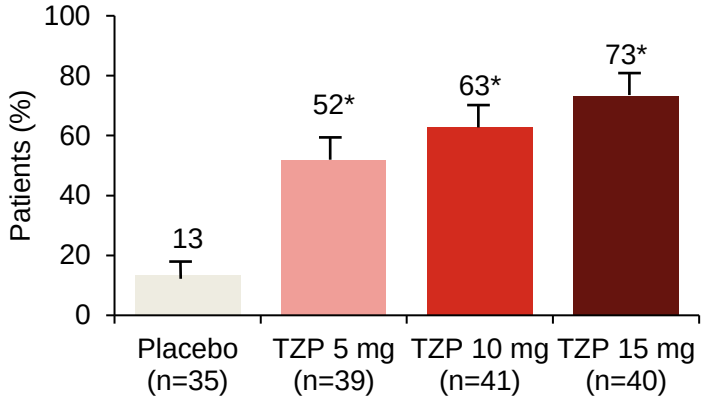
**Primary endpoint: Resolution of MASH and no worsening of fibrosis at Week 52**

**ITT**




| | | | | |
|---|---|---|---|---|
| Relative difference to PBO (95% CI) | -- | 33.8 (17.3, 50.3) | 45.7 (29.2, 62.2) | 52.6 (36.5, 68.8) |

**Per Protocol**

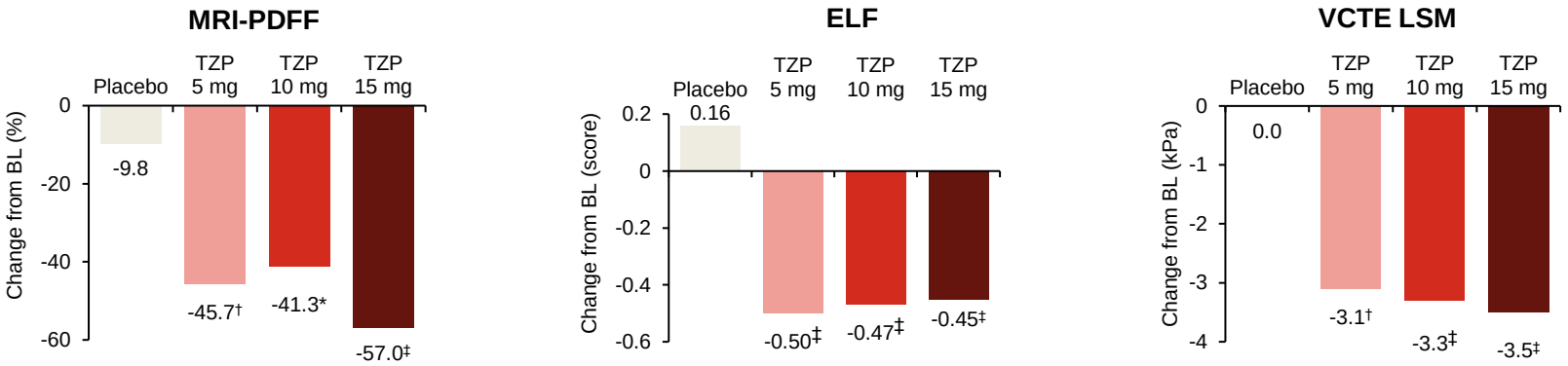



| | | | | |
|---|---|---|---|---|
| Relative difference to PBO (95% CI) | -- | 38.6 (19.6, 57.7) | 49.6 (31.1, 68.1) | 60.1 (42.4, 77.9) |

8% δ ITT vs PP

Loomba R, et al. EASL ILC 2024. LBO-001. Sponsored by Eli Lilly and Company

# SYNERGY-NASH: Phase 2 randomized, double-blind, placebo-controlled trial of tirzepatide (GLP-1/GIP dual agonist) for patients with MASH and F2–F3 fibrosis




Loomba R, et al. EASL ILC 2024. LBO-001. Sponsored by Eli Lilly and Company

# SYNERGY-NASH: Phase 2 randomized, double-blind, placebo-controlled trial of tirzepatide (GLP-1/GIP dual agonist) for patients with MASH and F2–F3 fibrosis

**ITT:**
**≥1 stage decrease in fibrosis and no worsening of MASH**


| | | | | |
|---|---|---|---|---|
| Relative difference to PBO (95% CI) | -- | 25.2 (4.7, 45.7) | 21.6 (1.1, 42.1) | 21.3 (0.6, 42.0) |

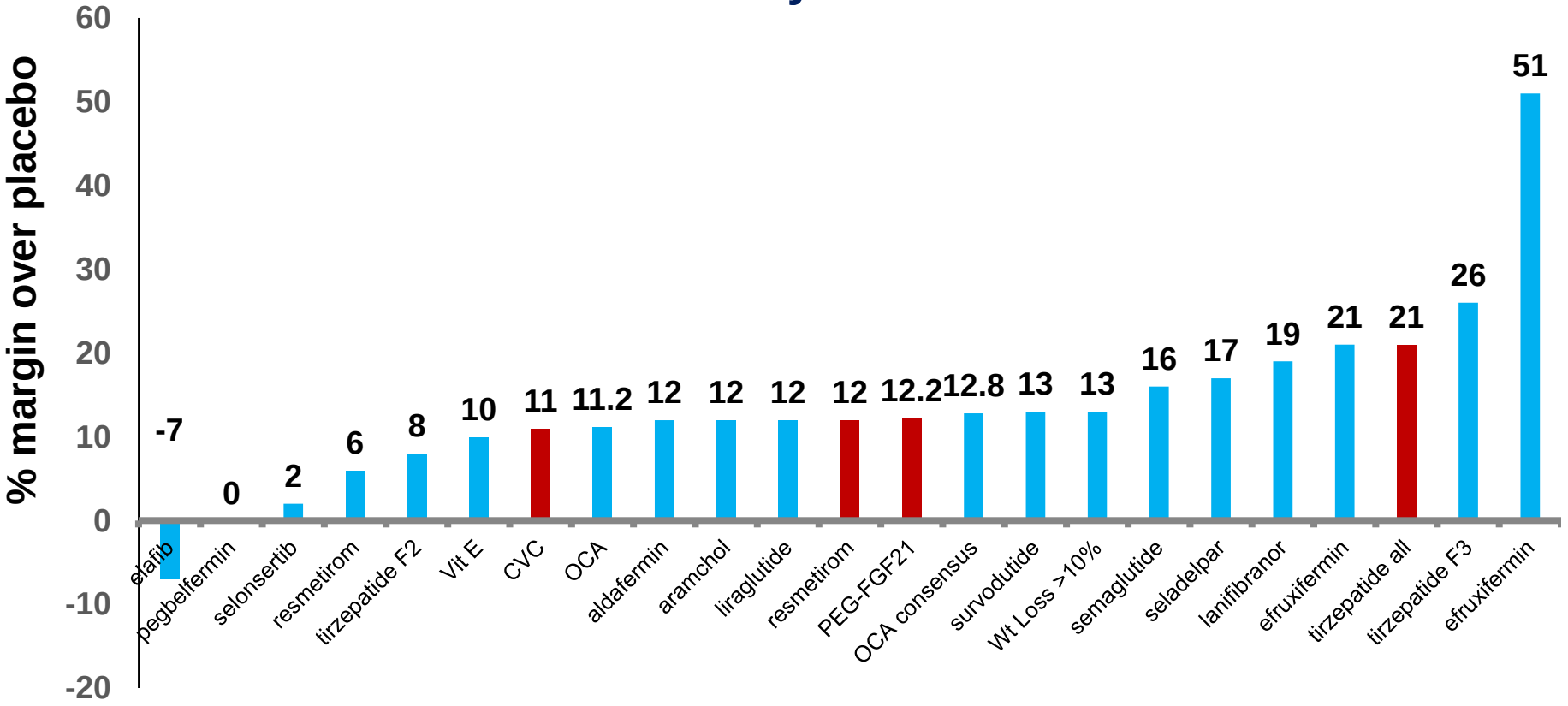
Wt decr 10.7-15.6%

**Safety**

- AEs: TZP, 92.3%; PBO, 83.3%
  - Most common AEs with TZP were GI
  - Treatment discontinuation due to AE: 4.2% with both TZP and PBO

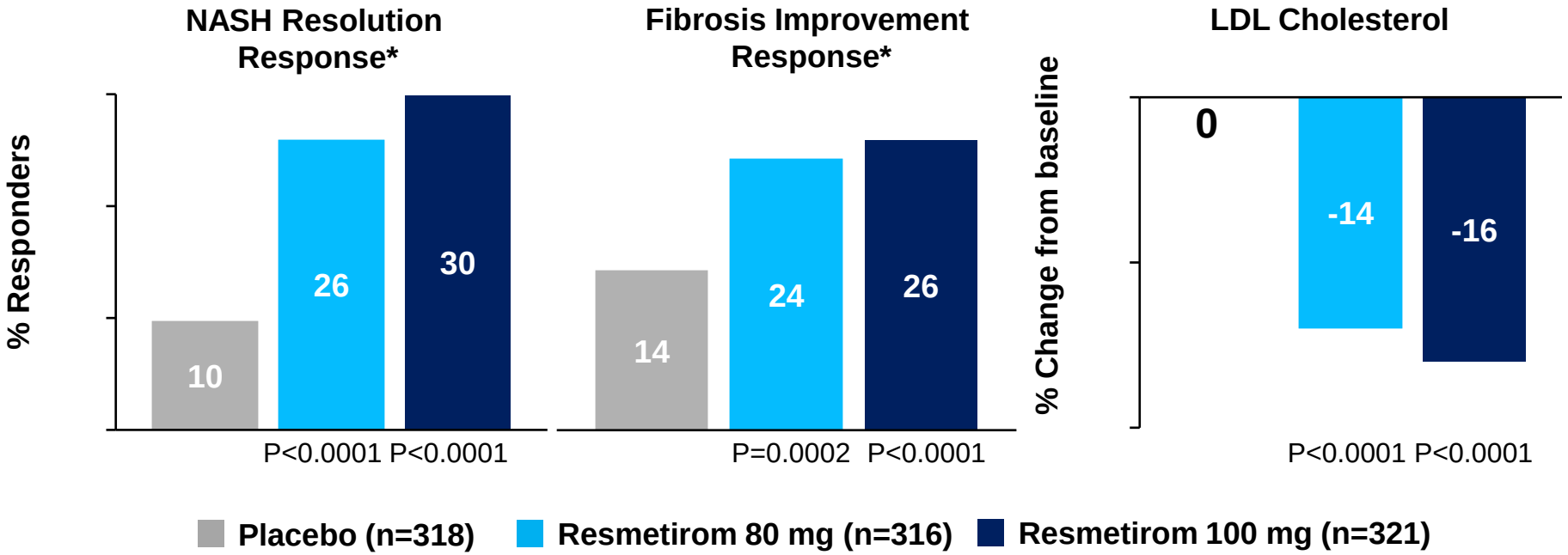
Loomba R, et al. EASL ILC 2024. LBO-001. Sponsored by Eli Lilly and Company

# MASH Therapeutic Agents in Late-Stage Development – Fibrosis Efficacy over Placebo



# Primary Liver Biopsy Endpoints and Key Secondary Endpoint of LDL Cholesterol Lowering

## MAESTRO NASH Week 52 Primary Analysis Population (ITT)




*NASH Resolution response: NASH resolution (ballooning 0,1) with at least a 2-point improvement in NAS and no worsening of fibrosis; Fibrosis improvement response: ≥1 stage improvement in fibrosis with no worsening of NAS

Harrison S, et al. NEJM 2024.

# Key questions for resmetirom use:

- Does use of GLP1 RAs, statins or thyroxine affect efficacy?
- Can VCTE, PDFF, CAP or ALT be used to determine efficacy (or futility)?
- When should resmetirom be discontinued?

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- Does use of GLP1 RAs, statins or thyroxine affect efficacy? *Insufficient data.*
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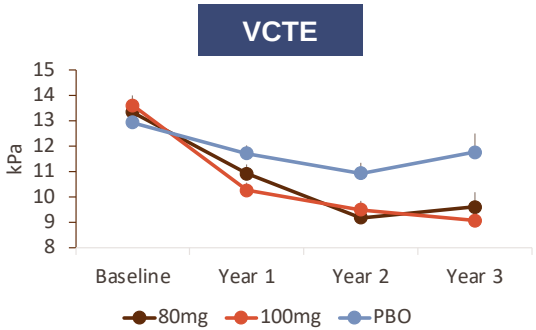
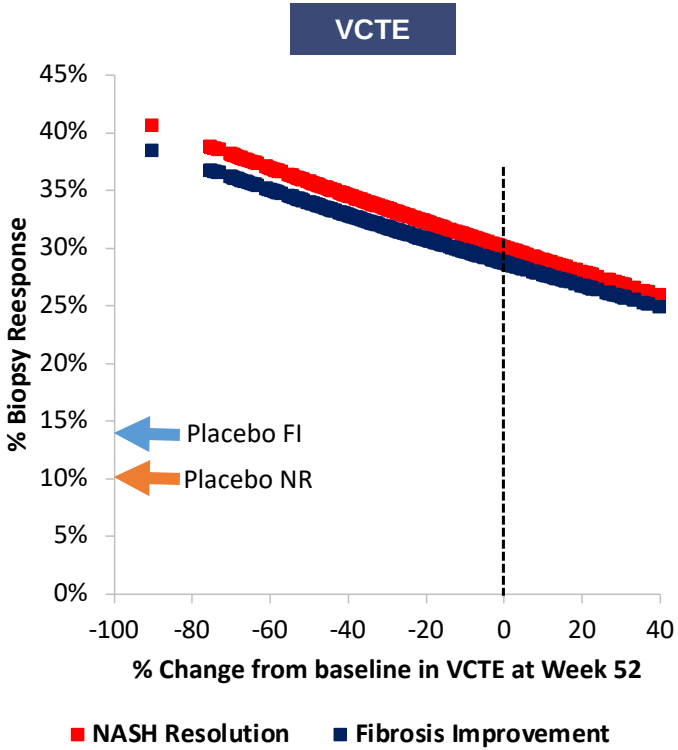
# VCTE as a Marker of Biopsy Response

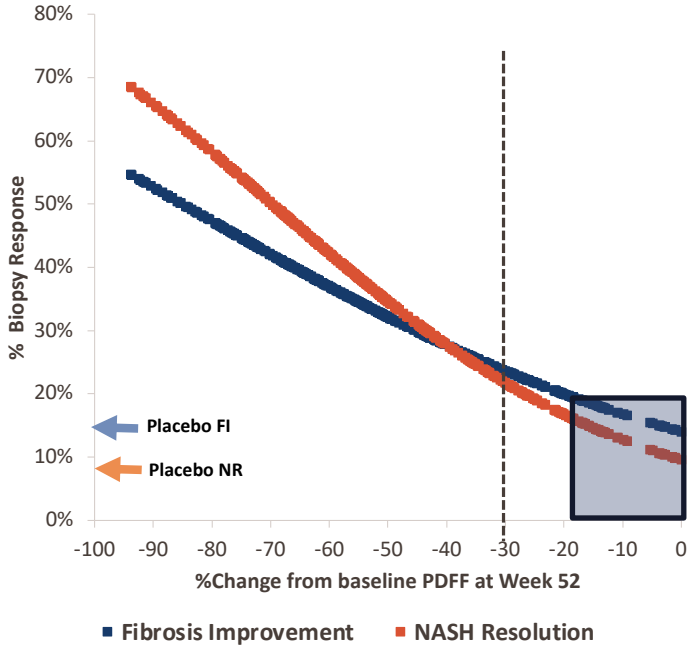



**All resmetirom treated patients (80 mg and 100 mg combined)**

- Resmetirom treated patients, *even those with no VCTE improvement*, had higher NASH resolution and fibrosis improvement responses than the mean placebo response rates
- VCTE improvement was poorly predictive of a placebo FI or NR response

# PDFF as a Marker of Resmetirom Biopsy Response

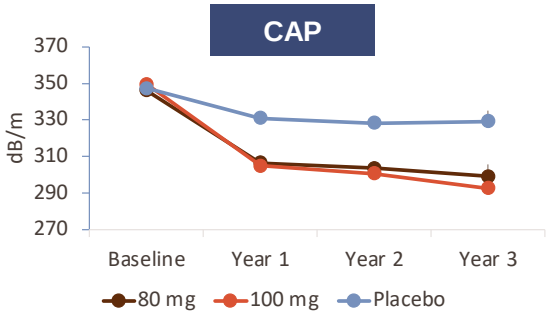


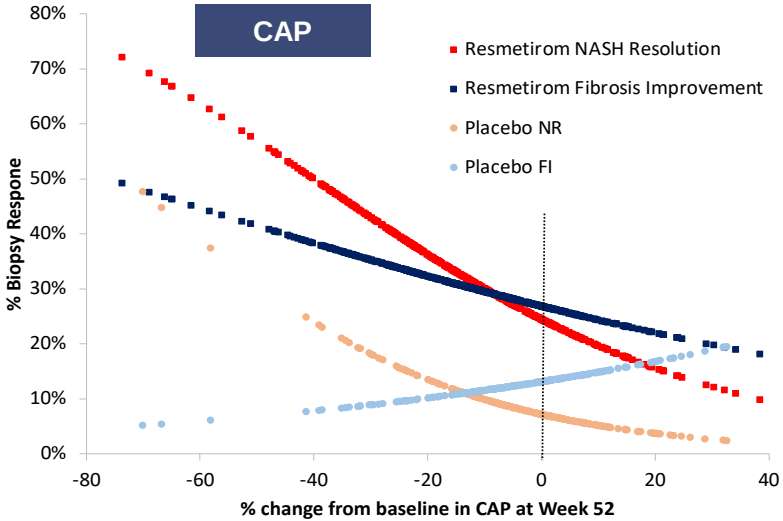

- PDFF reduction in resmetirom treated patients was highly associated with both NASH Resolution (NR) and Fibrosis Improvement (FI)
  - Placebo patients with PDFF reduction of 30% or higher did not associate with improvement in fibrosis
- A ≥30% PDFF response was observed in 96%, 88%, and 92% of resmetirom 100 mg responders for NASH resolution, Fibrosis improvement, and NASH resolution or Fibrosis improvement

**All resmetirom treated patients (80 mg and 100 mg combined)**

*Logistic regression model, predicting response on biopsy as a function of % change from baseline in MRI-PDFF*

# FibroScan CAP as a Marker of Biopsy Response

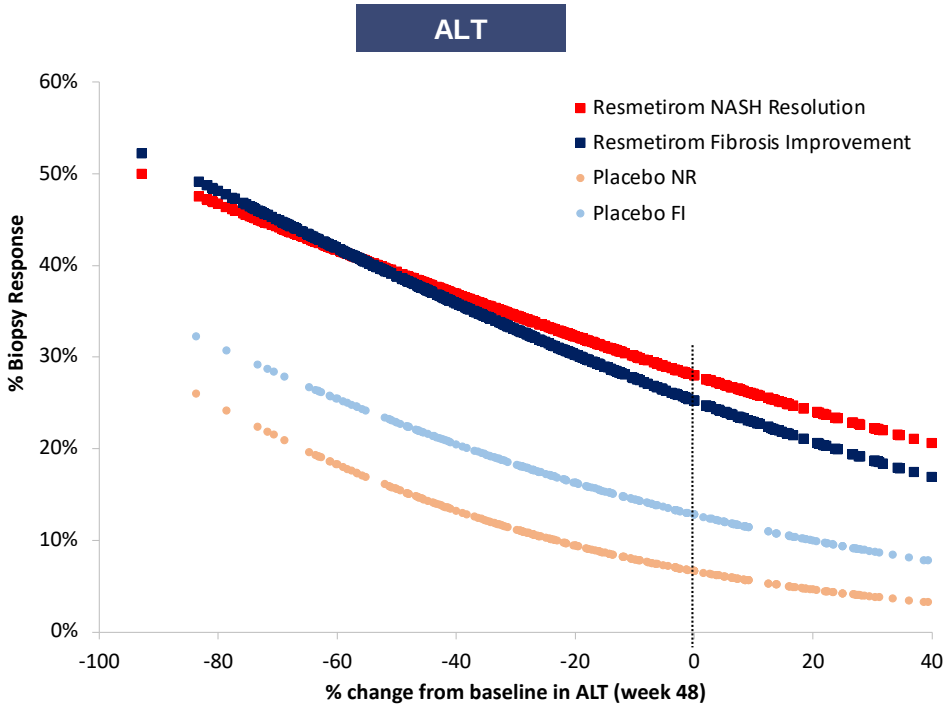



- CAP improved with resmetirom treatment
- CAP improvement in individual resmetirom patients predicted both NASH resolution and fibrosis improvement responses; however even no change in CAP predicted biopsy responses higher than the mean for placebo
- A CAP improvement in placebo patients did not predict a fibrosis improvement on biopsy

*All resmetirom treated patients (80 mg and 100 mg combined)*

# ALT as a Marker of Biopsy Response

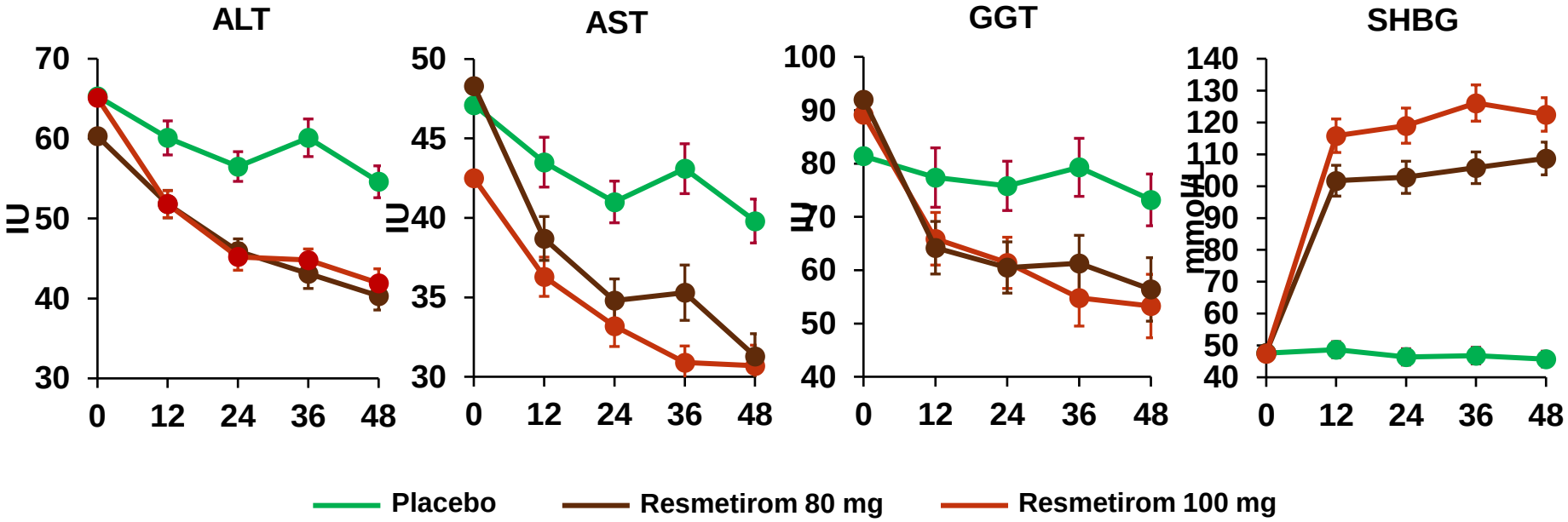



- Both doses of resmetirom significantly reduced ALT approximately 30% relative to placebo
- In resmetirom treated patients, higher % reductions in ALT were associated with slightly higher NASH resolution and Fibrosis improvement on biopsy
- For resmetirom treated patients without a reduction in ALT, the NASH resolution and fibrosis improvement responses were predicted to be higher than the mean placebo biopsy responses

**All resmetirom treated patients (80 mg and 100 mg combined)**

# Change Over Time From Baseline in Liver Enzymes[a] and SHBG – Biochemical Profile Did Not Plateau at EoT

MAESTRO NASH Week 52 Primary Analysis Population




a. Evaluated in patients with baseline ALT ≥30 IU.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PBO, placebo; SHBG, sex hormone binding globulin.

# Key questions for resmetirom use:

- Does use of GLP1 RAs, statins or thyroxine affect efficacy? *Insufficient data.*
- Can VCTE, PDFF, CAP or ALT be used to determine efficacy (or futility)? *Not with confidence and PDFF lacks practicality.*
- When should resmetirom be discontinued?

# Key questions for resmetirom use:

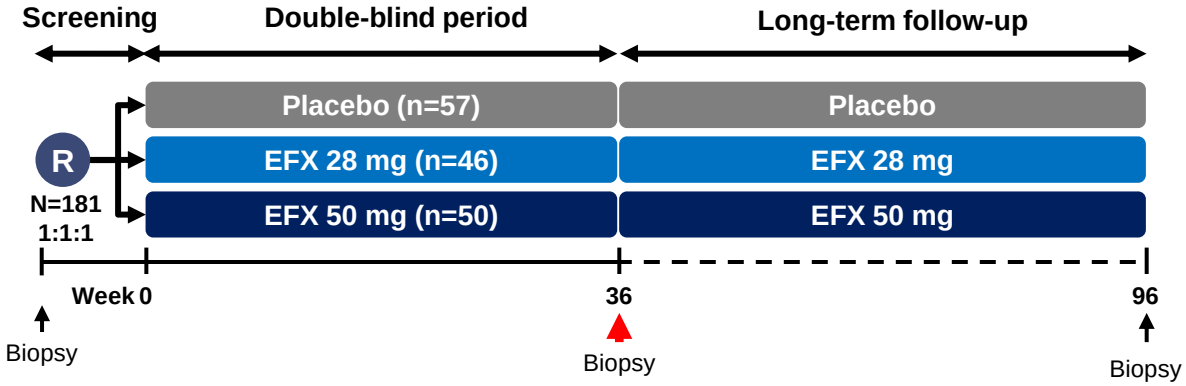
- Does use of GLP1 RAs, statins or thyroxine affect efficacy? *Not meaningfully.*
- Can VCTE, PDFF, CAP or ALT be used to determine efficacy (or futility)? *Not with confidence and PDFF lacks practicality.*
- When should resmetirom be discontinued?

# SYMMETRY: Phase 2b, randomized, double-blind, placebo-controlled trial of efruxifermin for patients with compensated cirrhosis due to MASH

- Efruxifermin is a long-acting FGF21 analog based on a fusion polypeptide of human IgG1 Fc with FGF21

**Key inclusion criteria**
- F4 NASH (compensated)
- T2D or 2 of 4 components of metabolic syndrome

**Primary endpoint:** ≥1-stage fibrosis improvement with no worsening of MASH at Week 36

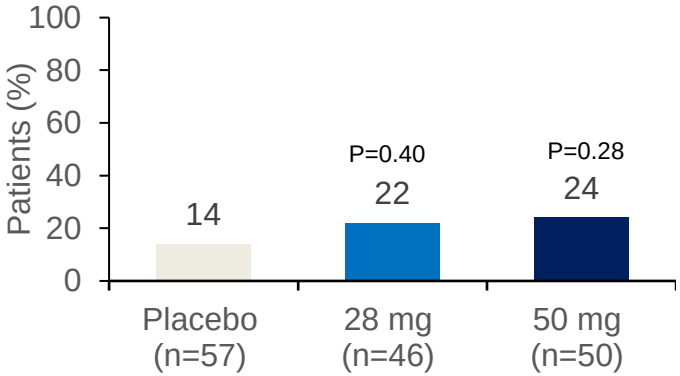



Analysis of all patients who have baseline & Week 36 liver biopsy results

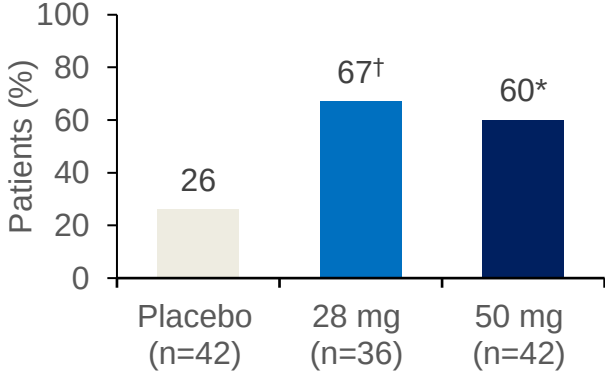
Harrison SA, et al. AASLD 2023. Late-breaking oral #5005

# SYMMETRY: Phase 2b, randomized, double-blind, placebo-controlled trial of efruxifermin for patients with compensated cirrhosis due to MASH

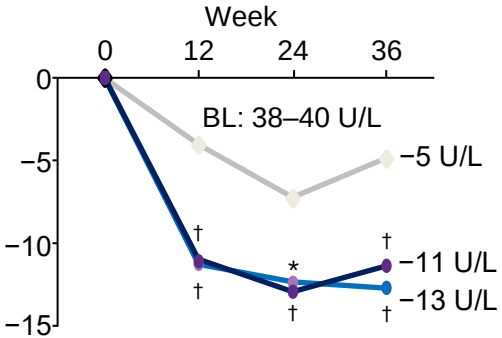
**Fibrosis improvement without worsening of MASH**




**MASH resolution**




**Delta ALT**




*P<0.01, †P<0.001 vs placebo

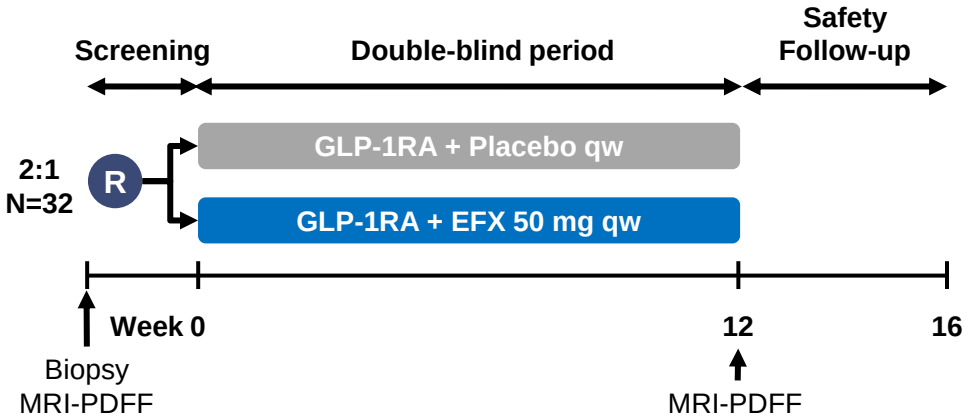
FAST, ELF, Pro-C3
all significantly improved

Harrison SA, et al. AASLD 2023. Late-breaking oral #5005.

# SYMMETRY Expansion Cohort D: Phase 2b, randomized, double-blind, placebo-controlled trial of efruxifermin (Fc–FGF21 analog) **in combination with a GLP-1 RA** in patients with MASH and T2D

**Key eligibility criteria:**

- MASH
- Fibrosis stage 1–3
- T2D
- On stable GLP-1RA therapy (≥90 days pre-screening)



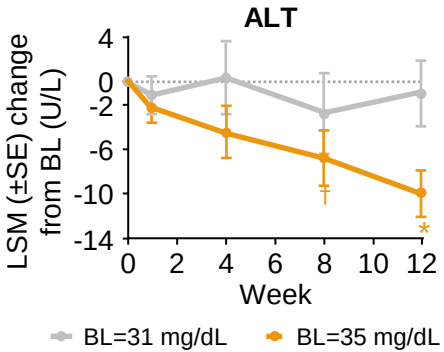

**Primary endpoint:** Safety and tolerability of EFX combined with a GLP-1RA

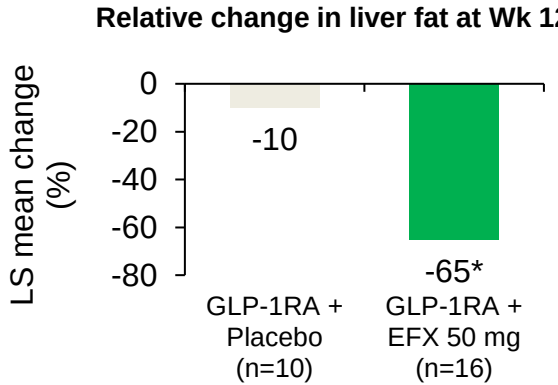
**Secondary endpoints:** Effects on liver fat, markers of liver injury, markers of glucose and lipid metabolism, and body weight

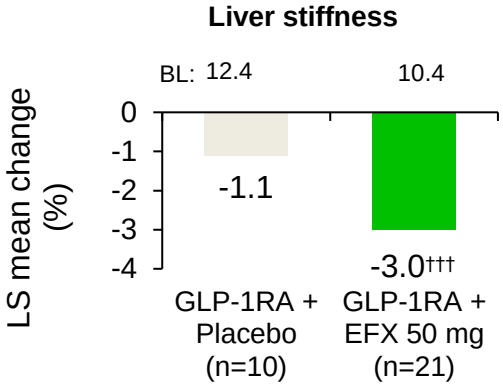
| Baseline characteristics [median dose] | GLP-1RA + Placebo (n=10) | GLP-1RA + EFX 50 mg (n=21) |
|---|---|---|
| Semaglutide: [1 mg qw] | 60% | 43% |
| Dulaglutide: [3 mg qw] | 30% | 52% |
| Liraglutide: [1.5 mg qd] | 10% | 5% |

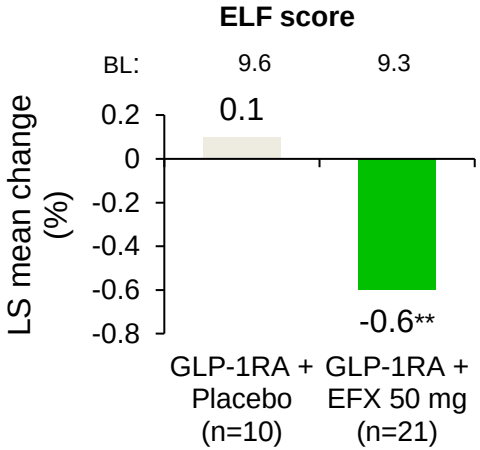
With 1 exception, all patients remained on baseline GLP-1 therapy through Week 12. Due to unavailability of semaglutide, 1 patient switched to tirzepatide after the Week-10 visit

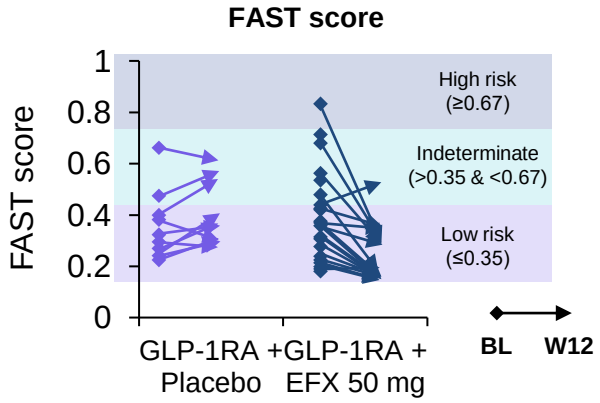
# SYMMETRY Expansion Cohort D: Phase 2b, randomized, double-blind, placebo-controlled trial of efruxifermin (Fc–FGF21 analog) **in combination with a GLP-1 RA** in patients with MASH and T2D



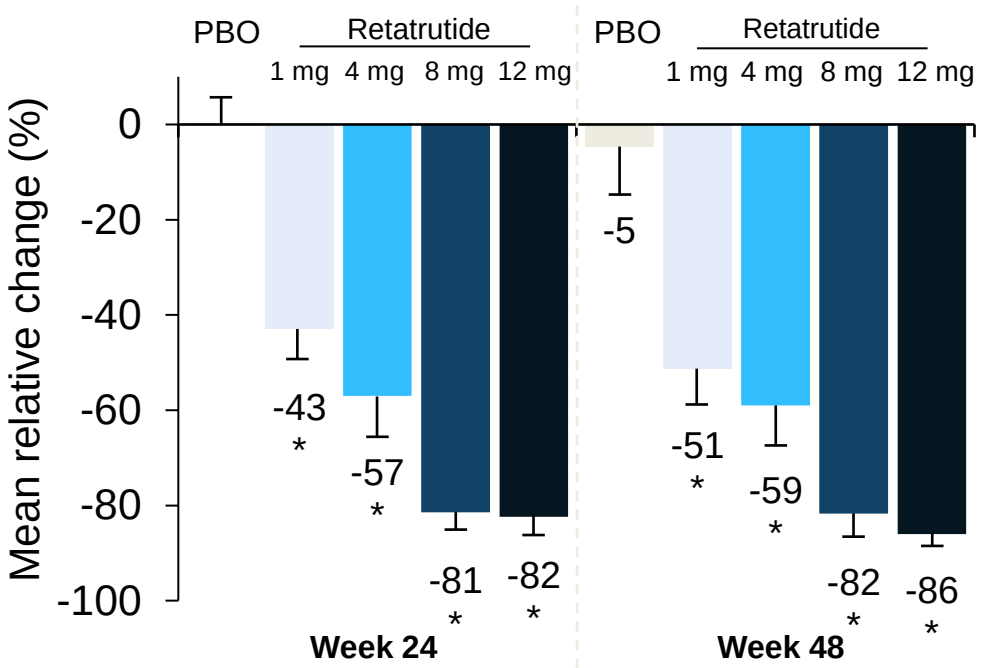



# Phase 2 MASLD substudy: Liver fat reduction among patients with obesity and MASLD treated with retatrutide (GIP, GLP-1, GCG receptor tri-agonist) for 48 weeks

**Primary endpoint:**
**Relative liver fat reduction at Weeks 24 and 48**




8 and 12mg doses poorly tolerated (N/V/D)

Sanyal A, et al. AASLD 2023. Oral #148.

# Phase 2 MASLD substudy: Liver fat reduction among patients with obesity and MASLD treated with retatrutide (GIP, GLP-1, GCG receptor tri-agonist) for 48 weeks

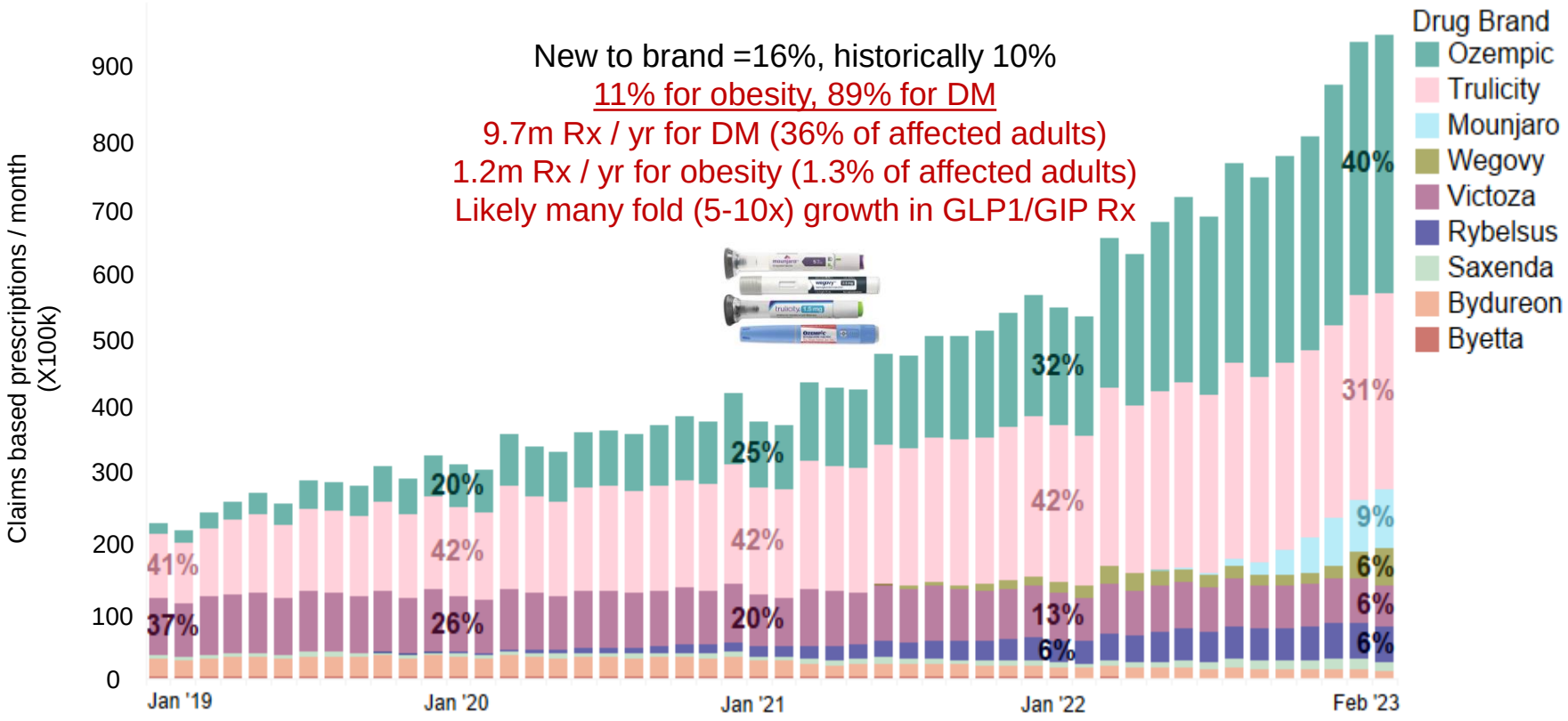
## AEs of special interest

| Data are n (%) | Placebo (n=70) | 1 mg (n=69) | 4 mg (ID, 2 mg) (n=33) | 4 mg (ID, 4 mg) (n=33) | 8 mg (ID, 2 mg) (n=35) | 8 mg (ID, 4 mg) (n=35) | 12 mg (ID, 2 mg) (n=62) |
|---|---|---|---|---|---|---|---|
| Hypersensitivity | 2 (3) | 7 (10) | 1 (3) | 2 (6) | 3 (9) | 7 (20) | 8 (13) |
| Antidrug antibodies during treatment | 1 (1) | 3 (4) | 4 (12) | 5 (16) | 5 (16) | 2 (6) | 11 (18) |
| Hyperesthesia or related AE | 1 (1) | 1 (1) | 2 (6) | 2 (6) | 1 (3) | 5 (14) | 8 (13) |
| Cardiac arrhythmia | 2 (3) | 3 (4) | 0 | 2 (6) | 0 | 5 (14) | 7 (11) |
| Hepatic disorder | 2 (3) | 5 (7) | 1 (3) | 0 | 1 (3) | 2 (6) | 2 (3) |
| Biliary disorder | 0 | 0 | 0 | 0 | 1 (3) | 2 (6) | 0 |
| Severe gastrointestinal AE | 0 | 0 | 0 | 1 (3) | 1 (3) | 1 (3) | 4 (6) |
| Injection-site reaction | 0 | 1 (1) | 0 | 1 (3) | 0 | 1 (3) | 5 (8) |
| Pancreatitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2) |

Sanyal A, et al. AASLD 2023. Oral #148.

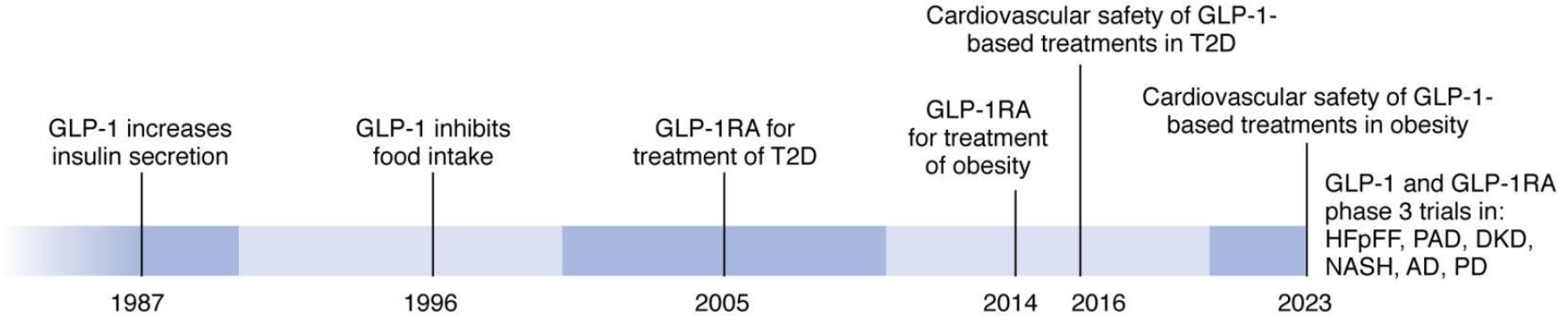
# Global Health Trends

# Share GLP1/GIP Prescriptions (any indication) in US



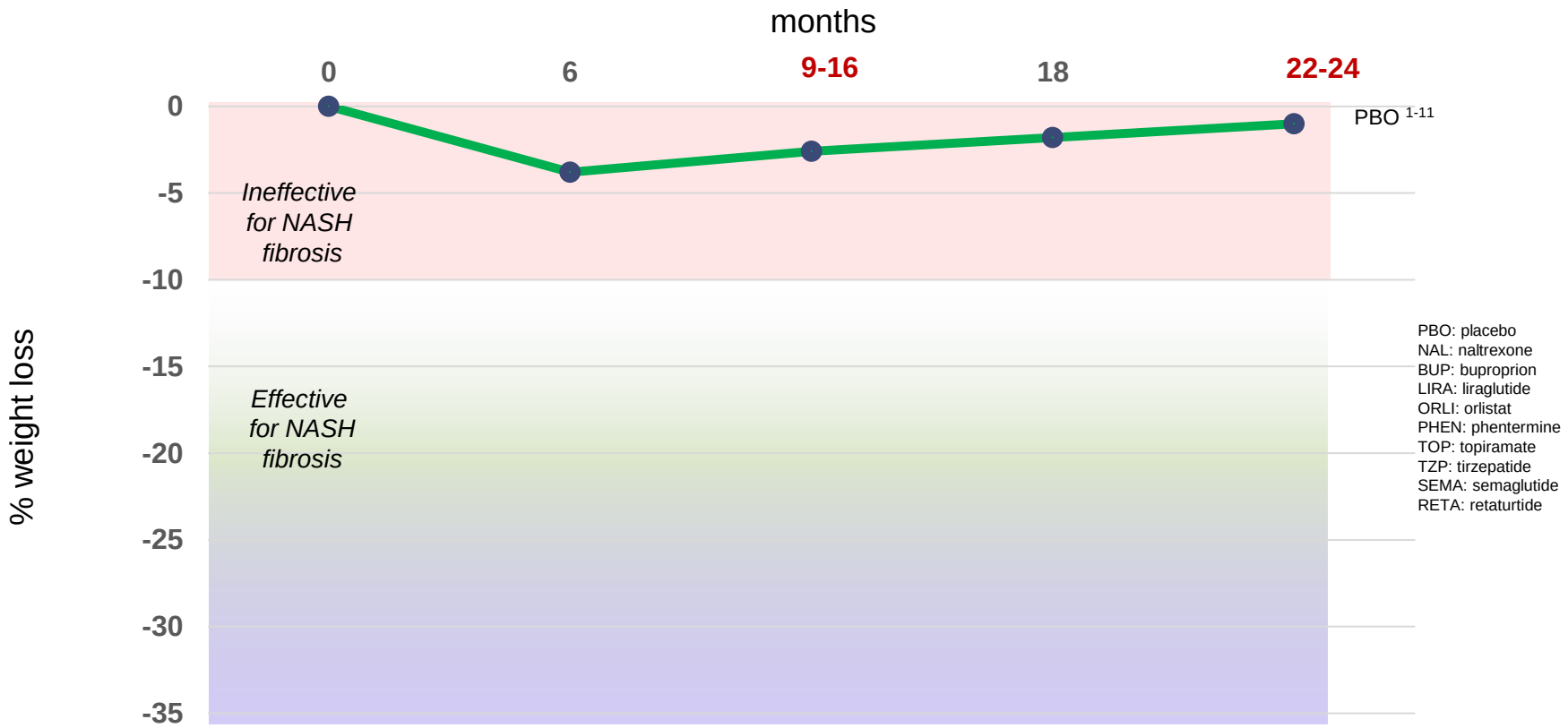

Source: JP Morgan analysis of IQVIA data

# The Spectacular Rise of GLP-1(GIP) Agonism

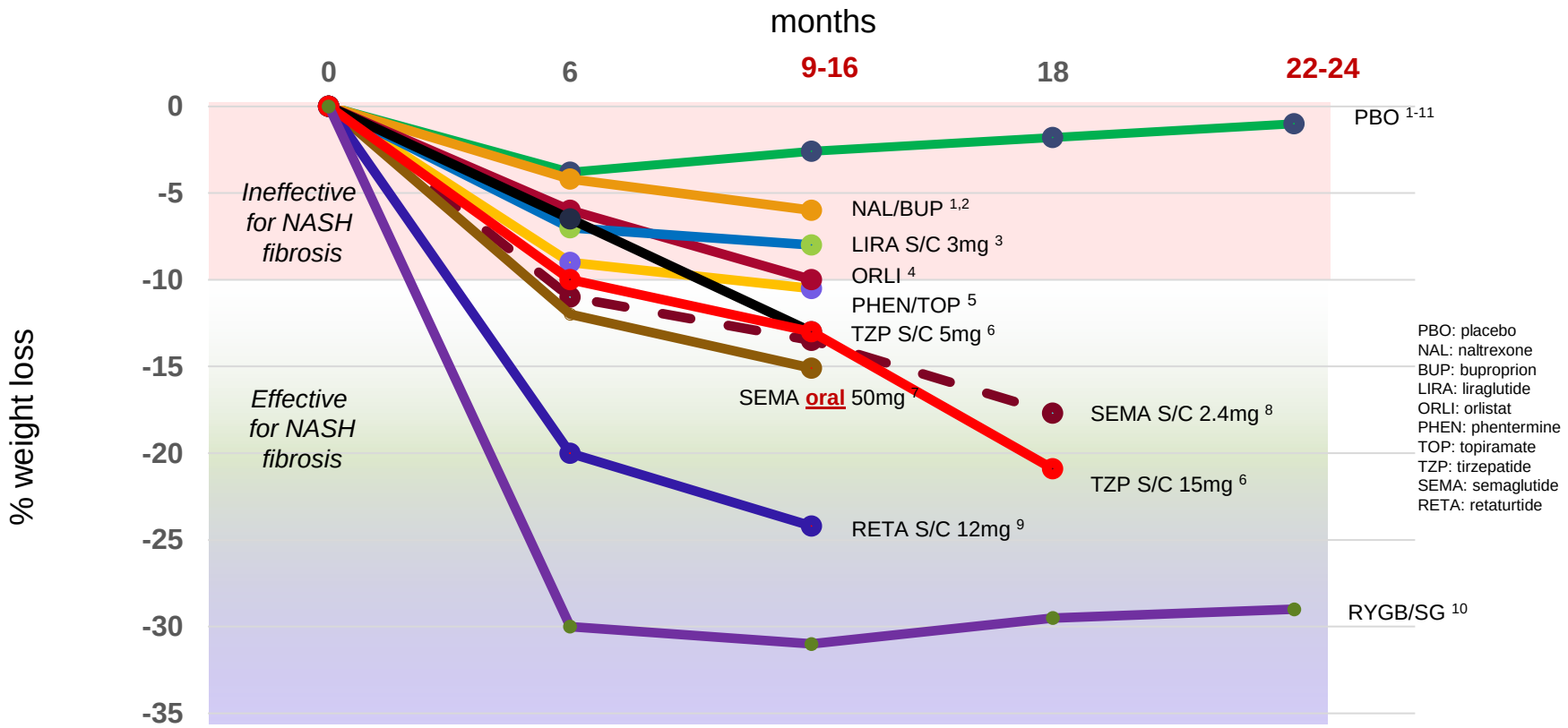

Drucker *J Clin Invest.* 2024; 134(2):e175634.

# Efficacy of Approved and Emerging Weight Loss Therapies in Clinical Studies




[1]*Eur J. Pharmacol*. 698, 292-298 (2013).; [2]*Lancet* 316, 595-605 (2010). [3]*NEJM*. 373, 11-22 (2015). [4]*Lancet* 352, 167-172 (1998).; [5]*Am J Clin Nutr* 95, 297-308 (2012).; [6] Lancet 398, 583-598 [2021).; [7] https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=165597 [8] *NEJM* 384,989 (2021). [9] *NEJM* EPUB ahead of print DOI: 10.1056/NEJMoa2301972 (2023).; [10] *NEJM* 376:641-651 (2017).; [11] *Diabetes Obes Metab.* 24: 8: 1553-1564. (2022); [12]*JAMA* *JAMA.* Published online December 11, 2023. doi:10.1001/jama.2023.24945

# Efficacy of Approved and Emerging Weight Loss Therapies in Clinical Studies




[1]*Eur J. Pharmacol*. 698, 292-298 (2013).; [2]*Lancet* 316, 595-605 (2010). [3]*NEJM*. 373, 11-22 (2015). [4]*Lancet* 352, 167-172 (1998).; [5]*Am J Clin Nutr* 95, 297-308 (2012).; [6] Lancet 398, 583-598 [2021).; [7] https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=165597 [8] *NEJM* 384,989 (2021). [9] *NEJM* EPUB ahead of print DOI: 10.1056/NEJMoa2301972 (2023).; [10] *NEJM* 376:641-651 (2017).; [11] *Diabetes Obes Metab.* 24: 8: 1553-1564. (2022); [12]*JAMA* *JAMA.* Published online December 11, 2023. doi:10.1001/jama.2023.24945

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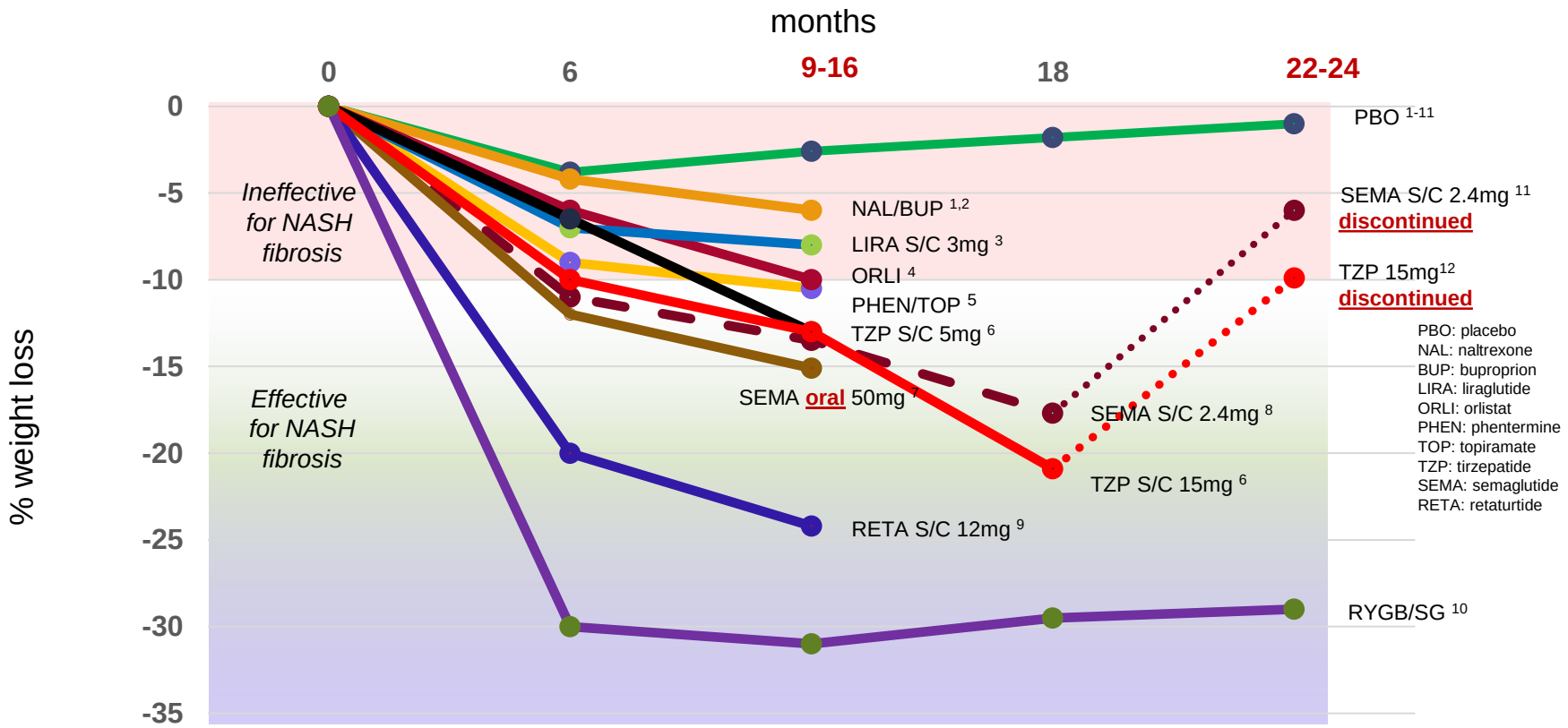


[1]*Eur J. Pharmacol*. 698, 292-298 (2013).; [2]*Lancet* 316, 595-605 (2010). [3]*NEJM*. 373, 11-22 (2015). [4]*Lancet* 352, 167-172 (1998).; [5]*Am J Clin Nutr* 95, 297-308 (2012).; [6] Lancet 398, 583-598 [2021).; [7] https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=165597 [8] *NEJM* 384,989 (2021). [9] *NEJM* EPUB ahead of print DOI: 10.1056/NEJMoa2301972 (2023).; [10] *NEJM* 376:641-651 (2017).; [11] *Diabetes Obes Metab.* 24: 8: 1553-1564. (2022); [12]*JAMA* *JAMA.* Published online December 11, 2023. doi:10.1001/jama.2023.24945

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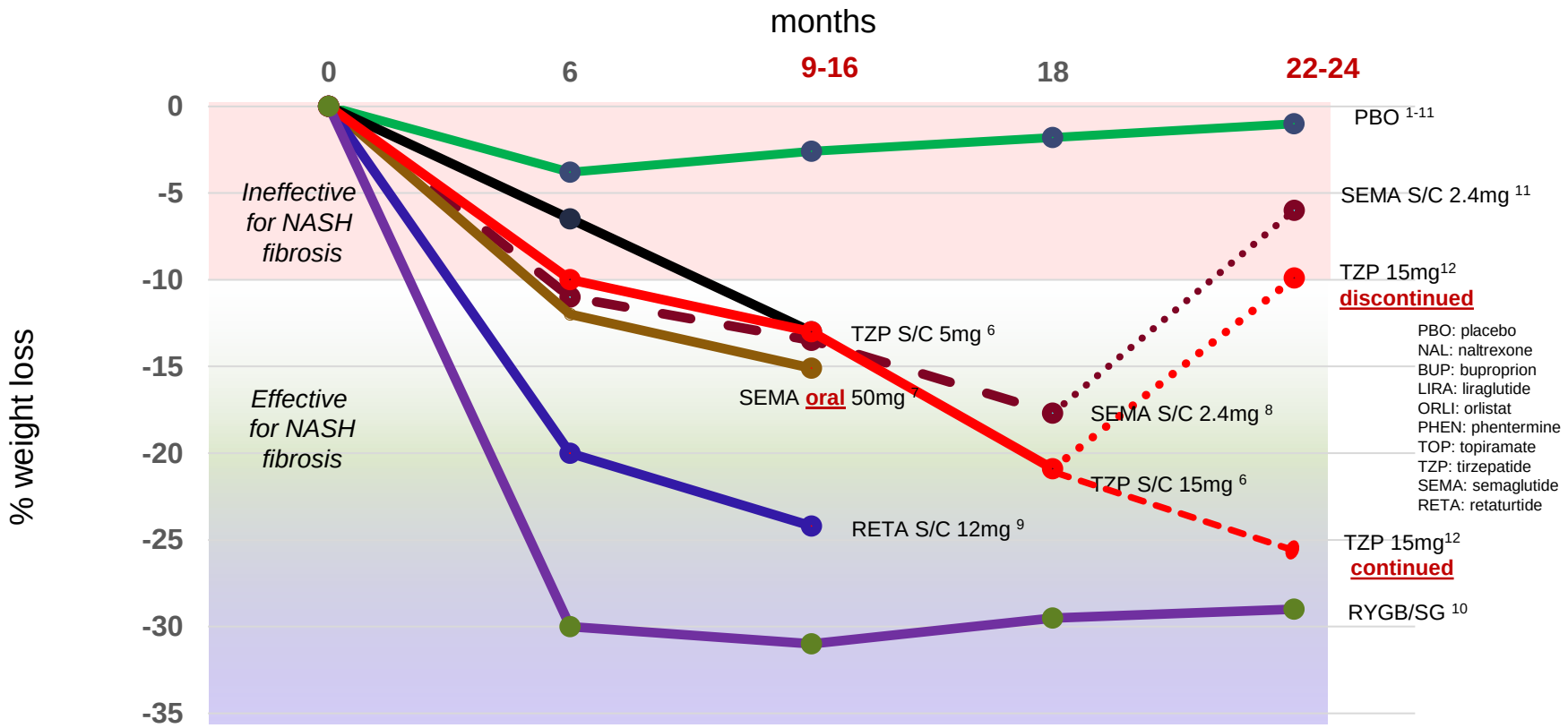
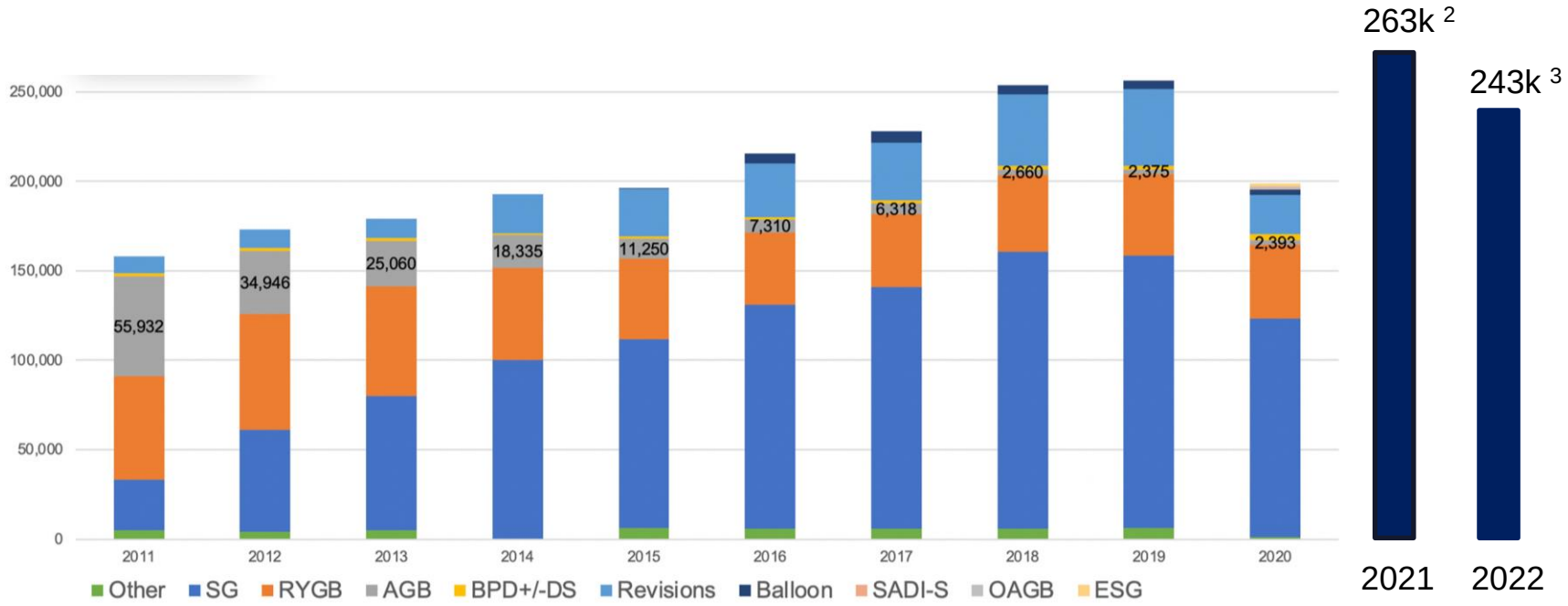



[1]*Eur J. Pharmacol*. 698, 292-298 (2013).; [2]*Lancet* 316, 595-605 (2010). [3]*NEJM*. 373, 11-22 (2015). [4]*Lancet* 352, 167-172 (1998).; [5]*Am J Clin Nutr* 95, 297-308 (2012).; [6] Lancet 398, 583-598 [2021).; [7] https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=165597 [8] *NEJM* 384,989 (2021). [9] *NEJM* EPUB ahead of print DOI: 10.1056/NEJMoa2301972 (2023).; [10] *NEJM* 376:641-651 (2017).; [11] *Diabetes Obes Metab.* 24: 8: 1553-1564. (2022); [12]*JAMA* *JAMA.* Published online December 11, 2023. doi:10.1001/jama.2023.24945

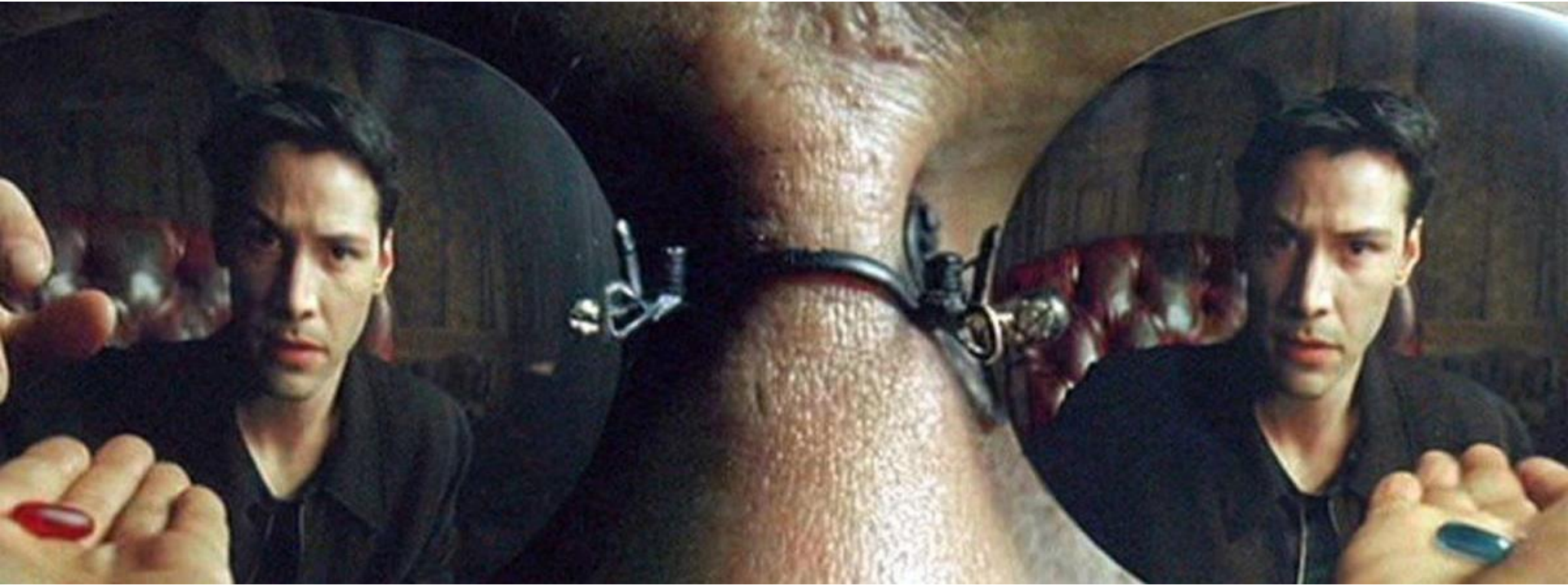
# Bariatric Surgery Procedure Volume By Year



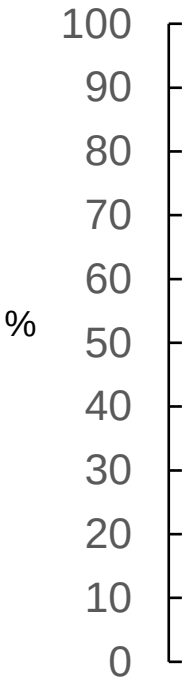

[1]Clapp et al., *Surgery for Obesity and Related Diseases*, Vol18, Issue 9, 2022,1134-1140.

[2] https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers/

[3] https://renewbariatrics.com/bariatric-surgery-statistics/



# Real World Analysis of GLP1 RA Adherence and Persistence




BlueCross BlueShield

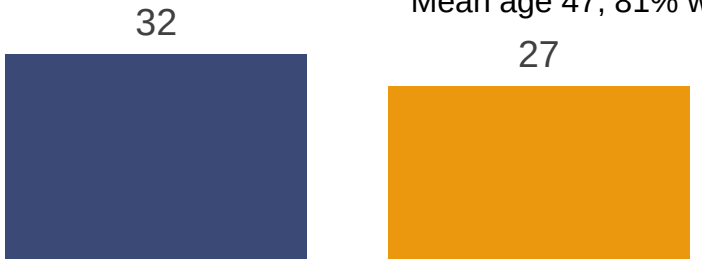
Adherence **61.2%** for metformin using blood spot analysis[2]

16 million members
4,255 GLP1RA users, 484,111 controls

GLP-1RA new prescription 01/01/2021-12/31/2021
Continuous Rx plan enrollment
Diagnosis code for obesity OR BMI ≥30 PLUS no DM

Persistence judged as stopped if >60 day gap
Adherence positive if >80% of days

Mean age 47, 81% women[1]

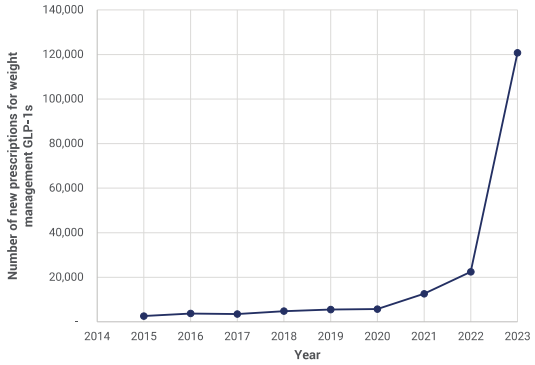



PRIME THERAPEUTICS

MagellanRx MANAGEMENT

[1] J Leach et al., *AMCP Nexus*, October 2023
[2] N Syafhan,. *J of Pharm Policy and Pract* 15, 61 (2022).

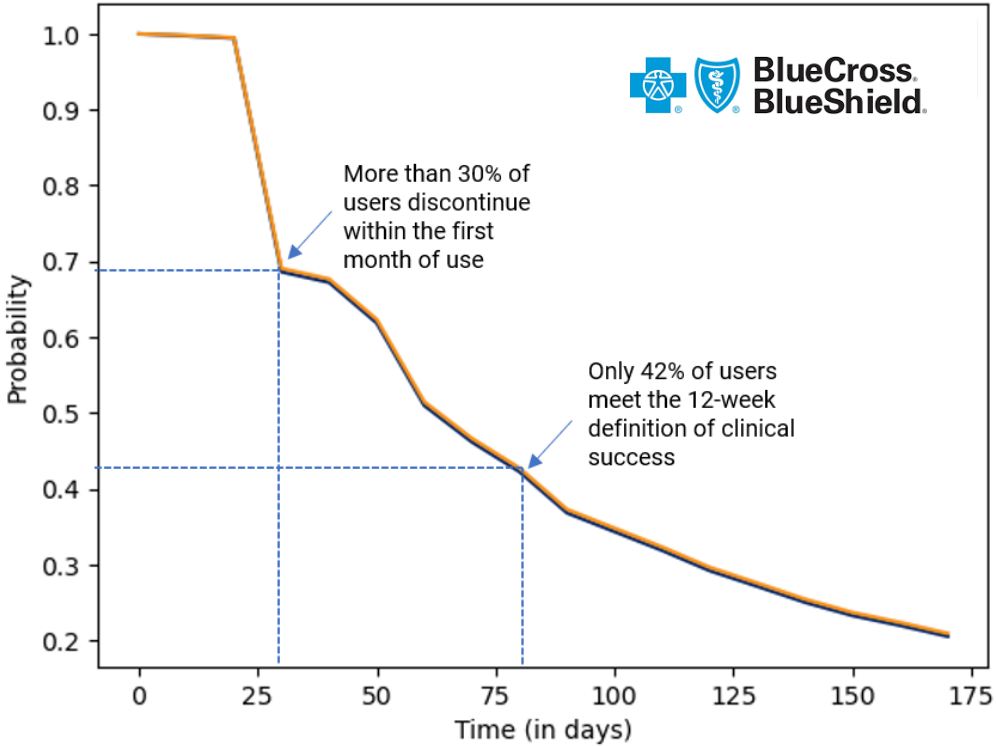
# GLP-1 RAs – Real World Experience




**169,250**
unique GLP-1 users for weight loss

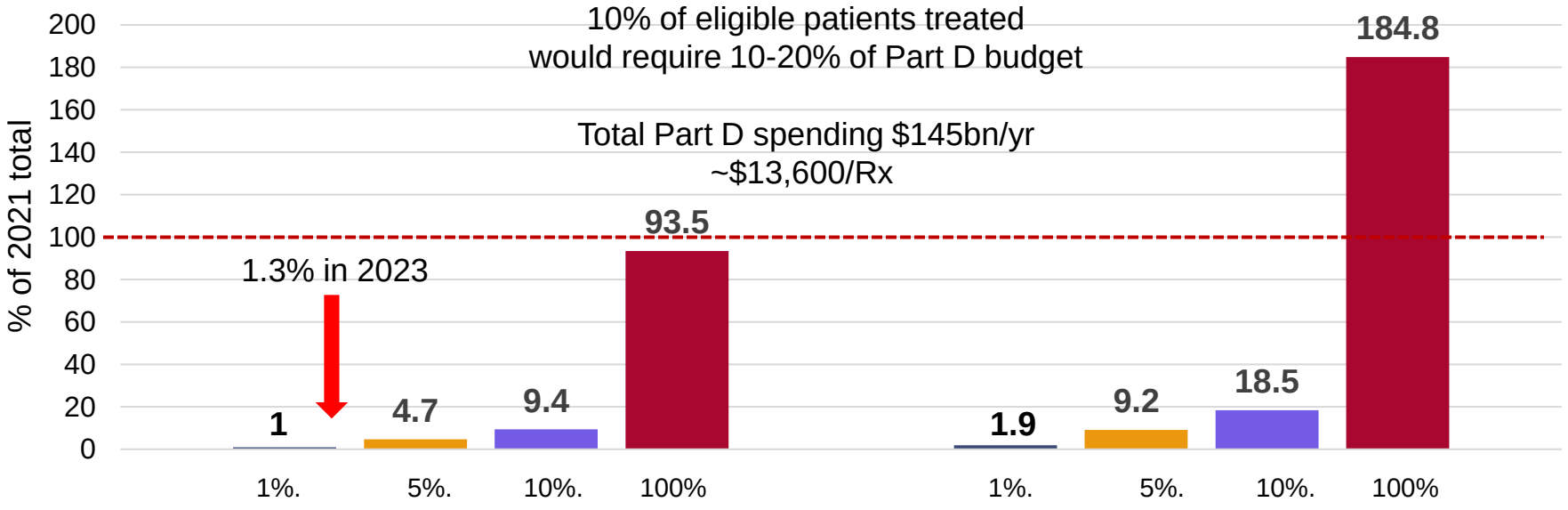
**79%**
female on average

**45 years**
average age




https://www.bcbs.com/sites/default/files/BHI_Issue_Brief_GLP1_Trends.pdf

# Models of GLP1 RA/GIP Treatment on CMS Part D Spending

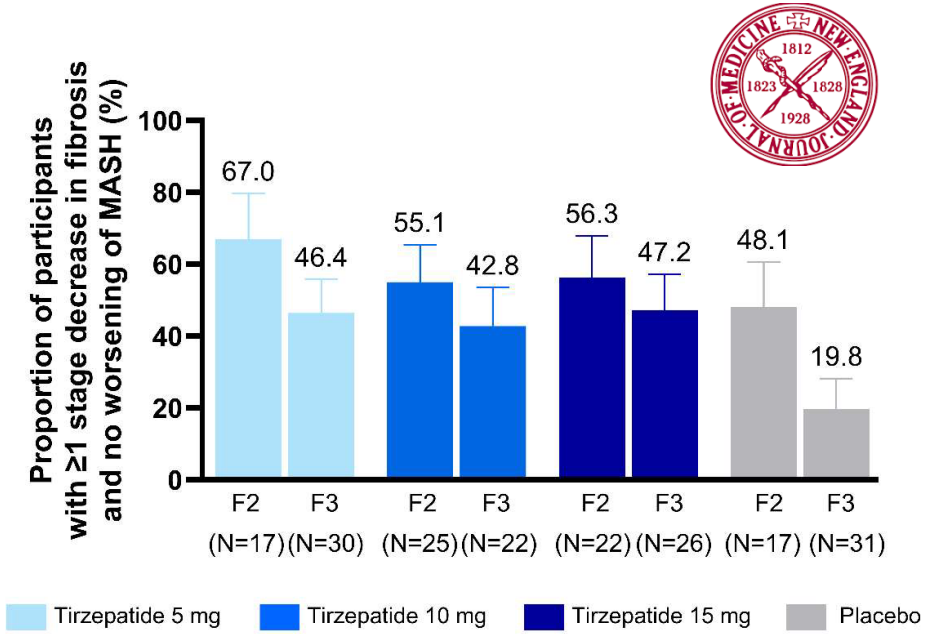



*21% identified BMI >30kg/m²*

*41% actual BMI >30kg/m²*

Baig et al., *N Engl J Med* 2023; 388:961-963.

# Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis



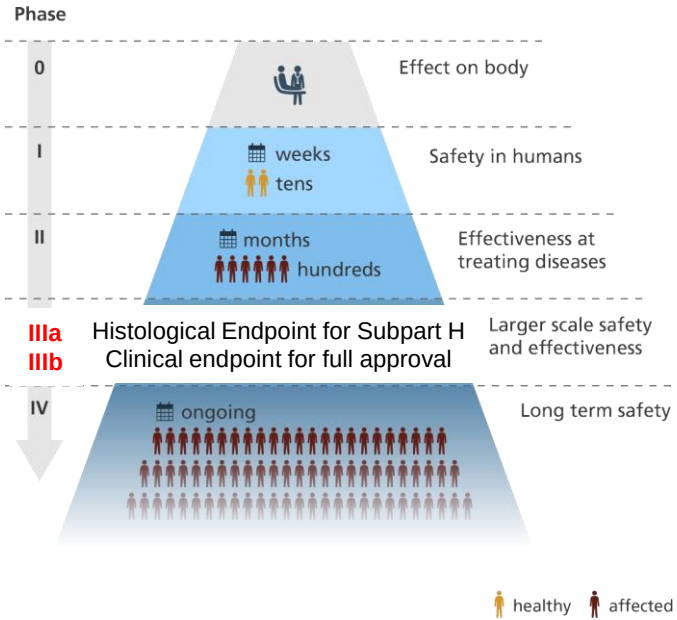

- TZP has no fibrosis benefit in F2
- x2 fold variation in PBO arm
- No dose response
- Needs phase 3 study

0.4 x 21 = 8.4%

Loomba et al., *NEJM* EPUB: June 8, 2024

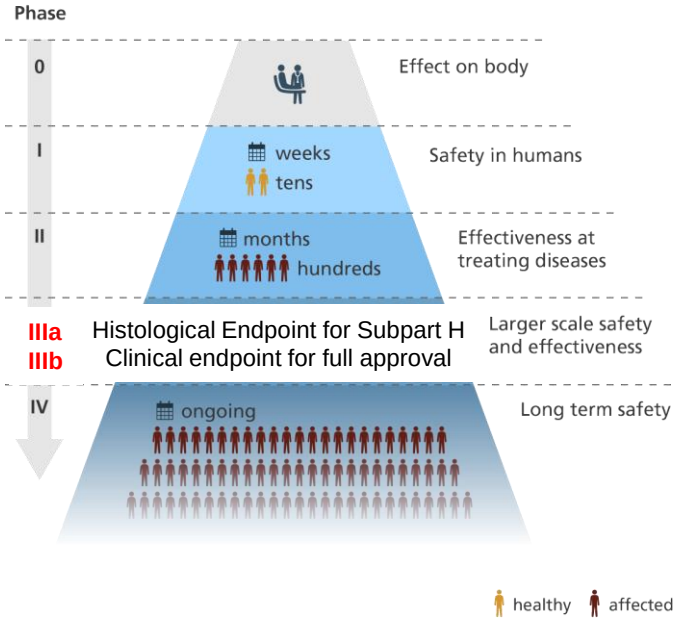
# Therapeutic Pipeline Attrition

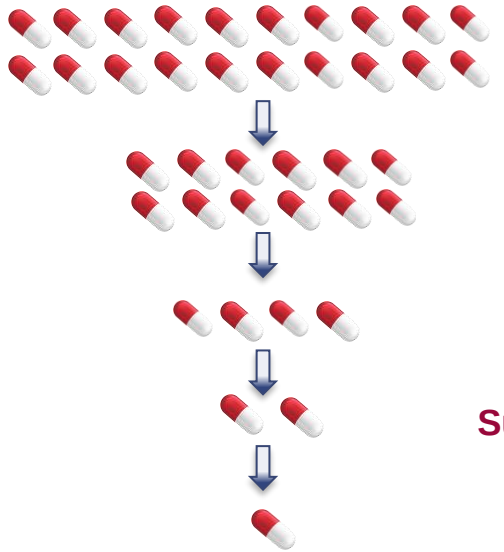
1,000s – 1,000,000s molecules screened



# Therapeutic Pipeline Attrition

1,000s – 1,000,000s molecules screened



**Phase 1**

**Phase 2**

**Phase 3**

**Subpart H**

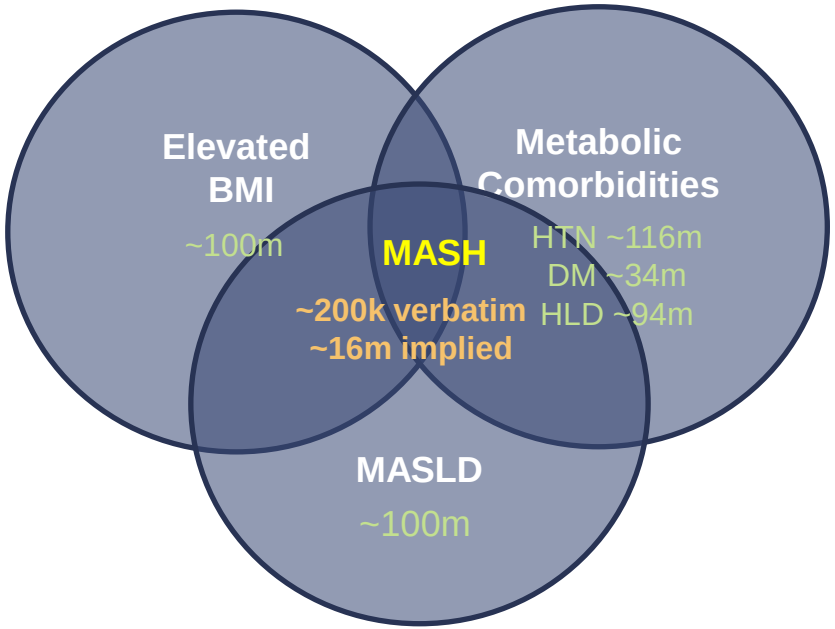
**Full Approval**

**~5% from ph1, ~8-16% from ph2**

Attrition rates derived from Wong et al., *Biostatisitics* 2018.

# Comorbidities in MASH

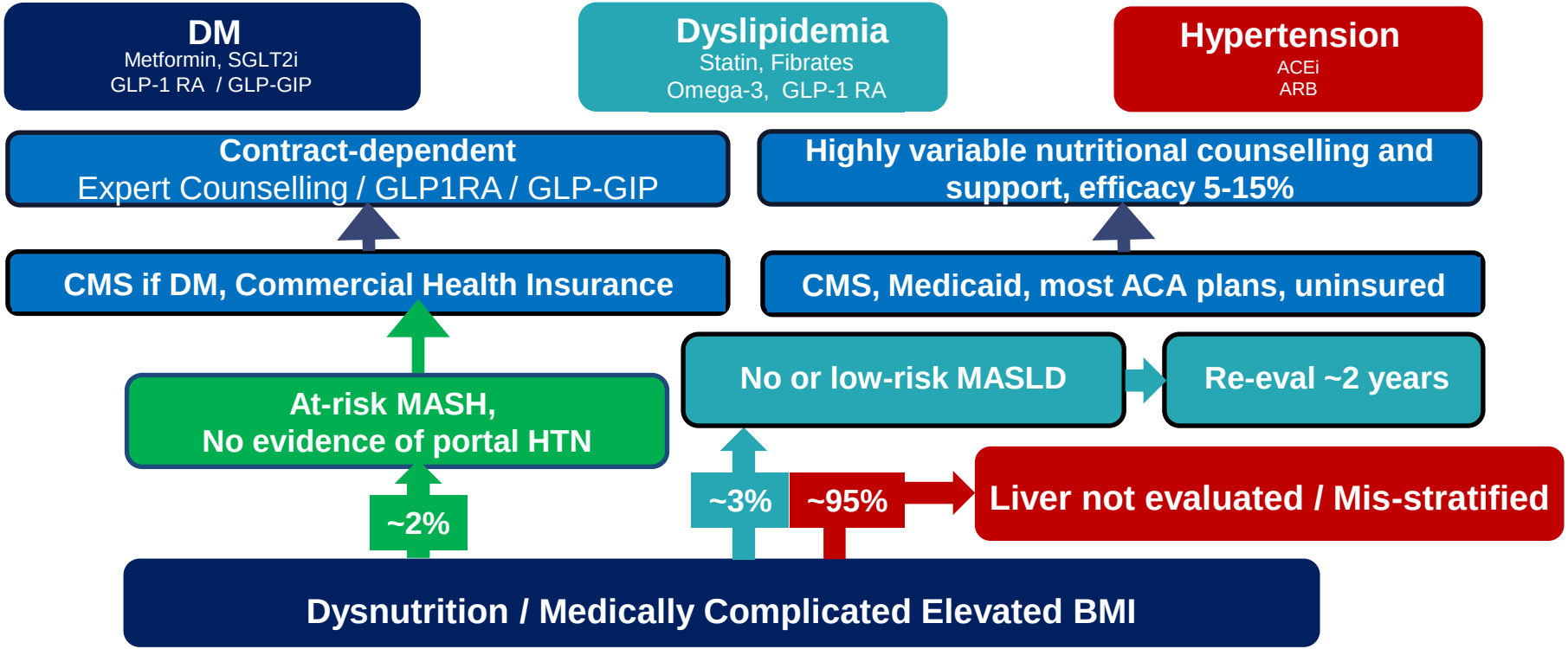
**FDA approved indications, Professional society guidelines**



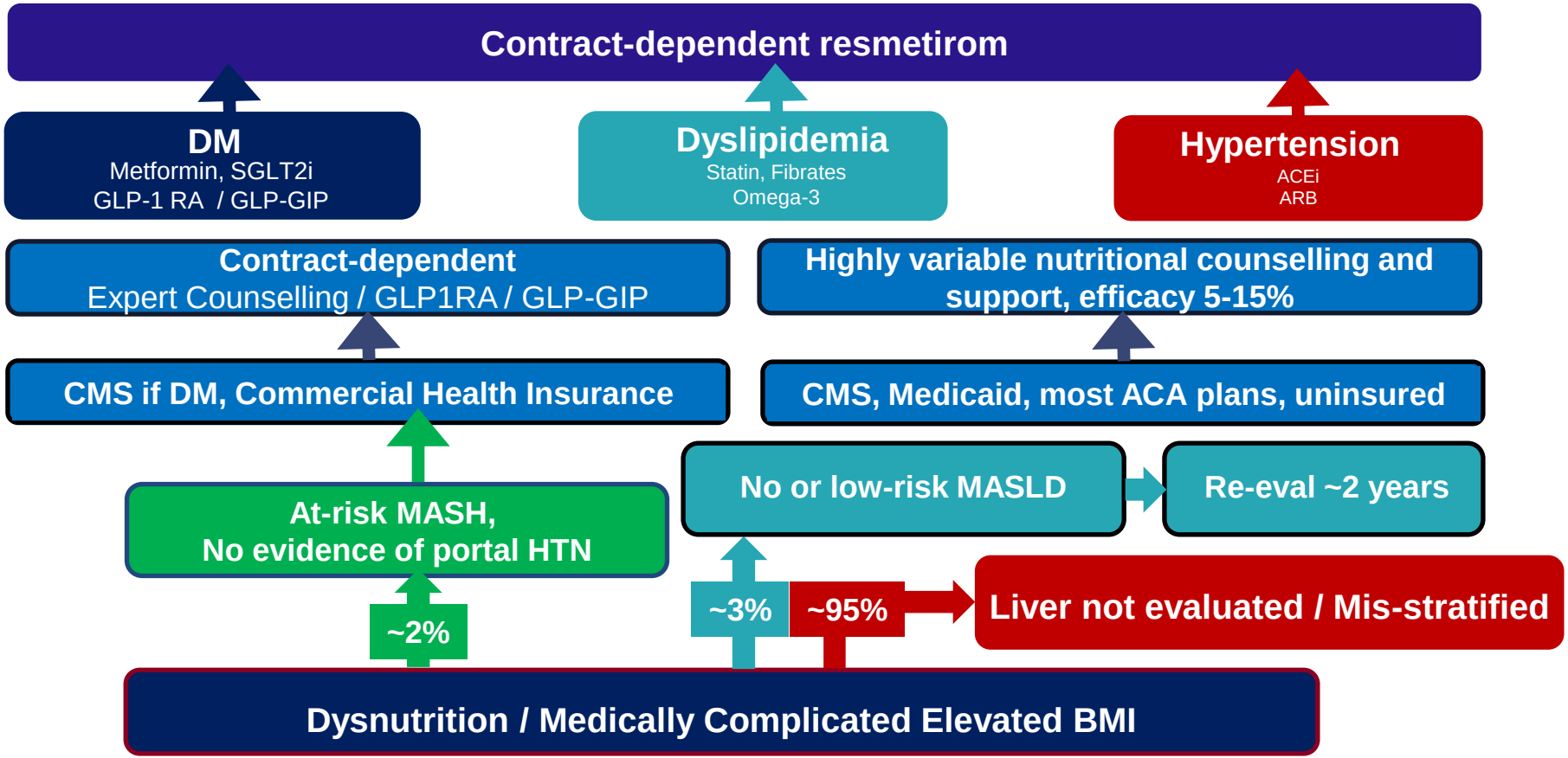

www.CDC.gov

**Evidence of MASH improvement in P2/3 Clinical trials**
**Professional society guidelines**

# Real World Management of Patients with MASH in Q 1-2 2024



# Real World Management of Patients with MASH in Q 3-4 2024




Barbieland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