Management of MAFLD/MASLD in people with obesity

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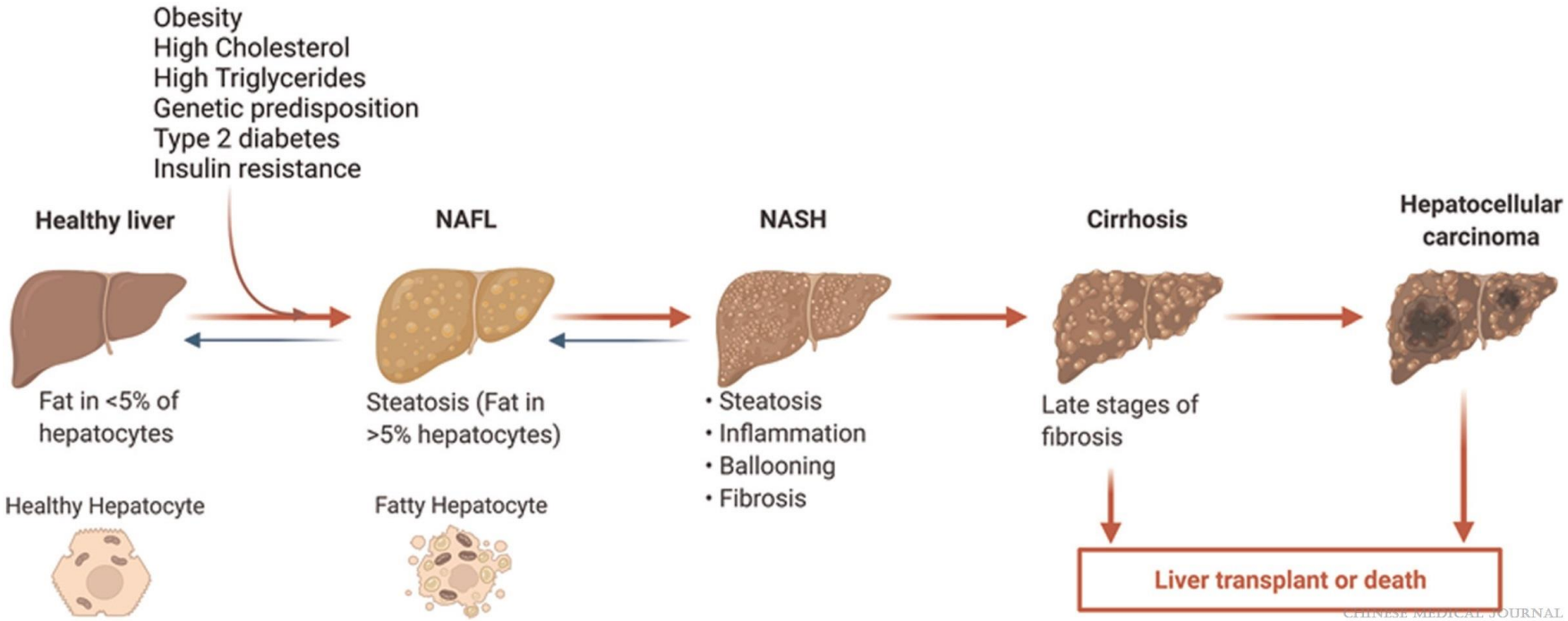
Conflict of Interest Disclosure

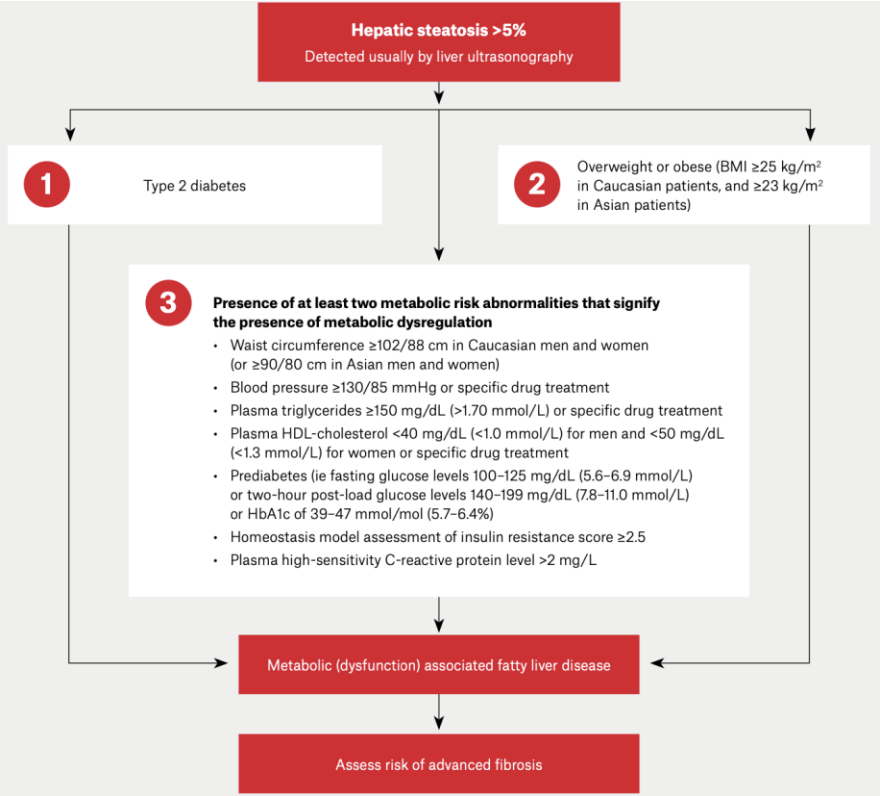
A/Prof Samantha L Hocking has received research grants from The Diabetes Australia Research Trust/Program and The National Health and Medical Research Council of Australia; received honoraria for lectures from Eli Lilly, Novo Nordisk, Inova, Sanofi Aventis, Astra Zeneca, Servier and Amgen and has been or is on advisory boards for Novo Nordisk, Eli Lilly, Inova, Seqirus and Pfizer; and has been an investigator for industry-sponsored clinical trials run by Novo Nordisk, Eli Lilly, Rhythm pharmaceuticals, Millendo, Spruce Biosciences and Amgen.

The spectrum of MAFLD



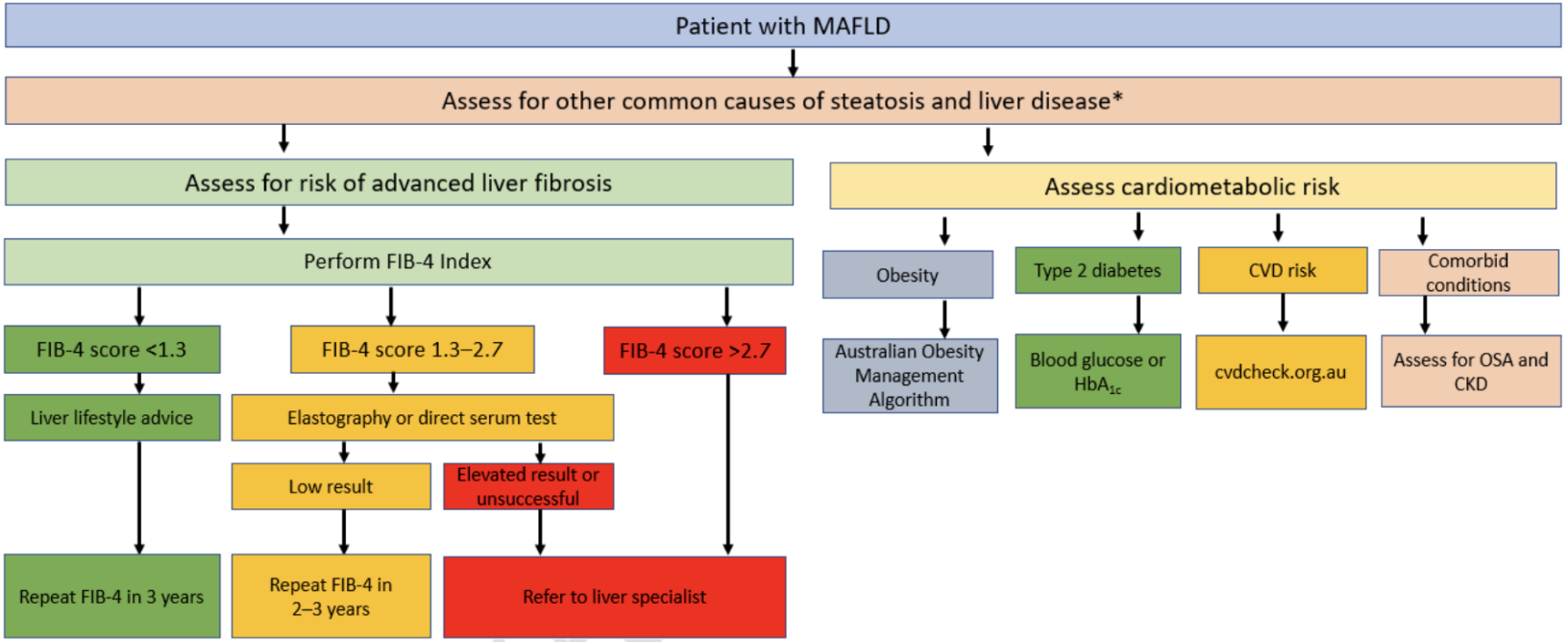
Chinese Medical Journal135(10):1163-1171, May 20, 2022.

Diagnostic criteria for metabolic (dysfunction)-associated fatty liver disease



AJGP Vol. 50, No. 10, October 2021

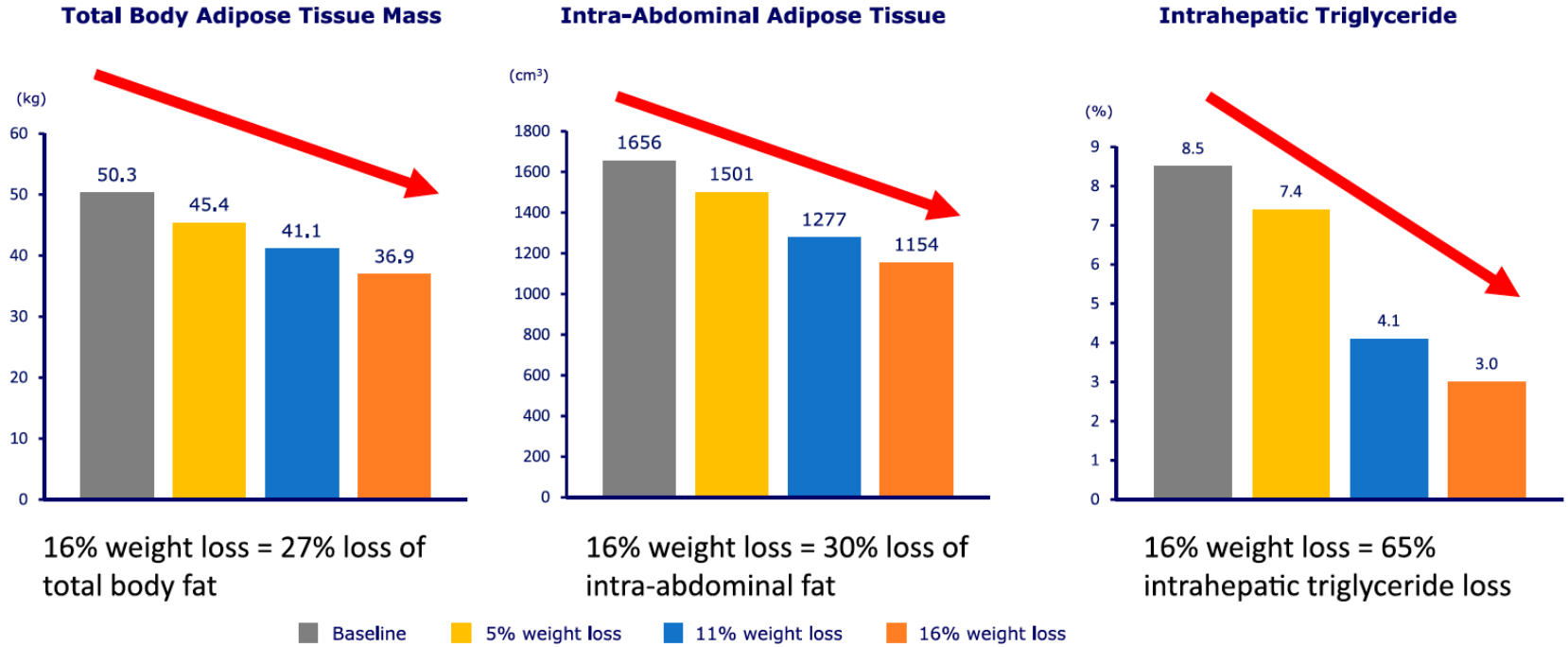
Assessment algorithm for a patient presenting with MAFLD



* Evaluate alcohol intake, medications, risk factors for viral hepatitis, and iron overload. CKD = chronic kidney disease; CVD = cardiovascular disease; FIB-4 = Fibrosis 4; HbA1c = glycated haemoglobin; MAFLD = metabolic (dysfunction)-associated fatty liver disease; OSA = obstructive sleep apnoea.

https://www.gesa.org.au/resources/clinical-practice-resources/metabolic-dysfunction-associated-fatty-liver-disease-mafld-consensus-statement/

Weight loss produces disproportionately greater loss of intra-abdominal and liver adipose tissue

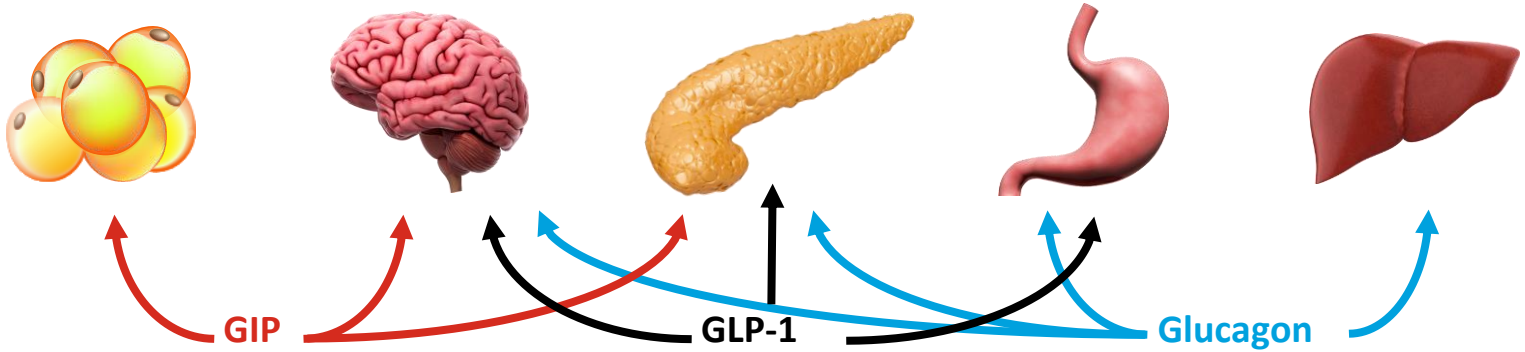


Ryan, D.H. Diabetes Spectrum 2020 May; 33(2): 117-124

Anti-obesity pharmacotherapies for MAFLD

- Semaglutide – weekly GLP-1 RA
- Tirzepatide – weekly GLP-1 / GIP agonist
- Survodutide – weekly GLP-1 / glucagon agonist
- Resmetirom – thyroid hormone receptor β-agonist

GIP / GLP-1 / Glucagon Receptor Agonists[1,2]



Adipose:
- ↑ Insulin sensitivity
- Improvements in lipid metabolism

CNS:
- Appetite
- Decrease in nausea

Islets:
- ↑ Insulin secretion
- ↑ Glucagon secretion

CNS:
- Appetite

Islets:
- ↑ Insulin secretion
- ↓ Glucagon secretion

Stomach:
- Delayed gastric emptying

CNS:
- ↑ Energy expenditure
- Appetite regulation

Islets:
- ↑ Insulin secretion

Stomach:
- Delayed gastric emptying

Liver:
- ↑ Glycogenolysis
- ↑ Gluconeogenesis
- Improvements in lipid metabolism

CNS=Central Nervous System; GIP=Glucose-dependent Insulinotropic Polypeptide; GLP-1=Glucagon-like Peptide-1.

1. Hædersdal S, et al. *Nat Rev Endocrinol.* 2023;19(6):321-335. 2. Hammoud R, Drucker DJ. *Nat Rev Endocrinol.* 2023;19(4):201-216.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

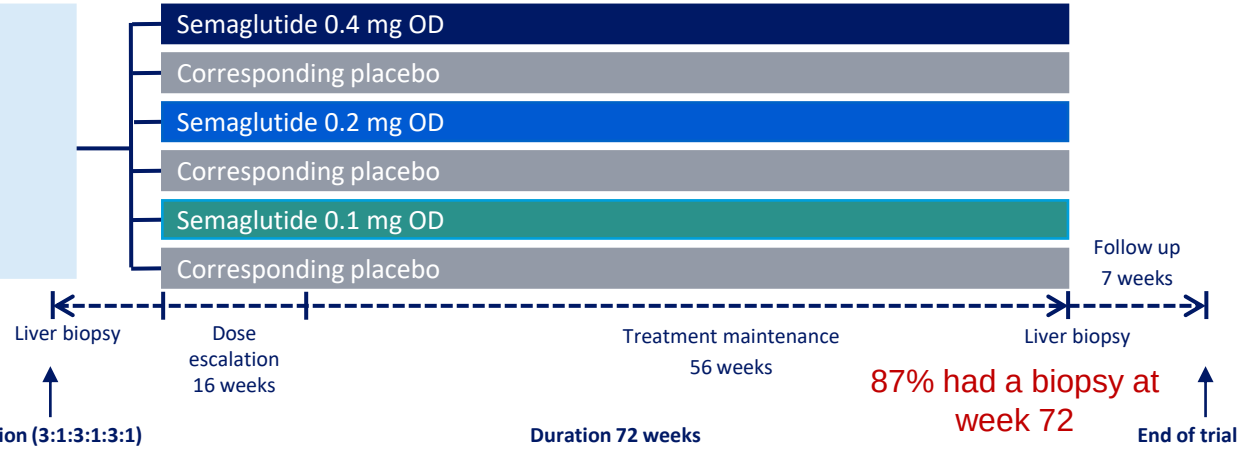
Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Sema-NASH phase 2: trial design

72-week randomised, placebo-controlled trial

320 patients

- Age 18–75 years
- NAS ≥4
- NASH fibrosis stage 1, 2 or 3
- BMI >25.0 kg/m^2
- HbA_{1c} ≤10%
- No chronic liver disease other than NASH



Trial objective

To compare the effect of semaglutide versus placebo on histological resolution of NASH

Key endpoints

- **Primary:** Resolution of steatohepatitis and no worsening in liver fibrosis in subjects with fibrosis*
- **Confirmatory secondary**: Improvement in liver fibrosis and no worsening in steatohepatitis†

**Resolution of steatohepatitis defined by the NASH clinical research network (CRN) as no more than mild residual inflammatory cells (0–1) and no ballooning (0). Fibrosis was graded on the NASH CRN fibrosis scale from 0 to 4. Primary analysis to assess efficacy in patients with stage 2 and 3 fibrosis. †Worsening of steatohepatitis as defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH CRN criteria.*

BMI, body mass index; HbA_{1c}, glycated haemoglobin; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis OD, once-daily.

Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Baseline characteristics

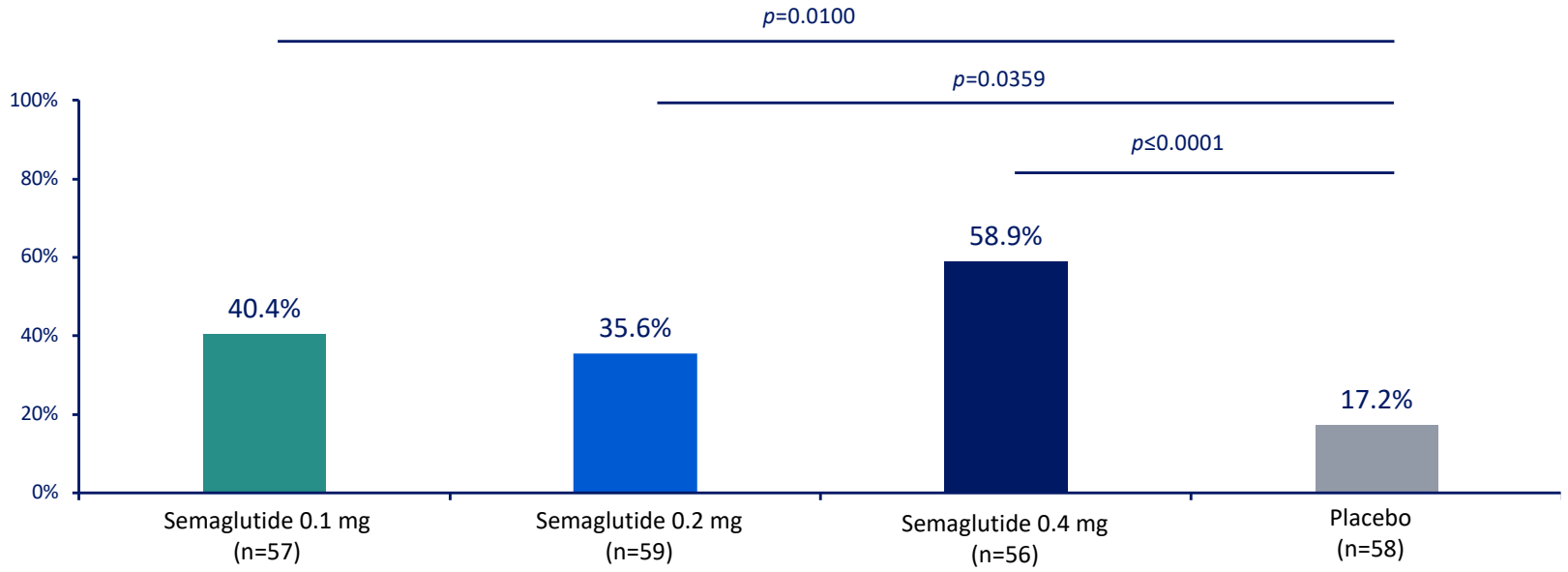
	Semaglutide 0.1 mg		Semaglutide 0.2 mg		Semaglutide 0.4 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age (years), mean (SD)	55.2	(10.9)	58.1	(9.9)	54.3	(10.2)	52.4	(10.8)	55.0	(10.6)
Sex, female, N (%)	51	(63.8)	52	(66.7)	47	(57.3)	44	(55.0)	194	(60.6)
Type 2 diabetes, N (%)	49	(61.3)	51	(65.4)	49	(59.8)	50	(62.5)	199	(62.2)
Body weight (kg), mean (SD)	98.4	(21.1)	97.1	(22.0)	96.6	(20.1)	101.3	(23.3)	98.4	(21.7)
Body mass index (kg/m^2), mean (SD)	36.1	(6.4)	35.6	(6.1)	35.2	(6.6)	36.1	(6.6)	35.8	(6.4)
Fibrosis stage (0–4), n (%)										
1	23	(28.8)	19	(24.4)	26	(31.7)	22	(27.5)	90	(28.1)
2	18	(22.5)	18	(23.1)	14	(17.1)	22	(27.5)	72	(22.5)
3	39	(48.8)	41	(52.6)	42	(51.2)	36	(45.0)	158	(49.4)
Hepatocyte ballooning (0–2), n (%)										
1	58	(72.5)	47	(60.3)	55	(67.1)	58	(72.5)	218	(68.1)
2	22	(27.5)	31	(39.7)	27	(32.9)	22	(27.5)	102	(31.9)
Lobular inflammation (0–3), n (%)										
1	30	(37.5)	32	(41.0)	40	(48.8)	33	(41.3)	135	(42.2)
2	47	(58.8)	44	(56.4)	37	(45.1)	46	(57.5)	174	(54.4)
3	3	(3.8)	2	(2.6)	5	(6.1)	1	(1.3)	11	(3.4)
Steatosis (0–3), n (%)										
1	21	(26.3)	21	(26.9)	31	(37.8)	17	(21.3)	90	(28.1)
2	42	(52.5)	43	(55.1)	31	(37.8)	46	(57.5)	162	(50.6)
3	17	(21.3)	14	(17.9)	20	(24.4)	17	(21.3)	68	(21.3)
Total NAFLD activity score (0–8), mean (SD)	4.9	(0.8)	4.9	(0.9)	4.8	(0.9)	4.9	(0.9)	4.9	(0.9)

Data based on full analysis set. N, number of patients; %, percentage of subject; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation..

Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Primary endpoint resolution of steatohepatitis with no worsening in liver fibrosis met for all doses

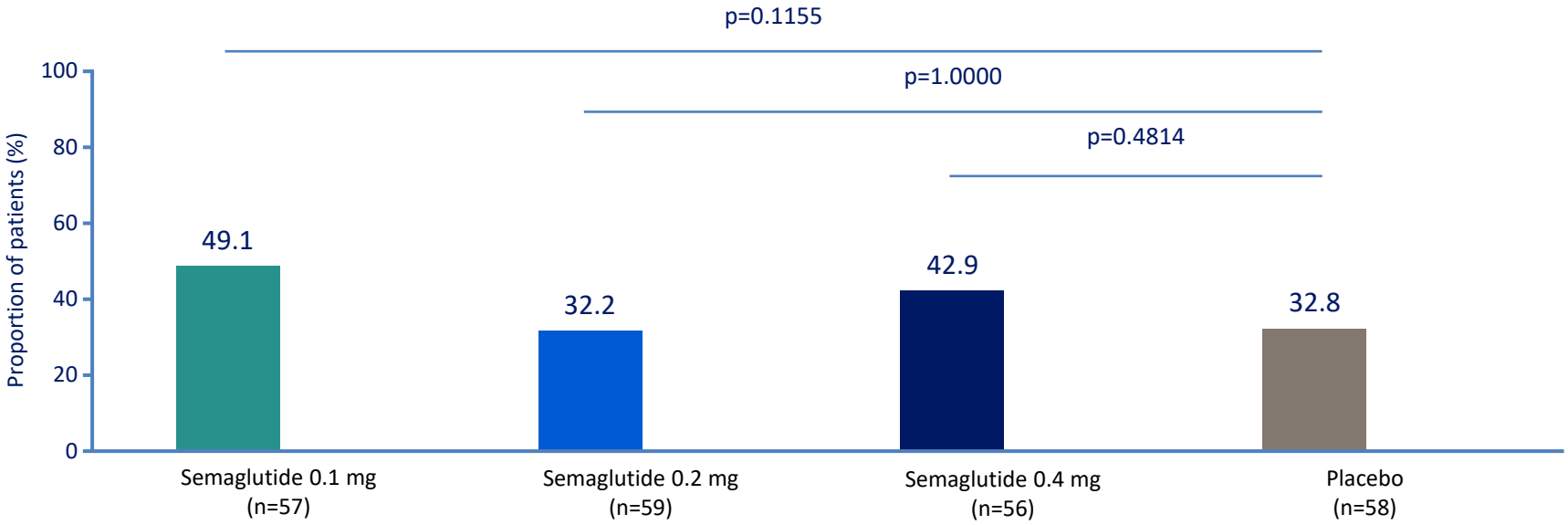
Subjects with fibrosis 2 or 3 at baseline



Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Secondary endpoint improvement in liver fibrosis and no worsening in steatohepatitis not met

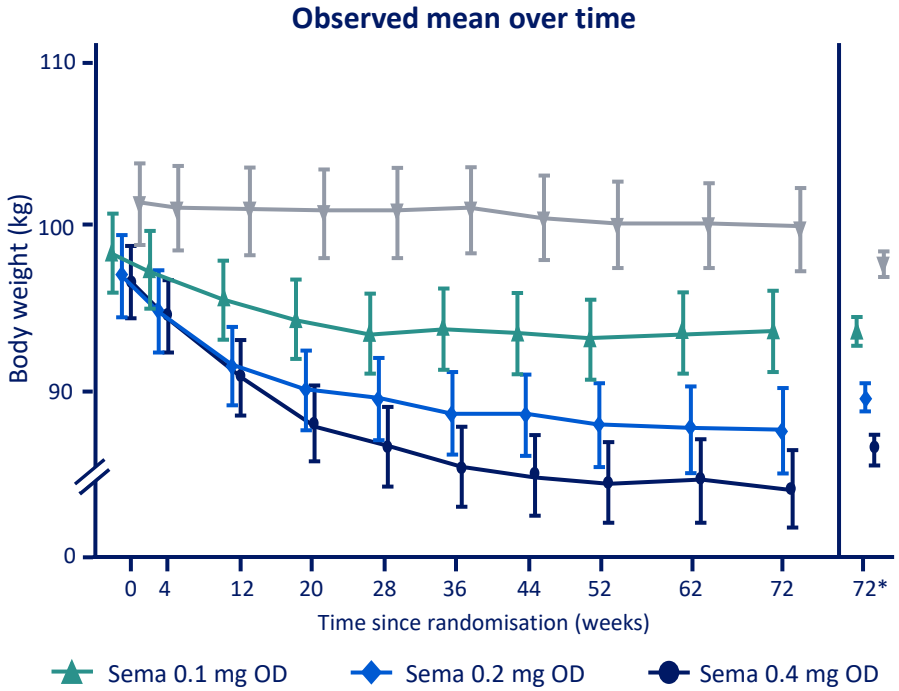
Subjects with fibrosis 2 or 3 at baseline

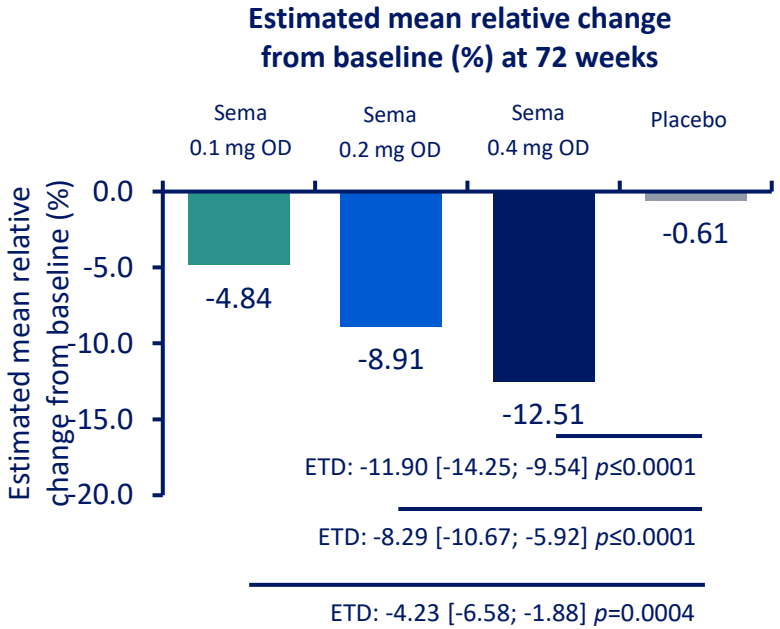


Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Change in body weight



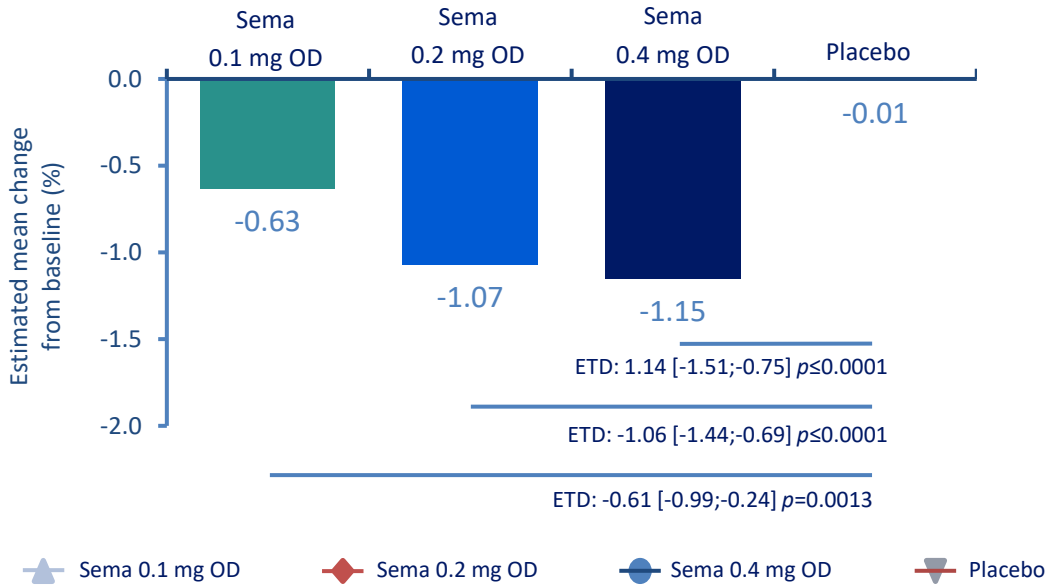


*Data based on in-trial period, all randomised subjects. *Estimates taken from an ANCOVA with missing data multiply imputed from placebo group. ANCOVA, analysis of covariance; OD, once-daily; sema, semaglutide..*

Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Change in HbA1c and lipids

Estimated mean relative change in HbA_{1c} from baseline (%) at 72 weeks
In subjects with type 2 diabetes



Changes in lipids in all randomised subjects

Semaglutide 0.4 mg versus placebo

↑ HDL cholesterol

↓ Free fatty acids triglycerides
↓ VLDL cholesterol

Data based on in-trial period. HbA_{1c} data from subjects with type 2 diabetes. Lipid data from all randomised subjects. ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein. Newsome PN et al. N Engl J Med 2020. doi: 10.1056/NEJMoa2028395.

Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

Conclusions

- Compared with placebo, semaglutide resulted in:
  - Significantly higher percentage of patients with NASH resolution without worsening of fibrosis
  - No difference in the percentage of patients with improvement in fibrosis without worsening in NASH
  - Fewer patients with worsening of fibrosis
  - Improvements in fibrosis biomarkers
- Treatment with semaglutide led to improvements in multiple metabolic characteristics, including body weight, HbA1c, and lipid profile
- The safety profile of semaglutide was consistent with that seen in patients with type 2 diabetes and obesity with no new safety concerns

Newsome PN et al N Engl J Med 2021; 384: 1113 - 24

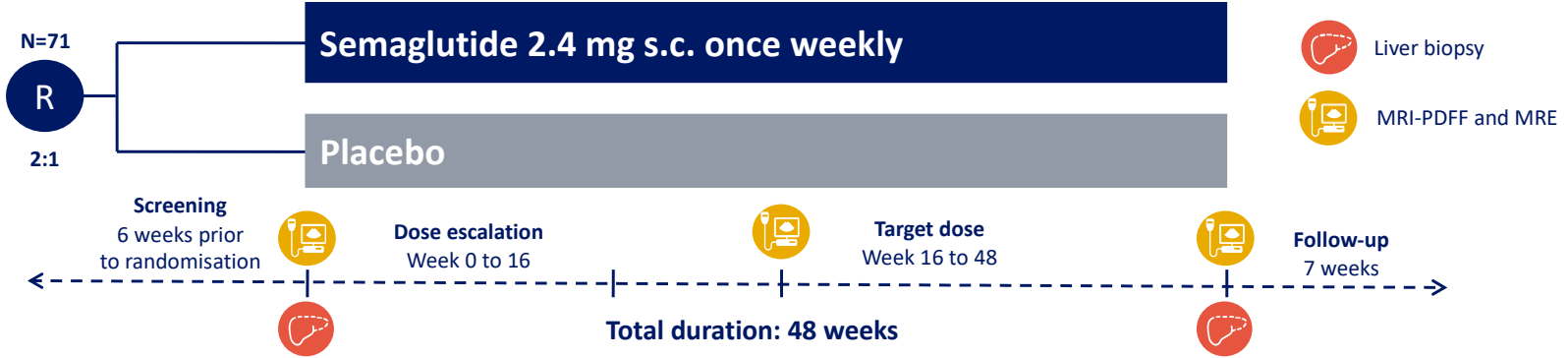
Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

Rohit Loomba, Manal F Abdelmalek, Matthew J Armstrong, Maximilian Jara, Mette Skalshøi Kjær, Niels Krarup, Eric Lawitz, Vlad Ratziu, Arun J Sanyal, Jörn M Schattenberg, Philip N Newsome*, on behalf of the NN9931-4492 investigators†*

Semaglutide NASH phase 2 in F4c: trial design

Inclusion criteria

- Age 18–75 years
- NAS ≥3*
- NASH fibrosis stage 4
- BMI ≥27.0 kg/m²
- No chronic liver disease other than NASH



Primary endpoint: At least one stage improvement in liver fibrosis with no worsening of NASH after 48 weeks†

Secondary endpoints: Liver histology, liver imaging, markers of liver injury and function, cardiometabolic parameters, exploratory biomarkers and safety

With a score of ≥1 for both lobular inflammation and hepatocyte ballooning; †Worsening of NASH defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis. BMI, body mass index; HbA1c , glycated haemoglobin; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; OW, once weekly; R, randomised. s.c. subcutaneous.

Loomba R et al. Lancet Gastroenterol Hepatol. 2023. doi:10.1016/S2468-1253(23)00068-7.

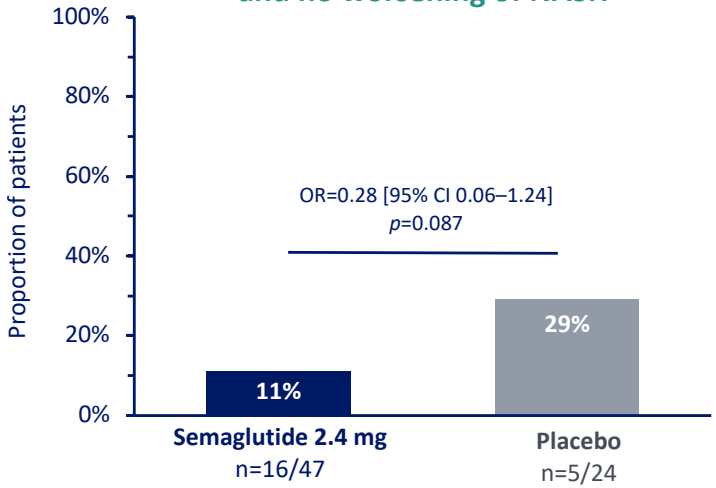
Semaglutide is not approved for treatment of NASH

Loomba R et al *Lancet Gastroenterol Hepatol* 2023; 8: 511–22

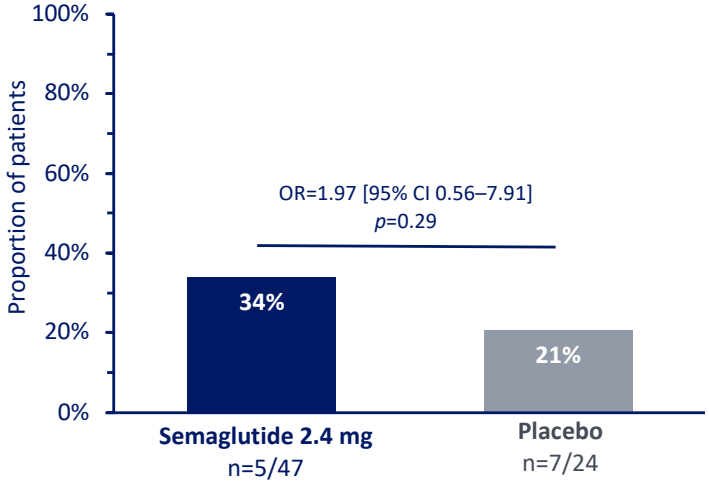
Primary and secondary histological endpoints not met

No statistically significant difference in improvements in liver fibrosis and NASH resolution between semaglutide and placebo treatments

Primary endpoint (amended): Improvement in liver fibrosis and no worsening of NASH



Key secondary endpoint: Resolution of NASH

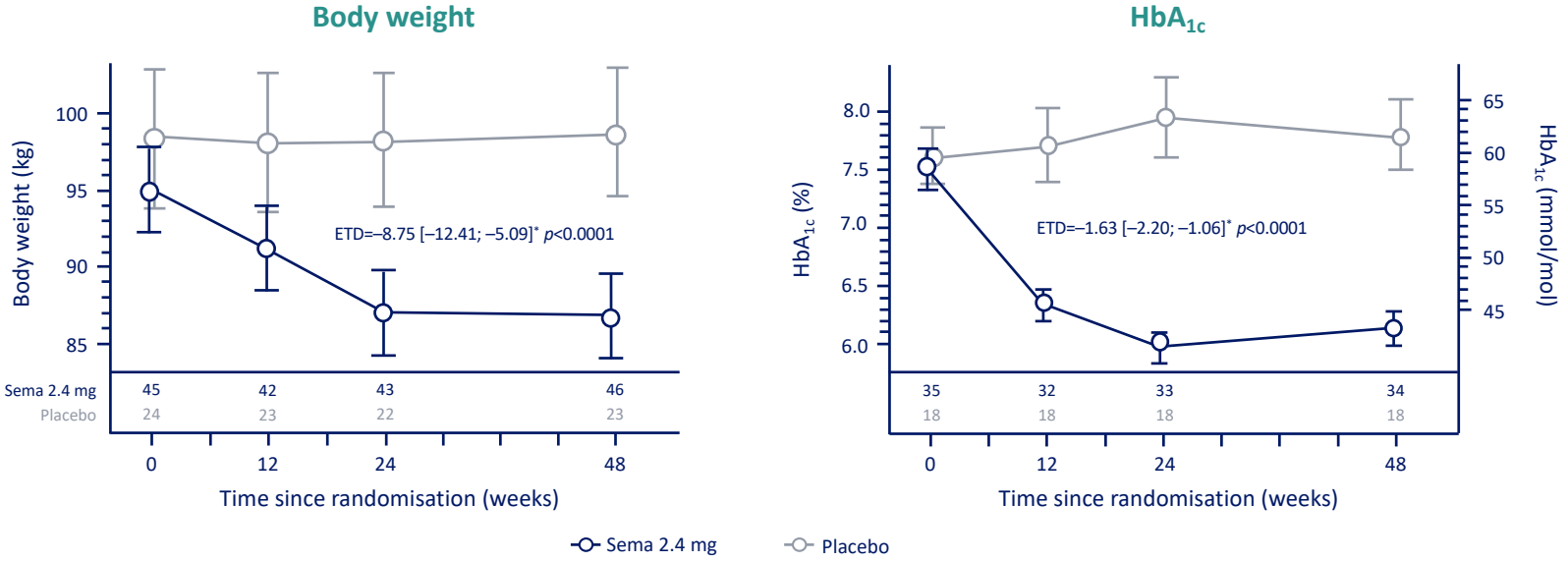


P-values are two-sided and taken from a Cochran-Mantel-Haenszel test stratified by baseline diabetes status. Patients with missing outcomes were imputed as non-responders. CI, confidence interval; n, number of patients; NASH, non-alcoholic steatohepatitis; OR, odds ratio.

Loomba R et al *Lancet Gastroenterol Hepatol* 2023; 8: 511–22

Change in body weight and HbA1c

Semaglutide significantly reduced body weight and improved glycaemic control



Number of observations per treatment group and visit is presented in the lower part of the plot. Error bars show the standard error of the mean for observed values. *ETDs with 95% confidence intervals and two-sided p-values are from the same analysis. Missing data were imputed from the observed data in the placebo group using the same ANCOVA model but without treatment as factor. ANCOVA, analysis of covariance, ETD, estimated treatment difference; HbA_{1c} , glycated haemoglobin; sema, semaglutide.

Loomba R et al *Lancet Gastroenterol Hepatol* 2023; 8: 511–22

Conclusions

- Although the primary endpoint was not met, semaglutide 2.4 mg appeared safe and was well tolerated in patients with NASH and compensated cirrhosis
- Consistent with the observed effects in other trials and disease areas, favourable effects of semaglutide were observed on cardiometabolic parameters in this patient population
- No new safety concerns for semaglutide were identified, providing evidence that semaglutide is **safe to use in patients with compensated liver cirrhosis**

- Raises questions
  - Is it too late to intervene when cirrhosis is present?
  - Was the weight reduction insufficient?
  - Was the length of the trial insufficient?

Loomba R et al *Lancet Gastroenterol Hepatol* 2023; 8: 511–22

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 25, 2024 VOL. 391 NO. 4

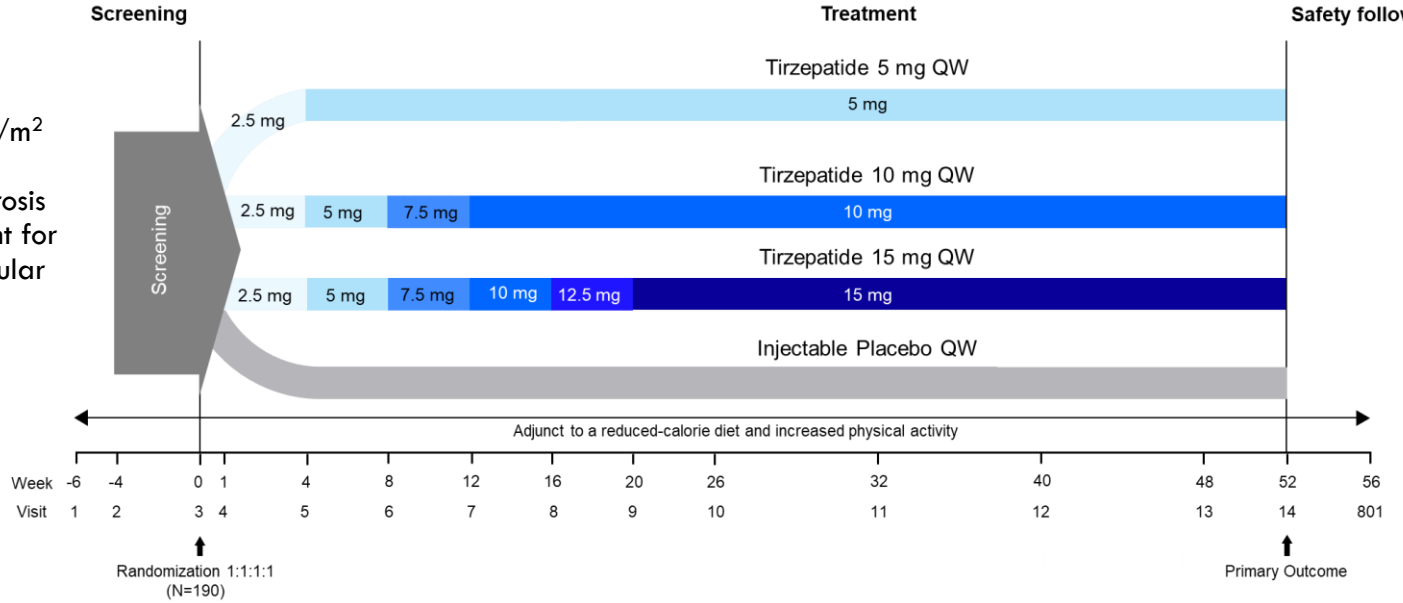
Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

STUDY DESIGN

Key inclusion criteria

- Adults 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 steatohepatitis without worsening of liver fibrosis at 52 weeks

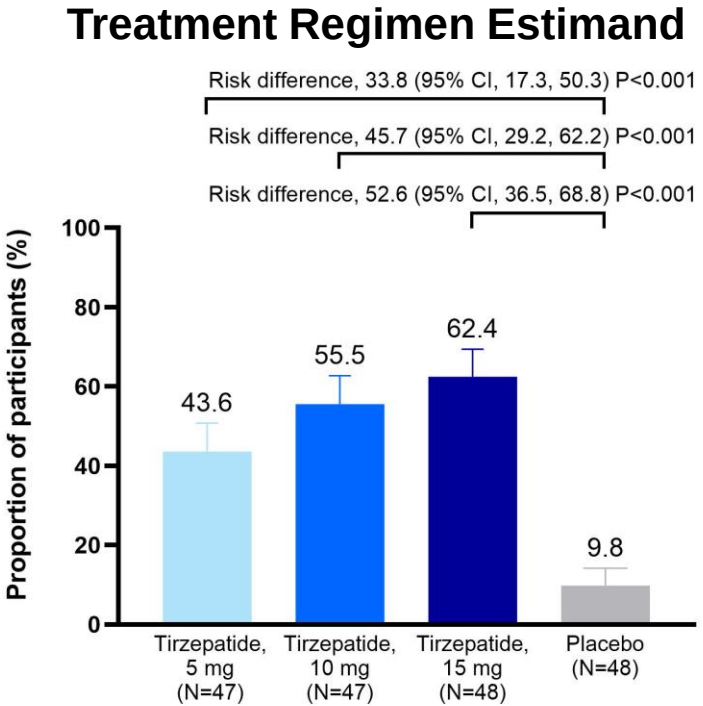
Secondary endpoint

- Improvement of at least 1 liver fibrosis stage without worsening in steatohepatitis

NAS = NAFLD activity score; QW = once weekly.

Loomba R et al N Engl J Med 2024; 391:299 - 310

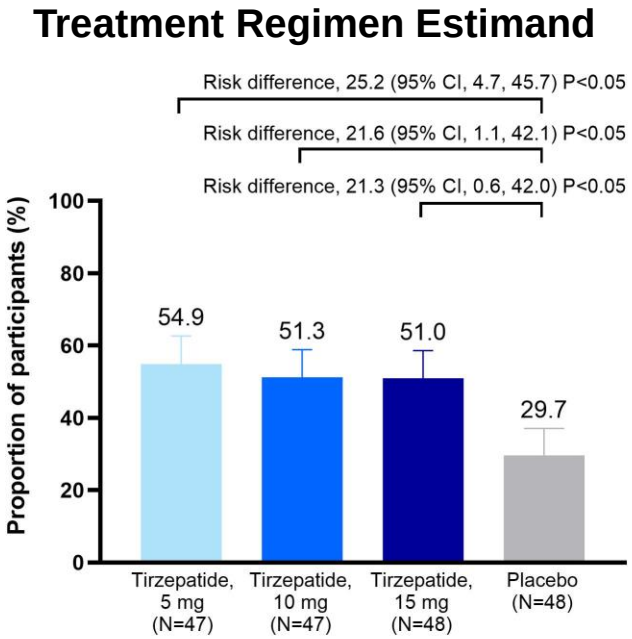
PRIMARY ENDPOINT: Resolution of MASH and no worsening of fibrosis met for all doses



Data are estimates; risk differences with 95% CI are presented. The CIs are not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Proportion estimate and risk difference are estimated based on logistic regression modelMASH = metabolic dysfunction-associated steatohepatitis; N = number of participants in the analysis population.

Loomba R et al N Engl J Med 2024; 391:299 - 310

SECONDARY ENDPOINT: ≥1 stage decrease in fibrosis and no worsening of MASH met for all doses

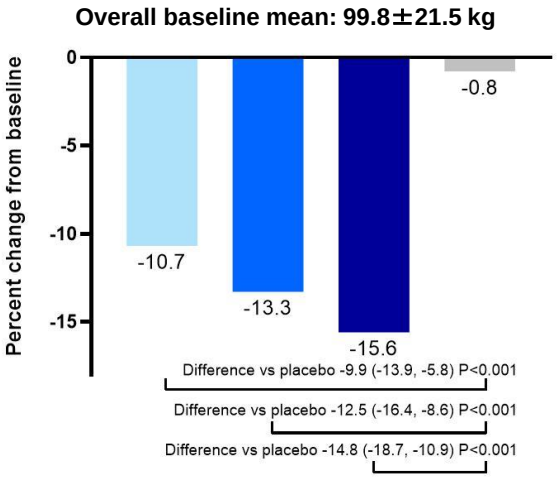


Data are estimates; Risk differences with 95% CI are presented. The CIs are not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Proportion estimate and risk difference are estimated based on logistic regression model. MASH = metabolic dysfunction-associated steatohepatitis; N = number of participants in the analysis population.

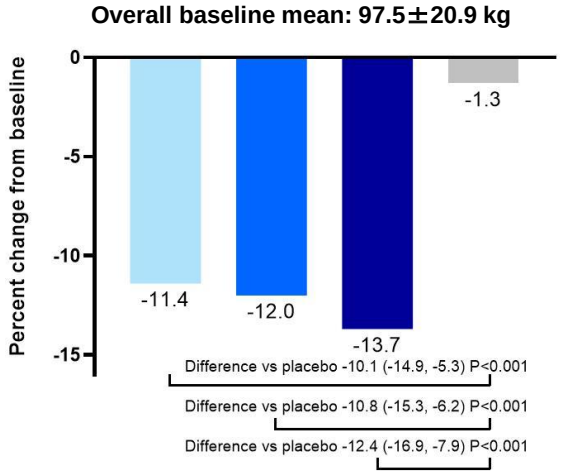
Loomba R et al N Engl J Med 2024; 391:299 - 310

Body weight change at 52 weeks in overall population, T2DM population, and non-T2DM population

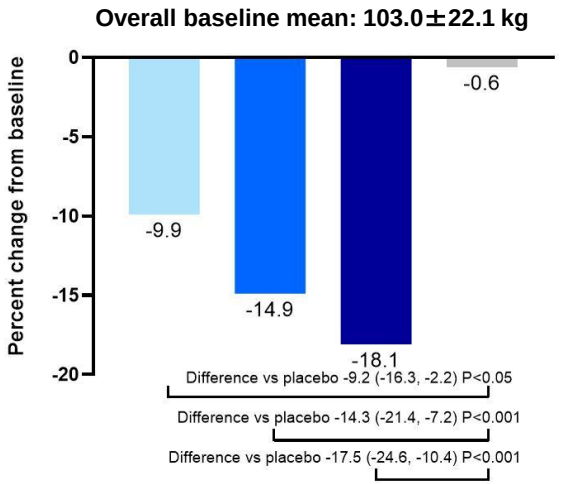
Overall population



T2DM



Non-T2DM



Results are consistent with those seen at 52 weeks in phase 3 T2DM and obesity trials

Baseline values are means ±SD. Data are estimates; differences versus placebo shown with 95% CI. The CIs are not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. T2DM = type 2 diabetes mellitus; CI = confidence interval.

Loomba R et al N Engl J Med 2024; 391:299 - 310

SAFETY

- Adverse events were reported in 92.3% of tirzepatide-treated participants and in 83.3% with placebo
  - The most common adverse events with tirzepatide were gastrointestinal and most (96%) were mild to moderate in severity
  - Treatment discontinuation due to an adverse event occurred in 4.2% of participants with both tirzepatide and placebo
  - Serious adverse events: 9 (6.3%) participants in tirzepatide groups and 3 (6.2%) in the placebo group
- Progression to cirrhosis: 4 (2.8%) tirzepatide-treated participants and 2 (4.2%) in the placebo group
  - No participants developed hepatic decompensation
- There was no evidence for drug-induced liver injury
- Gallbladder-related adverse events: 4 tirzepatide-treated participants (2.8%) and 1 on placebo (2.1%)
- No cases of acute pancreatitis were reported

Loomba R et al N Engl J Med 2024; 391:299 - 310

SUMMARY & CONCLUSIONS

- In this Phase 2 study of patients with biopsy-confirmed MASH and stage 2 or 3 fibrosis
  - 44-62% of participants treated with tirzepatide achieved MASH resolution compared to 9.8% of those treated with placebo
  - 51-55% of tirzepatide-treated participants achieved ≥1-stage fibrosis improvement without worsening of MASH compared to 30% of those treated with placebo
- The histology findings are supported by changes in biomarkers of MASH and fibrosis
- In a MASH population the safety profile was generally similar to that observed in phase 3 trials in T2DM and obesity
  - The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity
- Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for treatment of MASH

Loomba R et al N Engl J Med 2024; 391:299 - 310

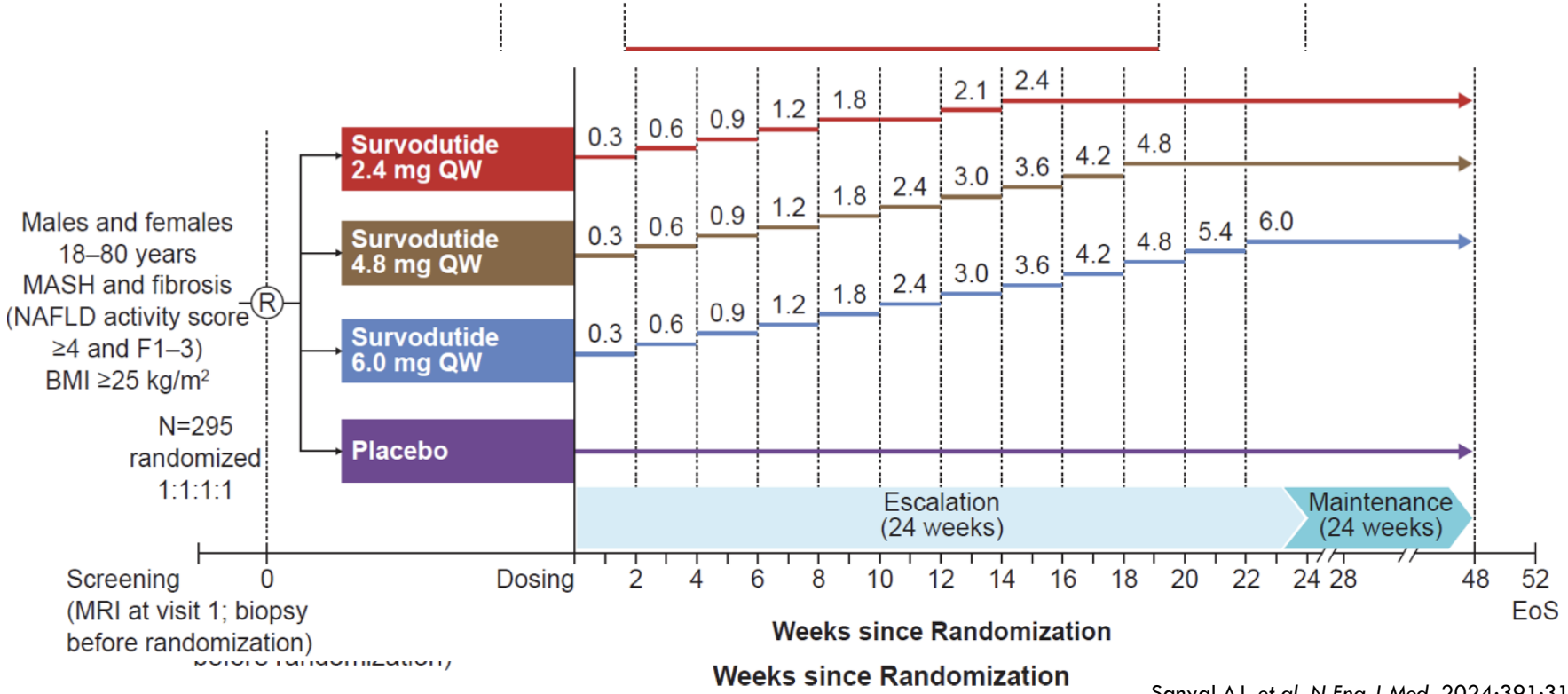
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., Samina Ajaz Hussain, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Vlad Ratziu, M.D., Azadeh Hosseini-Tabatabaei, Pharm.D., Ph.D., Jörn M. Schattenberg, M.D., Mazen Noureddin, M.D., M.H.Sc., Naim Alkhouri, M.D., and Ramy Younes, M.D., Ph.D., for the 1404-0043 Trial Investigators*

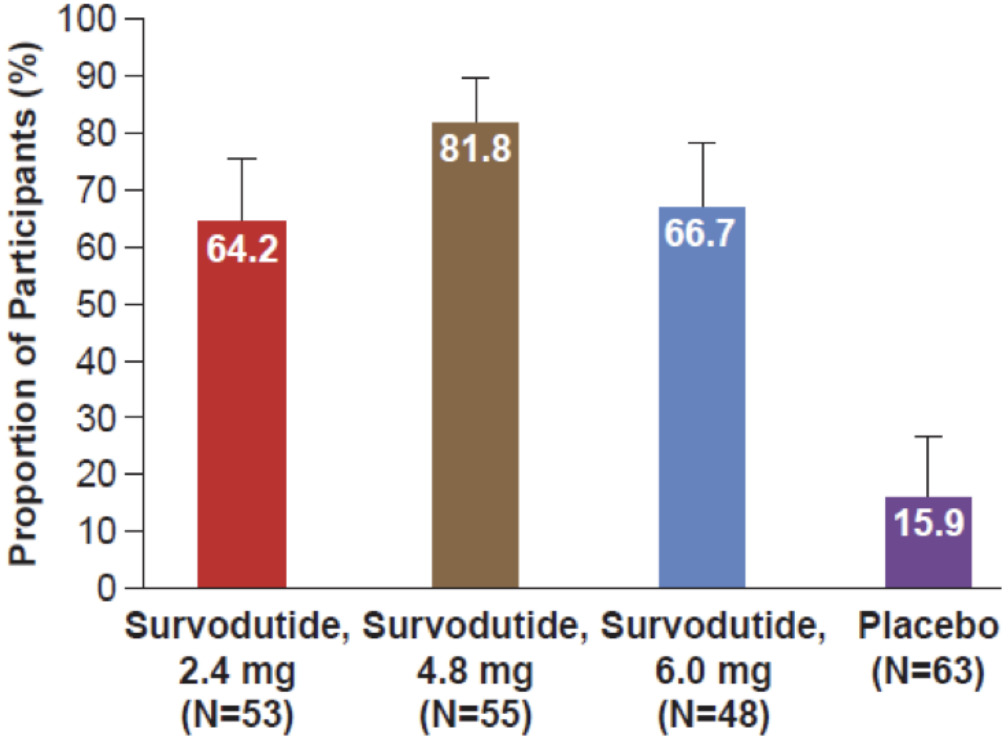
Study design



Weeks since Randomization

Sanyal AJ, *et al. N Eng J Med.* 2024;391:311–319

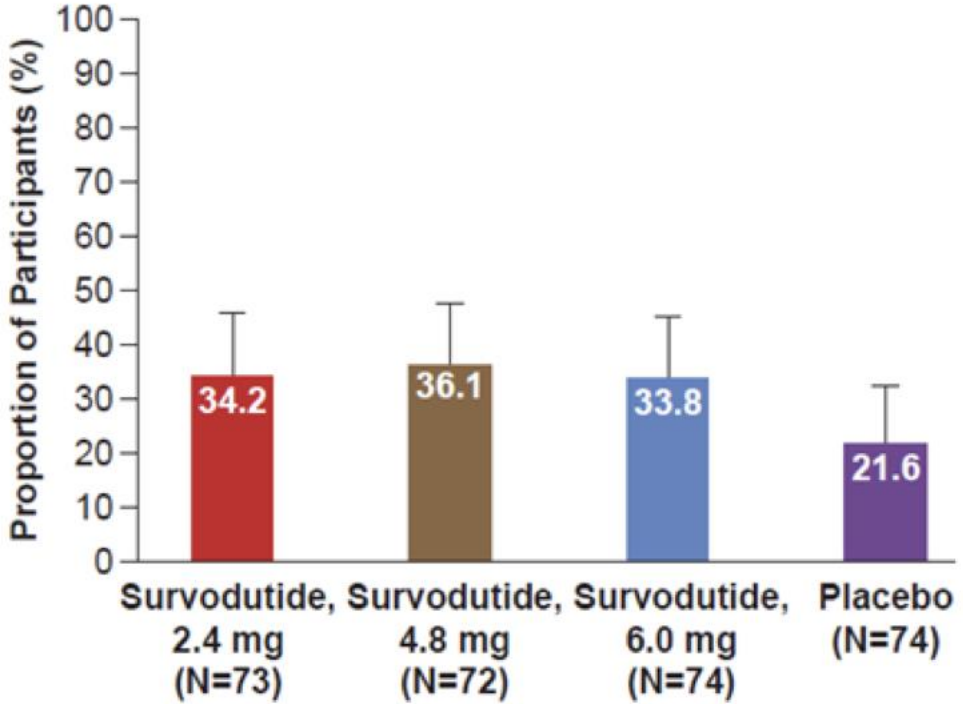
Primary endpoint resolution of steatohepatitis with no worsening in liver fibrosis met for all doses



Paired biopsy results

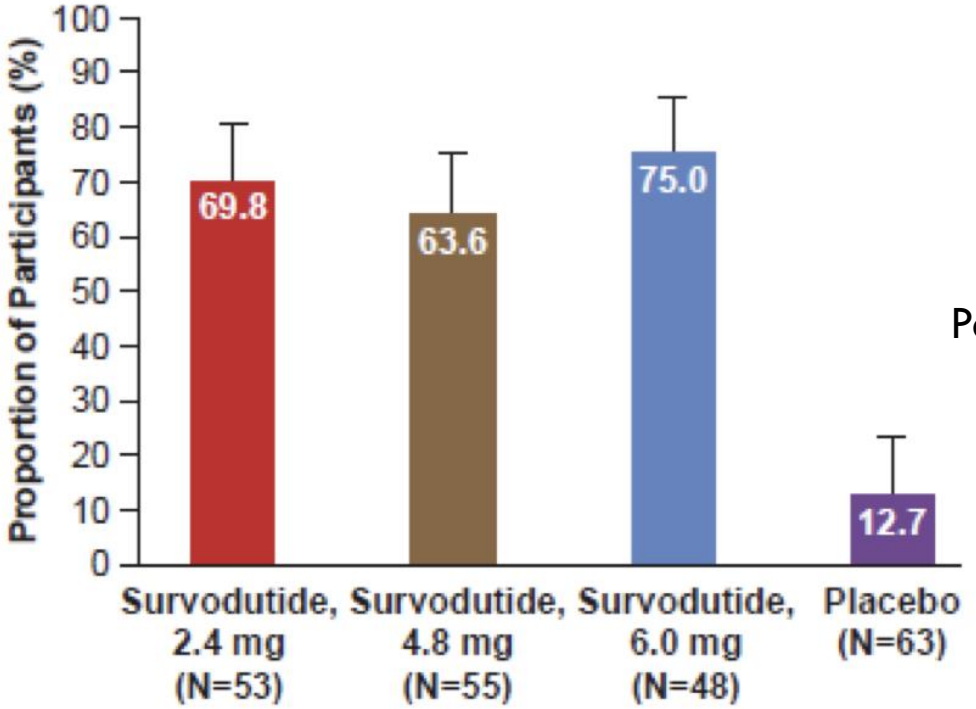
Sanyal AJ, *et al. N Eng J Med.* 2024;391:311–319

Secondary end point improvement in fibrosis by at least 1 stage



Sanyal AJ, *et al. N Eng J Med.* 2024;391:311–319

Further endpoints – resolution of MASH



Paired biopsy results

Sanyal AJ, *et al. N Eng J Med.* 2024;391:311–319

Other clinical endpoints at 48 weeks

End Point	Survodutide 2.4 mg QW		Survodutide 4.8 mg QW		Survodutide 6.0 mg QW		Placebo	
	Baseline value	Absolute change from baseline	Baseline value	Absolute change from baseline	Baseline value	Absolute change from baseline	Baseline value	Absolute change from baseline
Planned treatment								
Body weight — kg	101.44±18.20	-10.18±6.89	99.95±26.12	-12.93±8.53	103.87±23.70	-13.11±9.68	98.09±20.78	-0.60±3.71
BMI — kg/m^2	35.30±5.05	-3.51±2.39	35.00±6.97	-4.56±3.00	37.42±6.84	-4.83±3.66	35.49±6.44	-0.23±1.36
Waist circumference — cm	113.1±11.4	-7.7±6.2	112.1±14.9	-9.9±8.6	117.0±14.6	-9.6±8.8	113.0±14.2	-0.8±6.1
SBP — mmHg	128.78±14.77	-6.85±12.59	132.44±14.11	-7.58±14.10	127.00±14.80	-4.31±13.89	129.38±12.46	-0.42±11.91
DBP — mmHg	80.36±8.21	-2.62±7.18	81.79±9.37	-1.64±10.27	79.42±8.13	-1.29±7.53	81.22±8.41	0.44±8.65
HbA1c — %	6.27±1.02	-0.70±0.90	6.29±0.92	-0.80±0.47	6.19±0.96	-0.72±0.78	6.36±0.89	0.14±0.70
Cholesterol — mmol/L	3.399±1.112	-0.439±0.715	3.299±0.946	-0.730±0.711	3.192±1.232	-0.584±0.862	3.058±0.869	-0.170±0.706
HDL cholesterol — mmol/L	1.144±0.317	0.063±0.146	1.140±0.302	0.075±0.204	1.097±0.262	0.028±0.194	1.156±0.329	0.031±0.172
LDL cholesterol — mmol/L	0.733±1.016	-0.229±0.623	0.721±0.878	-0.529±0.776	0.628±1.042	-0.382±0.851	0.515±0.834	-0.150±0.726
Triglycerides — mmol/L	1.523±1.170	-0.547±1.157	1.283±0.797	-0.525±0.794	1.332±1.002	-0.455±0.762	1.284±0.717	0.002±0.924

Sanyal AJ, *et al. N Eng J Med.* 2024;391:311–319

News

https://doi.org/10.1038/d41573-024-00051-1

NASH field celebrates 'hurrah moment' with a first FDA drug approval for the liver disease

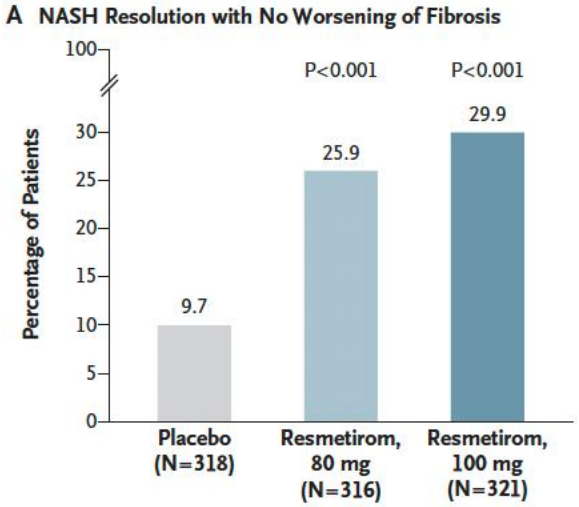
The NEW ENGLAND JOURNAL of MEDICINE

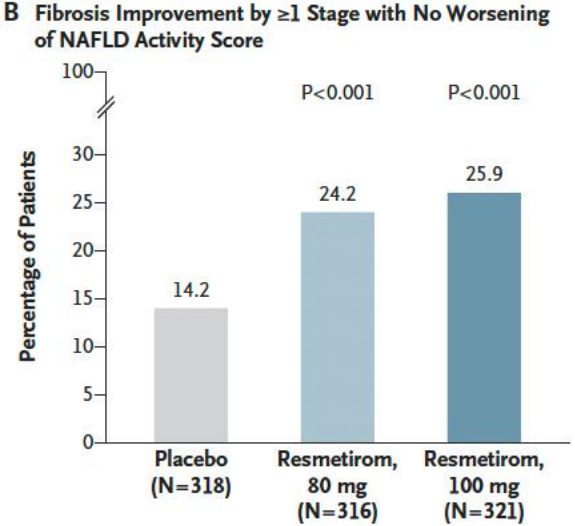
ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

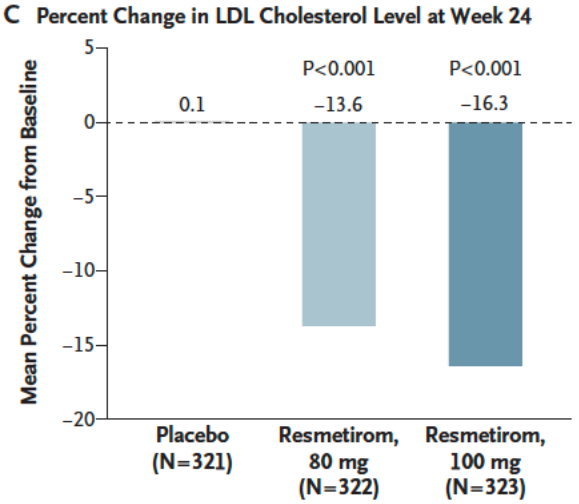
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

Resmetirom was superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage.

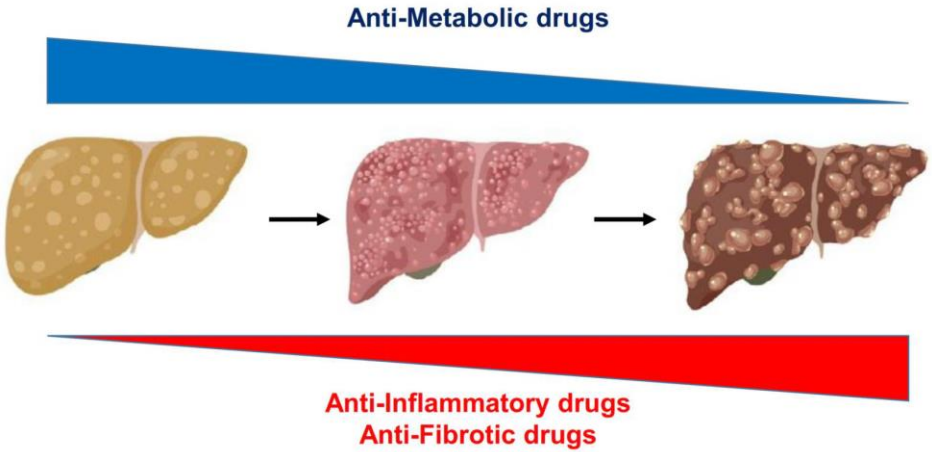






Harrison SA, *et al. N Eng J Med.* 2024;390:497–509

Key learning points



- NAFLD/MASLD is strongly linked to cardometabolic disease, Type 2 diabetes and obesity
- Incretin therapies have shown promise in NAFLD/MASLD/NASH
- Combination therapies may lead to better outcomes
  - drugs targeting underlying metabolic abnormalities could play a more significant role in the earlier stages of disease
  - drugs specifically targeting liver inflammation and collagen deposition are needed when significant damage has already occurred