

Weight-dependent and independent effects of semaglutide in participants with MASH: Secondary analysis of the phase 3 ESSENCE trial

Philip N. Newsome^{1,2}, Matthew J. Armstrong³, Igor Bakulin⁴, Adel Belloum⁵, Anja Geerts^{6,7}, Jacob George⁸, Ewa Janczewska⁹, Niels Krarup⁵, Chun-Jen Liu^{10,11}, Håvard Midgard¹², Kwabena Opuni⁵, Vlad Ratziu¹³, Mary Rinella¹⁴, Michael Roden¹⁵⁻¹⁷, Arun J. Sanyal¹⁸, Jörn Schattenberg¹⁹, Thea Vestergaard⁵, Elisabetta Bugianesi²⁰ on behalf of the ESSENCE Study Group

¹Roger Williams Institute of Liver Studies, Faculty of Life Sciences and Medicine, King's College London, Foundation for Liver Research and King's College Hospital, London, UK; ²College of Medicine and Health, University of Birmingham, Birmingham, UK; ³Liver Unit, Queen Elizabeth Hospital Birmingham and NIHR Biomedical Research Centre, University of Birmingham, Birmingham, UK; ⁴Central Scientific Research for Gastroenterology, North-Western State Medical University, St Petersburg, Russia; ⁵Novo Nordisk A/S, Bagsværd, Denmark; ⁶Department of Gastroenterology & Hepatology, University Hospital Ghent, Ghent, Belgium; ⁷Faculty of Medicine and Health Sciences, University of Ghent, Ghent, Belgium; ⁸Storr Liver Centre, The Westmead Institute for Medical Research, Westmead Hospital New South Wales, Westmead, NSW, Australia; ⁹Hepatology Outpatient Clinic, ID Clinic, Mysłowice, Poland; ¹⁰Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; ¹¹Hepatitis Research Center and Clinical Trial Center, National Taiwan University Hospital, Taipei, Taiwan; ¹²Department of Gastroenterology, Oslo University Hospital, Oslo, Norway; ¹³Institute of Cardiometabolism and Nutrition, INSERM UMRS 1138 CRC, Hospital Pitié Salpêtrière (ICAN), Sorbonne University, Paris, France; ¹⁴Division of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, IL, USA; ¹⁵Department of Endocrinology and Diabetology, Medical Faculty and University Hospital of Düsseldorf, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany; ¹⁶Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University of Düsseldorf, Düsseldorf, Germany; ¹⁷German Center for Diabetes Research, Partner Düsseldorf, München-Neuherberg, Germany; ¹⁸Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; ¹⁹Department of Internal Medicine II, Saarland University Medical Center, Homburg, Germany; ²⁰Department of Medical Sciences, University of Turin, Turin, Italy

Disclosures

- I have received consulting fees from 89bio, Akero Therapeutics, Aligos Therapeutics, Boehringer Ingelheim, Forth Therapeutics, Inventiva, Madrigal Pharmaceuticals, Novo Nordisk, Sagimet Biosciences and UCB
- I have received honoraria as a speaker from AiCME, Boehringer Ingelheim, Echosens, Eli Lilly, Ipsen and Novo Nordisk, and support for attending meetings from Boehringer Ingelheim and Novo Nordisk

Introduction



Metabolic dysfunction-associated steatohepatitis (MASH) is the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD)



Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has been extensively studied across a broad spectrum of cardiometabolic disease

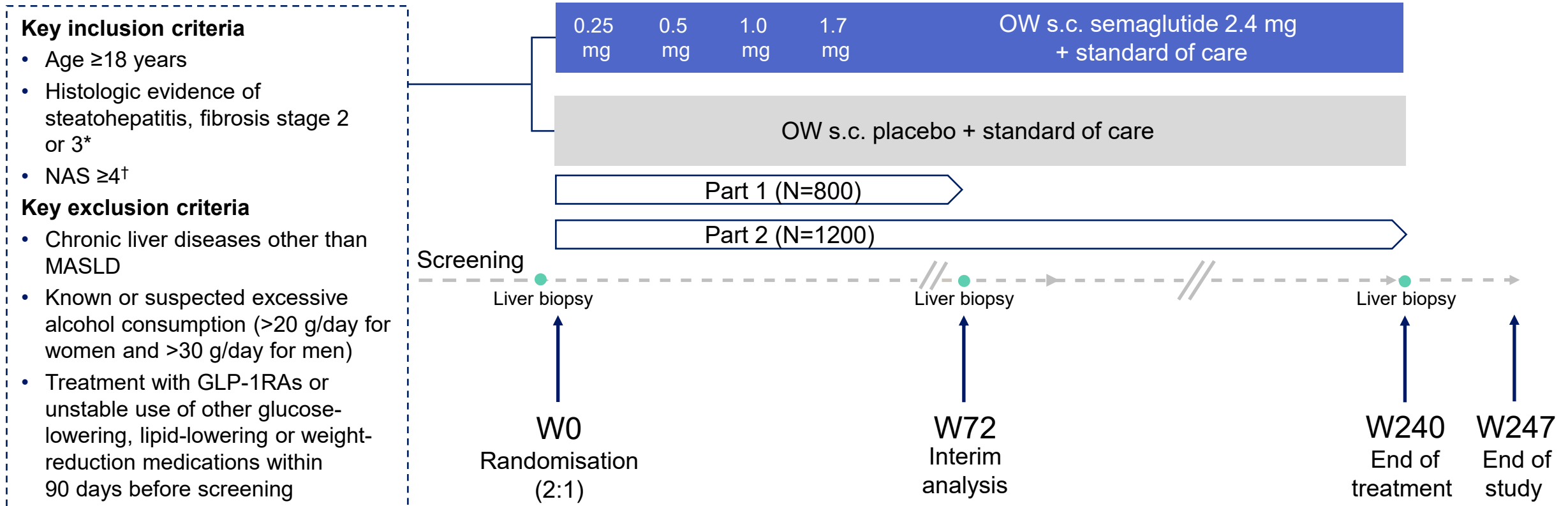


Semaglutide demonstrated efficacy in interim analysis of the ongoing phase 3 MASH trial, with superiority confirmed for semaglutide vs placebo with respect to histological end-points



Here, we report weight-dependent and independent effects of semaglutide in participants with MASH in a secondary analysis of the phase 3 ESSENCE trial

ESSENCE is an ongoing phase 3 trial to evaluate the efficacy of semaglutide in people with MASH and fibrosis stage 2 or 3

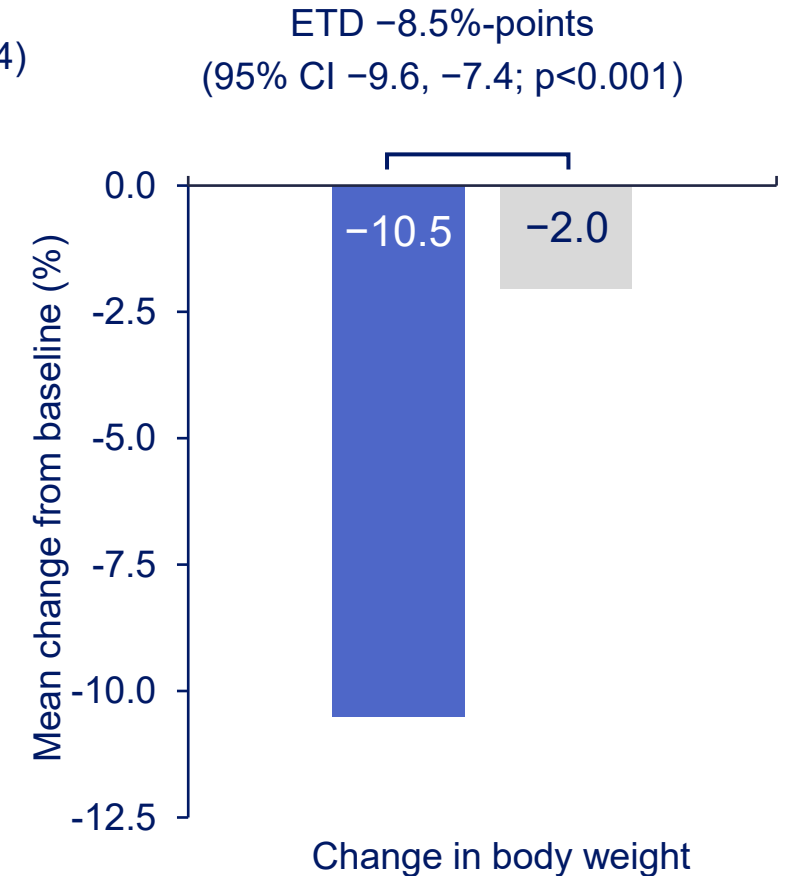
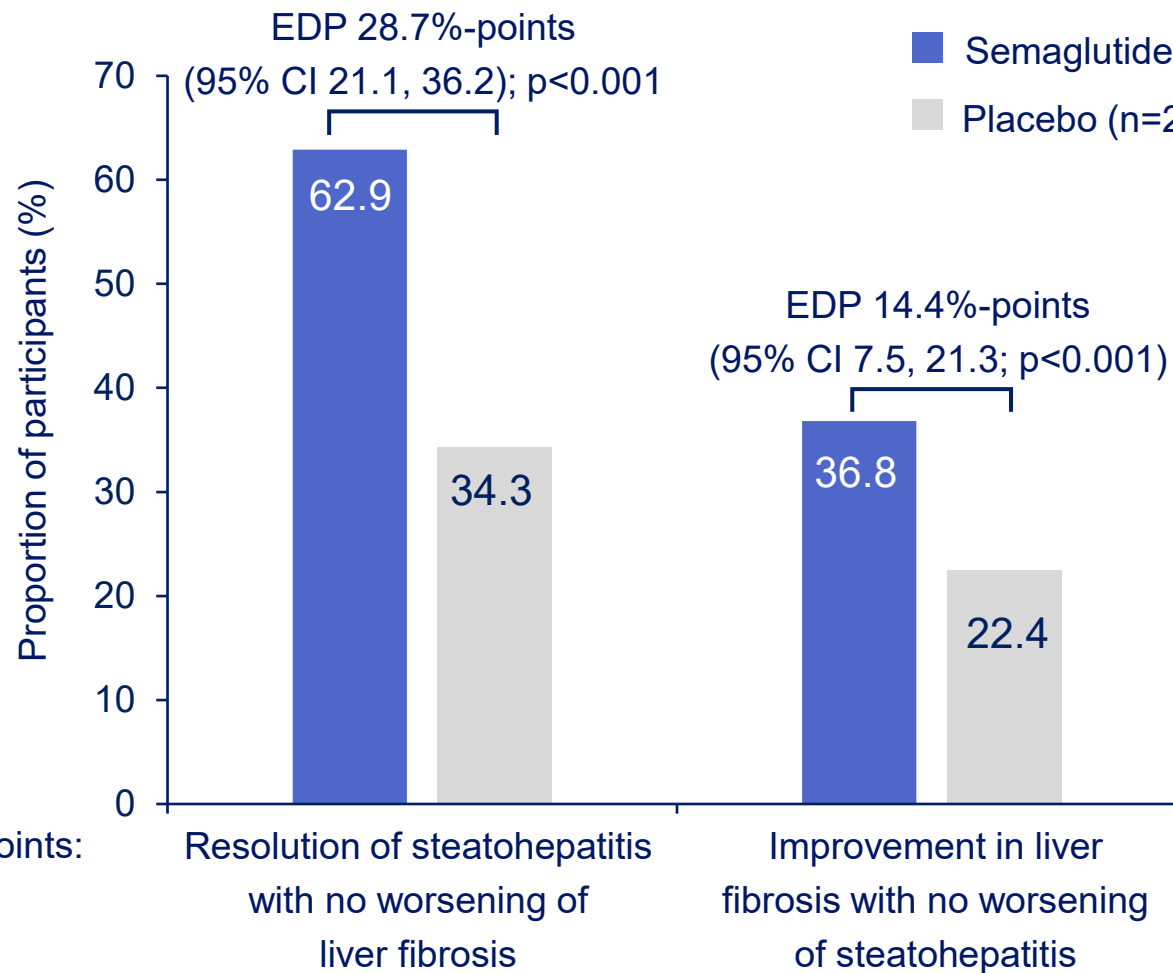


*According to the NASH Clinical Research Network classification; †With a score of ≥1 in steatosis, lobular inflammation and hepatocyte ballooning, based on central pathologist evaluation; ‡Uptitration every 4 weeks. One or more dose steps can be prolonged, or the dose lowered if the actual dose is not tolerated. If the designated target dose of OW s.c. semaglutide 2.4 mg is not tolerated, patients may stay at a lower dose level. GLP-1RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, non-alcoholic fatty liver disease activity score; OW, once weekly; s.c., subcutaneous; W, week. Sanyal AJ, Newsome PN et al. *N Engl J Med* 2025;392:2089–2099. Presented at AASLD, 7–11 November 2025, Washington, DC, USA.

Baseline characteristics

Baseline characteristic	Semaglutide 2.4 mg (n=534)	Placebo (n=266)	Total (N=800)
Age, years, mean (SD)	56.3 (11.4)	55.4 (12.0)	56.0 (11.6)
Sex, female, n (%)	313 (58.6)	144 (54.1)	457 (57.1)
Body weight, kg, mean (SD)	95.4 (24.5)	97.6 (24.6)	96.1 (24.5)
Waist circumference, cm, mean (SD)	111.8 (15.6)	113.1 (16.0)	112.3 (15.8)
BMI, kg/m ² , mean (SD)	34.3 (7.2)	35.0 (7.1)	34.6 (7.2)
<25	36 (6.7)	17 (6.4)	53 (6.6)
≥25 to <30	116 (21.7)	48 (18.0)	164 (20.5)
≥30 to <35	173 (32.4)	79 (29.7)	252 (31.5)
≥35	209 (39.1)	121 (45.5)	330 (41.3)
T2D, n (%)	296 (55.4)	151 (56.8)	447 (55.9)
HbA _{1c} , %, mean (SD) – with T2D	7.2 (1.1)	6.9 (1.0)	7.1 (1.1)
HbA _{1c} , %, mean (SD) – without T2D	5.8 (0.5)	5.8 (0.5)	5.8 (0.5)

Semaglutide 2.4 mg delivered significant improvements in liver histology and substantial body weight reductions



Primary endpoints:

Analysis based on intention-to-treat.

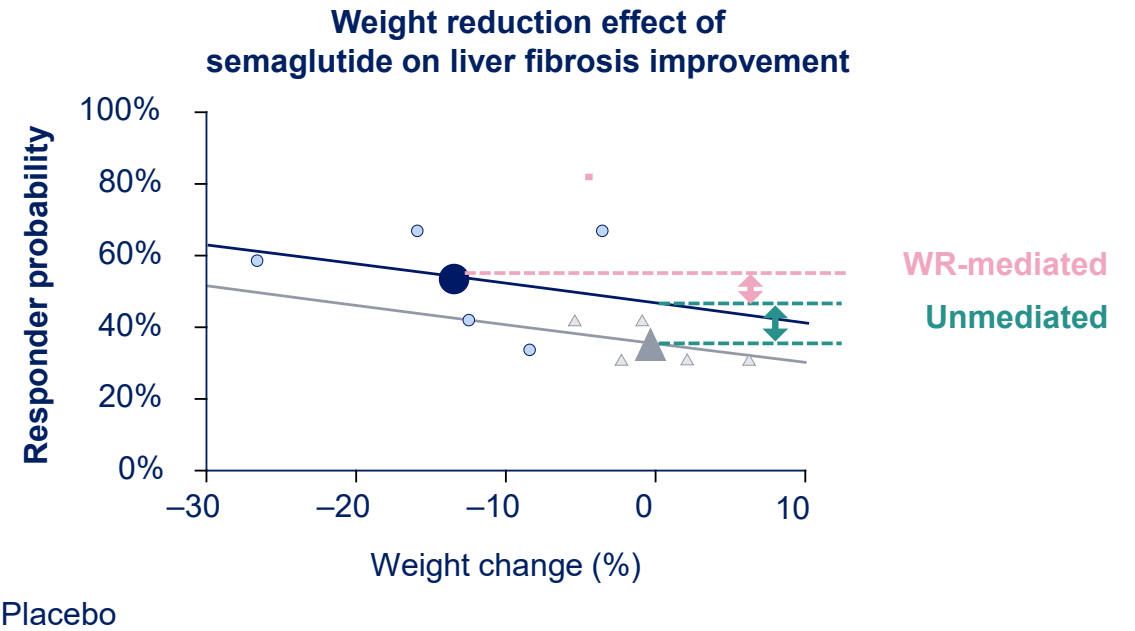
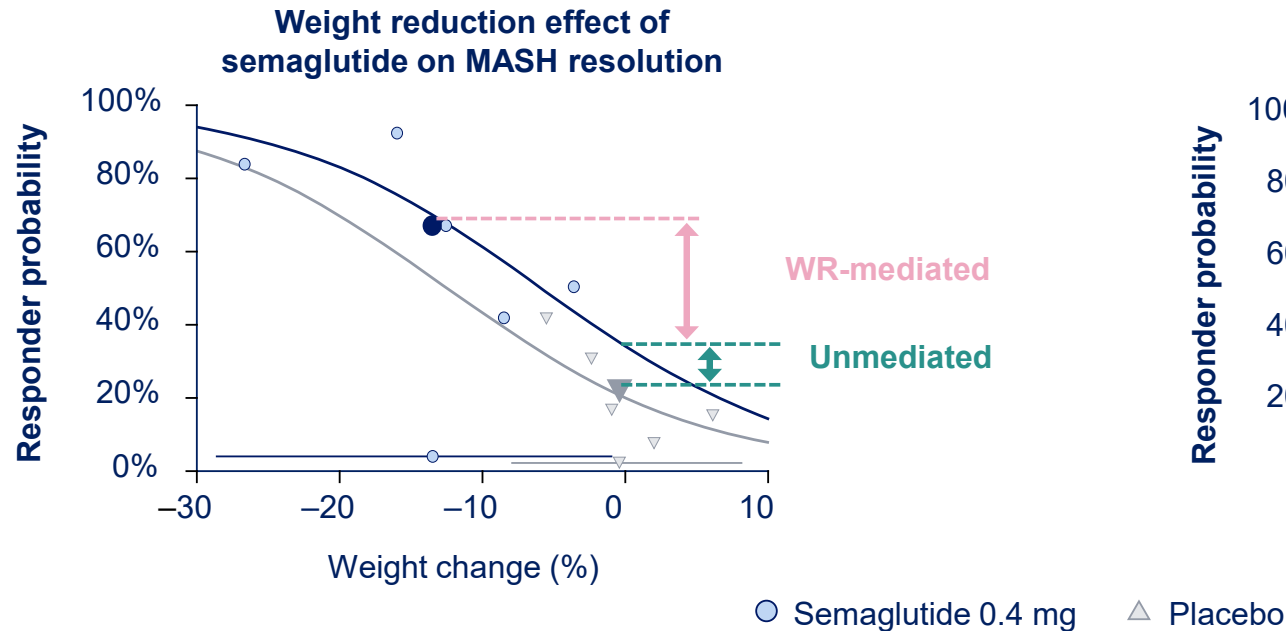
CI, confidence interval; EDP, estimated difference in responder proportions; ETD, estimated treatment difference.

Sanyal AJ, Newsome PN et al. *N Engl J Med* 2025;392:2089–2099.

Presented at AASLD, 7–11 November 2025, Washington, DC, USA.

Weight-independent effects of liraglutide and semaglutide

Treatment and change in body weight (kg)	OR (95% CI)	p value
Liraglutide ¹	4.12 (0.66, 25.88)	0.131



SomaScan identified 26 proteins for which there was no association between body weight reduction and MASH resolution²

1. Armstrong MJ et al. *Lancet* 2016;387:679–690; 2. Jara M et al. *Nat Med* 2025;31:3128–3140.
 CI, confidence interval; MASH, metabolic dysfunction-associated steatohepatitis; OR, odds ratio; WR, weight reduction.
 Presented at AASLD, 7–11 November 2025, Washington, DC, USA.

Figure adapted from Jara M et al. *Nat Med* 2025;31:3128–3140.

Aim 1

A post hoc analysis of the ESSENCE trial to evaluate the magnitude of body weight reduction on liver outcomes

The analyses assessed histologic and NIT response endpoints

MASH-related histologic and NIT endpoints

Resolution of steatohepatitis with no worsening of liver fibrosis

Change from baseline in **ALT**

Change from baseline in **FAST** score

Fibrosis-related histologic and NIT endpoints

Improvement in liver fibrosis with no worsening of steatohepatitis

Change from baseline in **VCTE LSM**

Change from baseline in **ELF** score

- Histologic and NIT responses at week 72 were stratified by body weight reduction thresholds ($\leq 2\%$, 2-5%, $\leq 5\%$, 5-7%, $\leq 7\%$ and $> 7\%$)

Analyses were based on complete case data using the full analysis set (interim) and the on-treatment observation period.

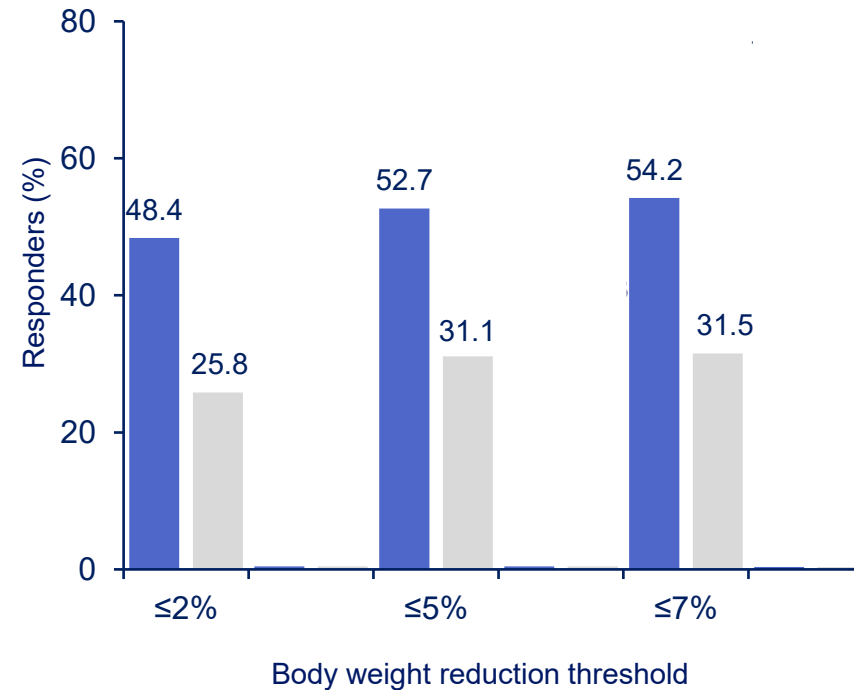
ALT, alanine aminotransferase; ELF, Enhanced Liver Fibrosis; FAST, FibroScan®-aspartate aminotransferase; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test; VCTE, vibration-controlled transient elastography.

Presented at AASLD, 7–11 November 2025, Washington, DC, USA.

Improvements in MASH-related histologic and NIT responses were observed across all body weight reduction thresholds

MASH-related endpoints according to defined body weight reduction thresholds

Resolution of steatohepatitis
with no worsening of liver fibrosis



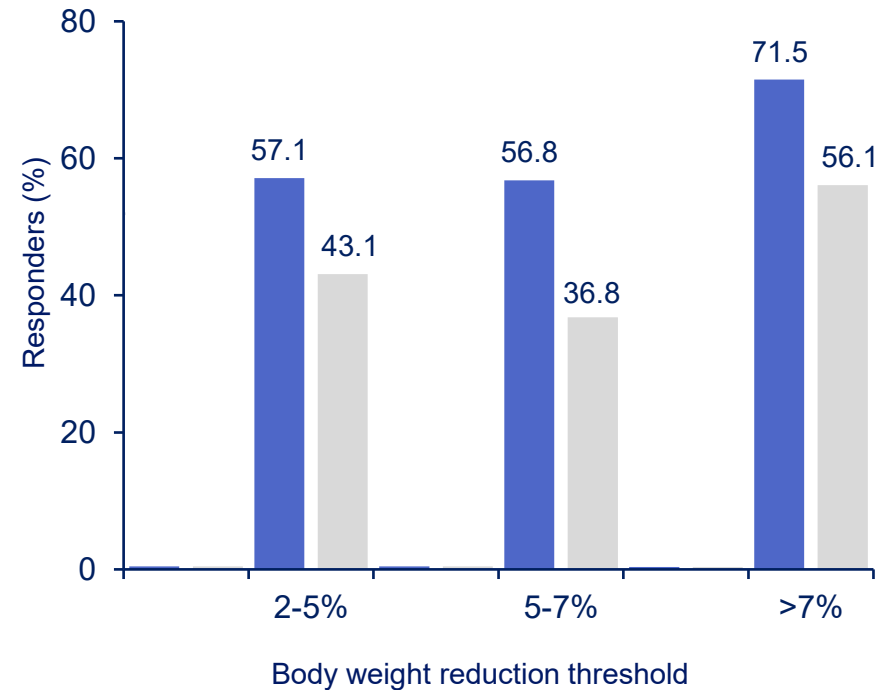
■ Semaglutide 2.4 mg ■ Placebo

n= 52 128 104 185 164 204

Improvements in MASH-related histologic and NIT responses were observed across all body weight reduction thresholds

MASH-related endpoints according to defined body weight reduction thresholds

Resolution of steatohepatitis with no worsening of liver fibrosis

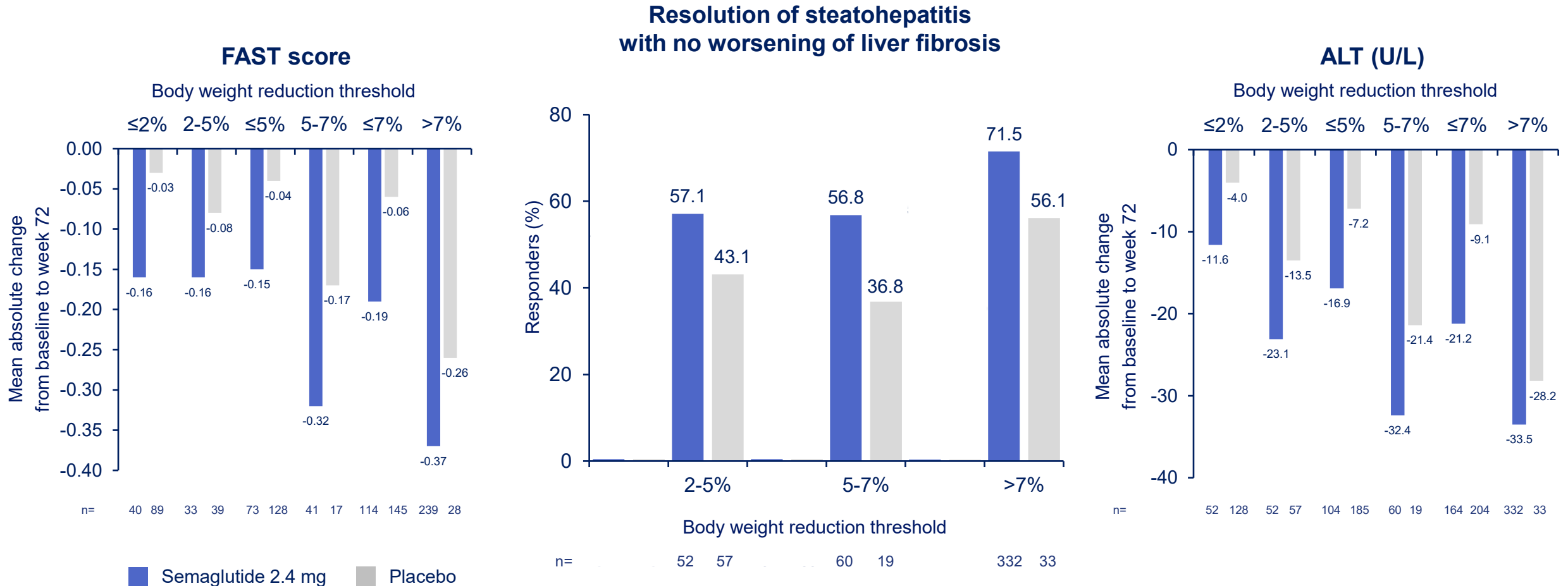


■ Semaglutide 2.4 mg ■ Placebo

n= 52 57 60 19 332 33

Improvements in MASH-related histologic and NIT responses were observed across all body weight reduction thresholds

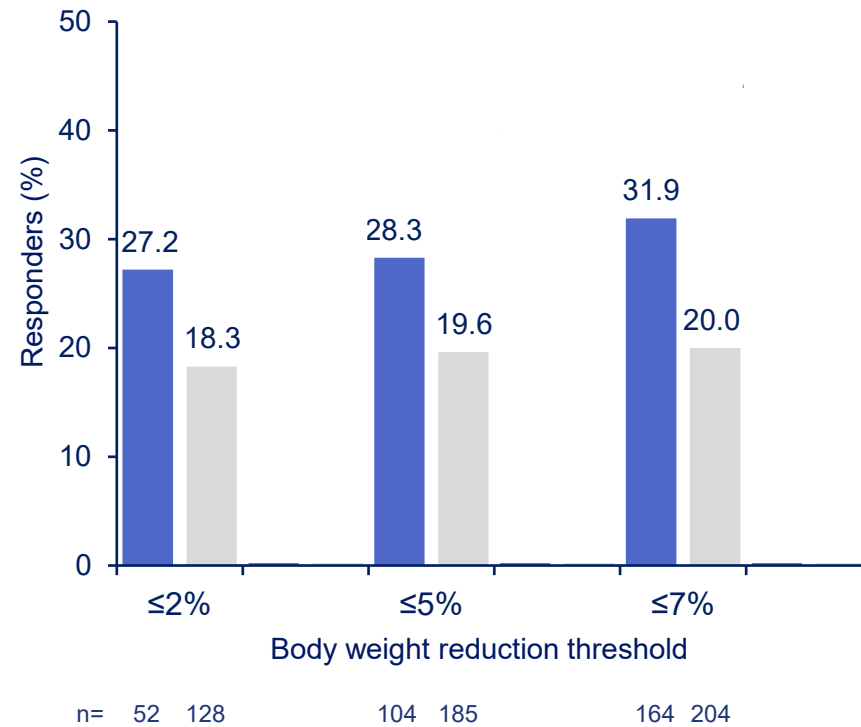
MASH-related endpoints according to defined body weight reduction thresholds



Improvements in fibrosis-related histologic and NIT responses were observed across all body weight reduction thresholds

Fibrosis-related endpoints according to defined body weight reduction thresholds

Improvement in liver fibrosis without worsening of steatohepatitis

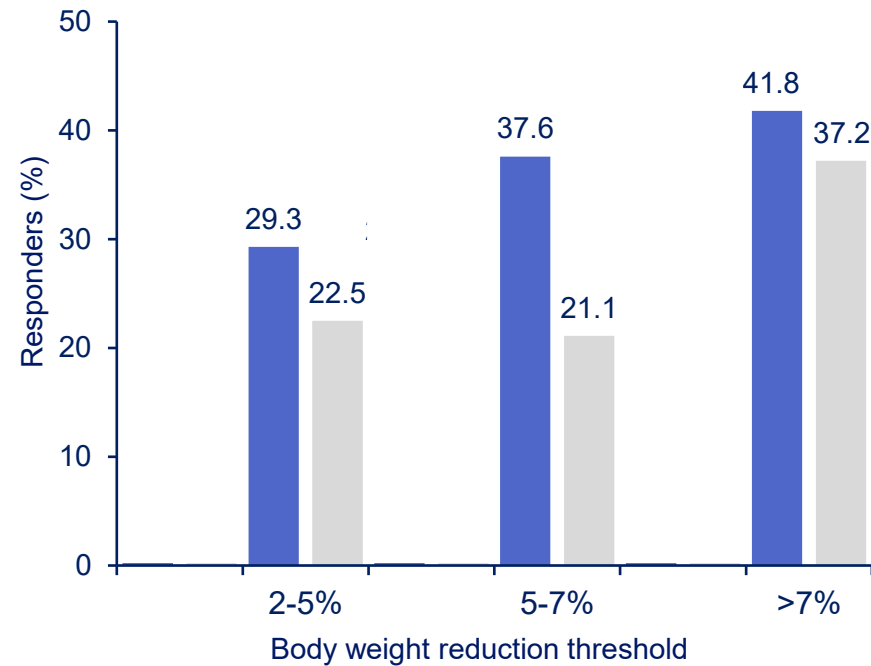


■ Semaglutide 2.4 mg ■ Placebo

Improvements in fibrosis-related histologic and NIT responses were observed across all body weight reduction thresholds

Fibrosis-related endpoints according to defined body weight reduction thresholds

Improvement in liver fibrosis without worsening of steatohepatitis



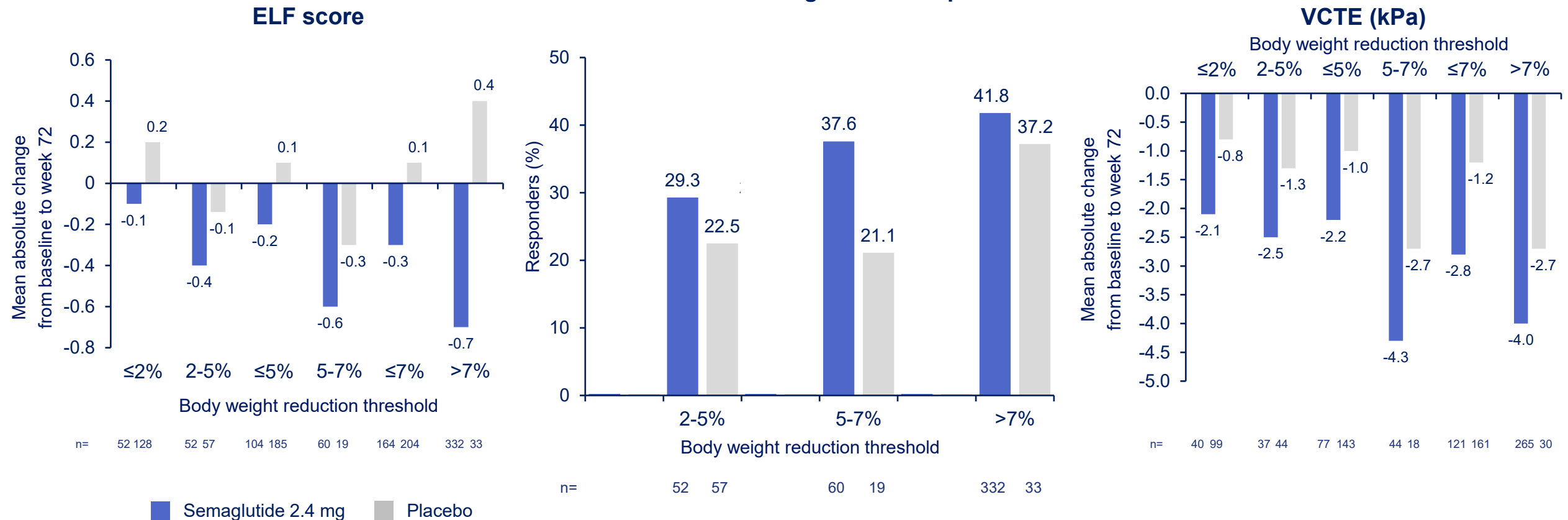
n= 52 57 60 19 332 33

■ Semaglutide 2.4 mg ■ Placebo

Improvements in fibrosis-related histologic and NIT responses were observed across all body weight reduction thresholds

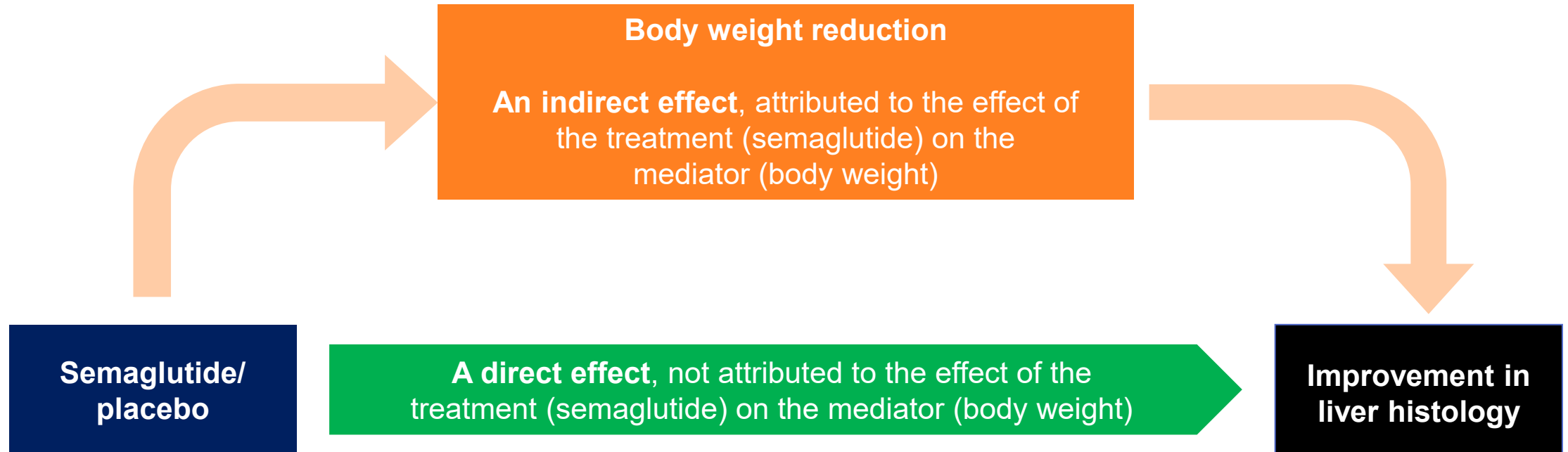
Fibrosis-related endpoints according to defined body weight reduction thresholds

Improvement in liver fibrosis without worsening of steatohepatitis



Aim 2

Mediation analysis: To what extent is the efficacy of semaglutide on MASH liver parameters mediated through body weight reduction?



All endpoints were assessed using Medflex R package with treatment as exposure and percentage body weight reduction from baseline to week 72, baseline T2D status and fibrosis stage as covariates using an underlying logistic regression. The total and body weight reduction-independent and -dependent effect sizes were calculated as natural effects ORs. Analyses were based on complete case data using the full analysis set (interim) and the on-treatment observation period.

The analyses assessed histologic and NIT responder endpoints

Mediation analysis

MASH-related histologic and NIT responder endpoints

Resolution of steatohepatitis with no worsening of liver fibrosis

Change in **ALT**
(≥ 17 -unit reduction)¹

Change in **FAST** score
(≥ 0.22 reduction)²

Fibrosis-related histologic and NIT responder endpoints

Improvement in liver fibrosis with no worsening of steatohepatitis

Change in **VCTE LSM**
($\geq 30\%$ reduction)³

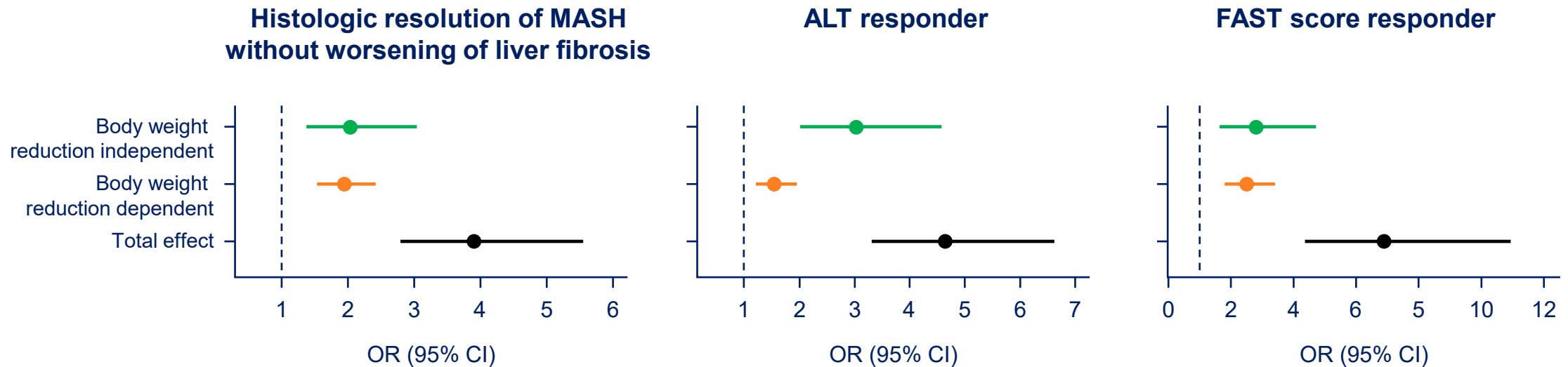
Change in **ELF** score
(≥ 0.5 -unit reduction)⁴

ALT, alanine aminotransferase; ELF, Enhanced Liver Fibrosis; FAST, FibroScan®-aspartate aminotransferase; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test; VCTE, vibration-controlled transient elastography.

1. Nouredin M et al. *Clin Gastroenterol Hepatol* 2024;22:2367–2377; 2. Wong VW-S et al. *eClinicalMedicine* 2023;66:102310; 3. Lin H et al. *JAMA* 2024;331:1287–1297; 4. Gee M. Siemens Healthineers. 2023. <https://www.forumresearch.org/storage/documents/LiverForum14/Session2/2.2%20gee%20-%20nits%20and%20treatment%20reponse%20elf%20vs.%202.pdf> (accessed May 2025).

Presented at AASLD, 7–11 November 2025, Washington, DC, USA.

The effect of semaglutide on MASH-related histologic and NIT responder endpoints is only partially mediated by body weight reduction



Data are based on the full analysis set from the on-treatment observation period. All endpoints were assessed for body weight reduction-independent effects (where the change in the outcome is not attributed to the effect of the treatment [semaglutide] on the mediator [body weight]) and body weight reduction-dependent effects (where the change in the outcome is attributed to the effect of the treatment on the mediator [body weight reduction]). Effects were considered statistically significant if the lower bound of the CI exceeded 1.0.

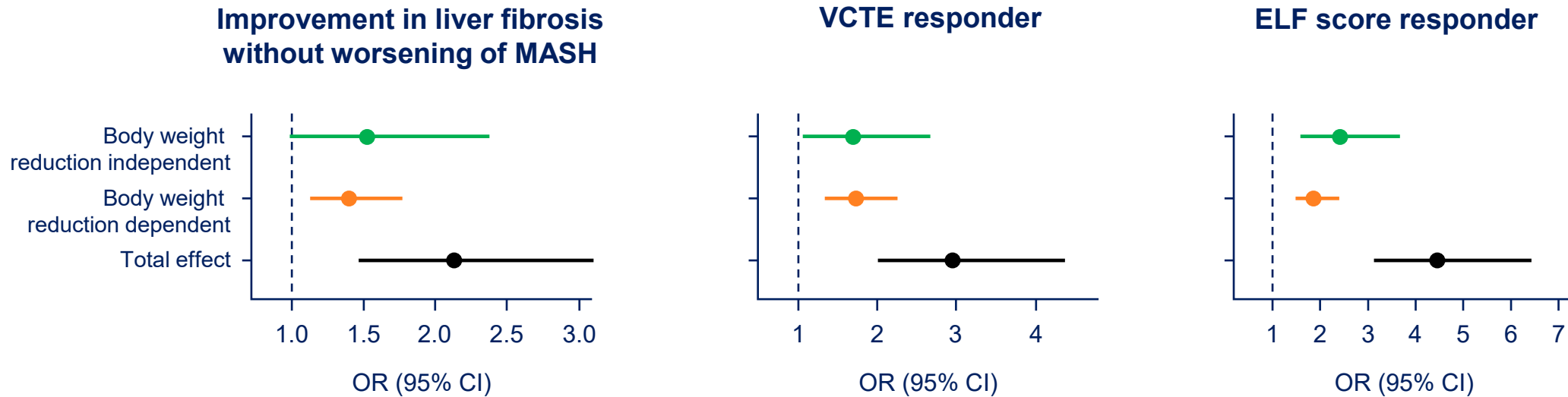
Responder definitions: ALT reduction of ≥ 17 U/L, FAST score reduction of ≥ 0.22 and histologic resolution of MASH (NAS 0 for ballooning and 0–1 for inflammation).

ALT, alanine aminotransferase; CI, confidence interval; FAST, FibroScan[®]-aspartate aminotransferase; MASH, metabolic dysfunction-associated steatohepatitis;

NAS, non-alcoholic fatty liver disease activity score; OR, odds ratio.

Presented at AASLD, 7–11 November 2025, Washington, DC, USA.

The effect of semaglutide on fibrosis and related NIT responder endpoints is only partially mediated by body weight reduction



Data are based on the full analysis set from the on-treatment observation period. All endpoints were assessed for body weight reduction-independent effects (where the change in the outcome is not attributed to the effect of the treatment [semaglutide] on the mediator [body weight]) and body weight reduction-dependent effects (where the change in the outcome is attributed to the effect of the treatment on the mediator [body weight reduction]). Effects were considered statistically significant if the lower bound of the CI exceeded 1.0.

Responder definitions: VCTE LSM reduction of 30%, ELF score reduction of ≥ 0.5 units, and ≥ 1 fibrosis stage improvement.

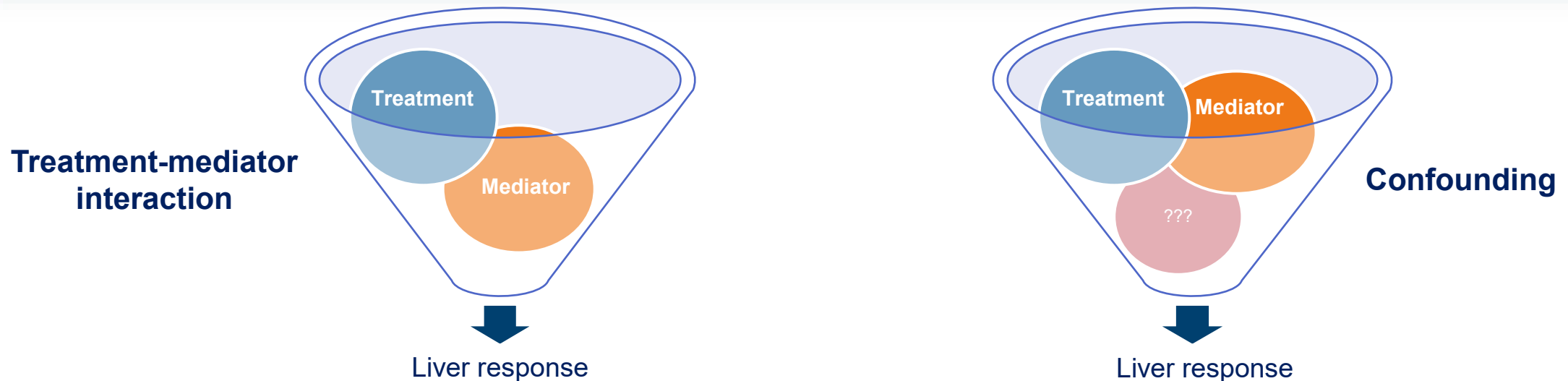
CI, confidence interval; ELF, Enhanced Liver Fibrosis; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; OR, odds ratio;

VCTE, vibration-controlled transient elastography.

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Limitations

- ❖ Mediation analyses attempt to quantify the extent to which measured risk factors (e.g. body weight) may mediate treatment effects in outcomes
- ❖ Interaction and confounding effects may hinder the interpretation of a mediation analysis
- ❖ Mediation analyses are exploratory; they may support hypotheses, but will not provide conclusive evidence
- ❖ In the current work:
 - ❖ Not many people on placebo lost large amounts of weight
 - ❖ Model needs assumptions to be fulfilled, some of which are not testable
 - ❖ Confounding and interactions may hinder interpretation



Conclusions

- ❖ People with MASH receiving semaglutide demonstrate improvements in liver health-related parameters even at low levels of weight reduction
- ❖ For a similar amount of weight reduction, people with MASH receiving semaglutide have greater improvements in liver parameters compared with those receiving placebo
- ❖ Liver health-related benefits seen with semaglutide are not driven solely by weight reduction

Acknowledgements

Thanks to the following:

- The trial participants and their relatives
- The clinical investigators, site staff and the Global Expert Panel members
- All personnel involved in the ESSENCE trial