Improvements in liver histology and non-invasive tests are independent of baseline BMI in participants with obesity and MASH: A *post hoc* analysis of the ESSENCE trial

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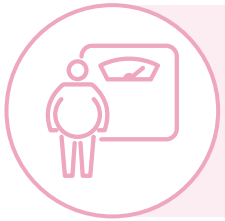
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Background and aim



The ESSENCE trial is investigating once-weekly semaglutide 2.4 mg versus placebo in participants with biopsy-defined MASH and liver fibrosis stage 2–3: 87% (694/800) met regulatory guidance thresholds for obesity pharmacotherapy[†1]



As overweight/obesity and MASH frequently coexist and share important metabolic drivers, and adiposity may influence disease burden and treatment response, evaluation of semaglutide in participants with BMI ≥27 kg/m^2 is clinically relevant



We examined the efficacy and safety of semaglutide across baseline BMI strata in participants with BMI ≥27 kg/m^2

[†]BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one cardiometabolic risk factor.
BMI, body mass index; MASH, metabolic dysfunction-associated steatohepatitis.
1. Sanyal AJ et al. *N Engl J Med* 2025;392:2089–2099.

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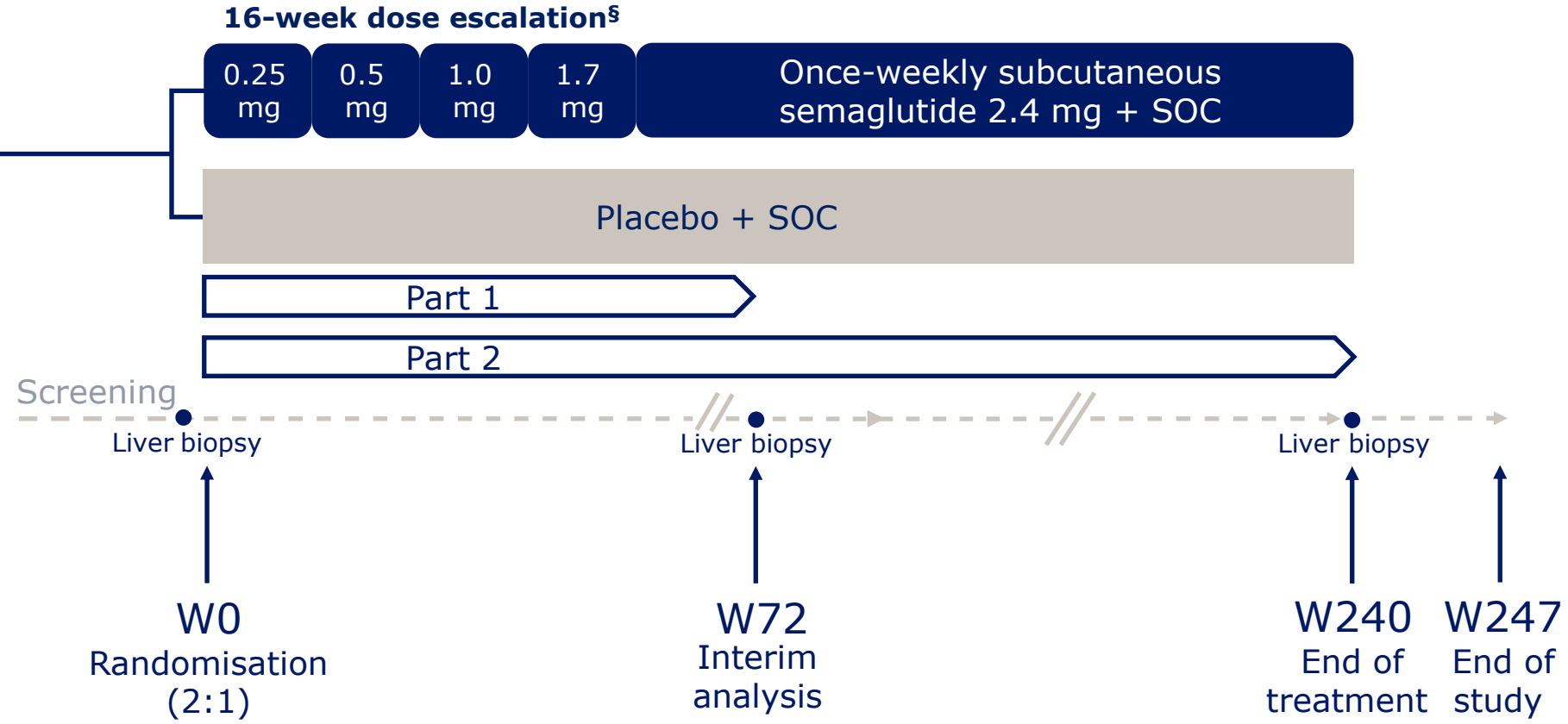
ESSENCE study design[1]

Key inclusion criteria

- Aged ≥18 years
- Histological evidence of fibrosis stage 2 or 3†
- NAS ≥4‡

Key exclusion criteria

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



†According to NASH Clinical Research Network classification; ‡With a score of ≥1 for steatosis, lobular inflammation and hepatocyte ballooning, based on central pathologist evaluation; §Up-titration every 4 weeks. One or more dose steps can be prolonged, or the dose can be lowered if the current dose is not tolerated; If the designated target dose of once-weekly subcutaneous semaglutide 2.4 mg is not tolerated, patients may stay at a lower dose.
GLP-1RA, glucagon-like peptide-1 receptor agonist; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; SOC, standard of care; W, week.
1. Sanyal AJ et al. *N Engl J Med* 2025;392:2089–2099.

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Methods

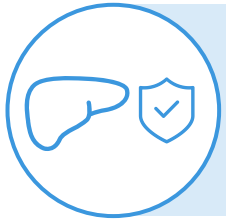


Post hoc analysis of week 72 responses to the following:

- Primary histological endpoints of resolution of steatohepatitis with no worsening of fibrosis and improvement in liver fibrosis with no worsening of steatohepatitis
- ELF score decrease of ≥0.5 units
- VCTE decrease of ≥30%



Continuous NIT results (ALT, ELF, FAST and VCTE) were evaluated using estimated treatment differences or ratios for semaglutide versus placebo



Endpoints, including safety, were assessed in participants with baseline BMI ≥27 kg/m^2, who were further stratified into BMI categories (≥27–<35, ≥35–<40 and ≥40 kg/m^2)

ALT, alanine aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis; FAST, FibroScan-AST; NIT, non-invasive test; VCTE, vibration-controlled transient elastography.

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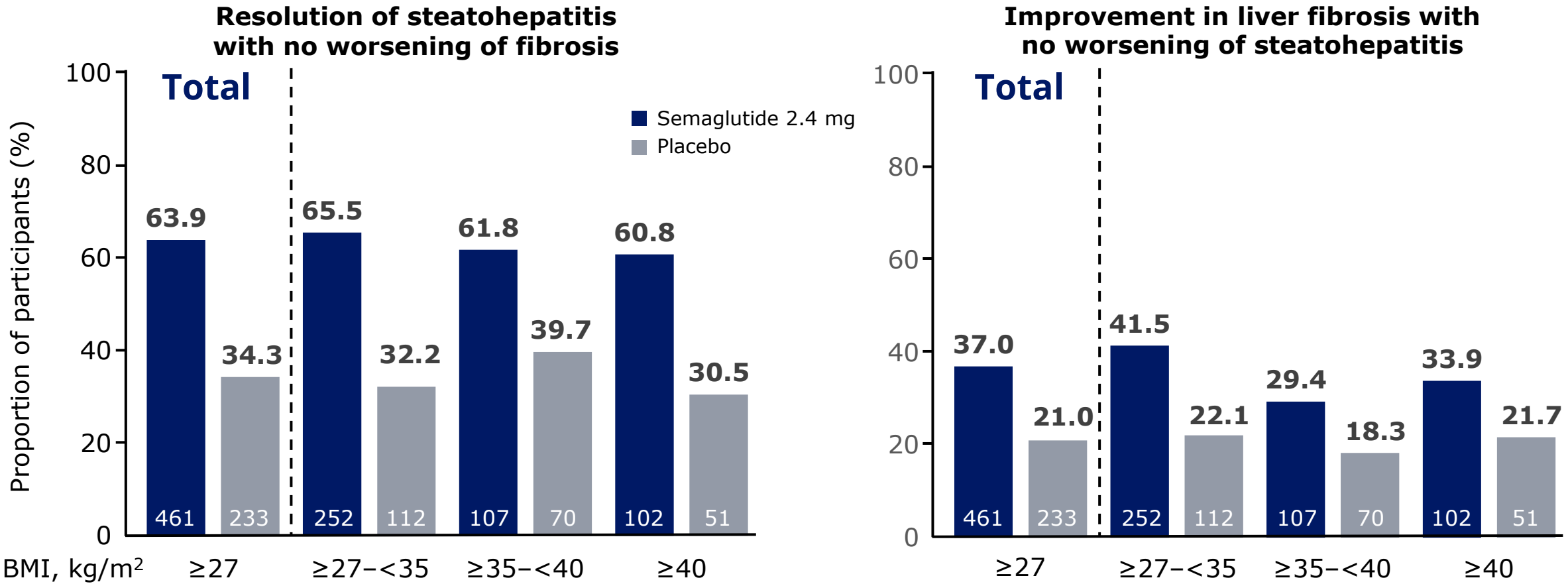
Baseline characteristics

	BMI ≥27–<35 kg/m²		BMI ≥35–<40 kg/m²		BMI ≥40 kg/m²	
	Semaglutide 2.4 mg (n=252)	**Placebo (n=112)**	**Semaglutide 2.4 mg (n=107)**	**Placebo (n=70)**	**Semaglutide 2.4 mg (n=102)**	**Placebo (n=51)**
Age, years	58.0 (10.3)	56.6 (11.8)	53.6 (10.9)	54.5 (10.9)	50.4 (12.0)	51.4 (12.7)
Sex, female, n (%)	141 (56.0)	62 (55.4)	56 (52.3)	38 (54.3)	61 (59.8)	27 (52.9)
T2D, n (%)	146 (57.9)	70 (62.5)	56 (52.3)	37 (52.9)	52 (51.0)	30 (58.8)
HbA_{1c}, %						
With T2D	7.1 (1.0)	6.9 (1.1)	7.5 (1.1)	6.7 (0.8)	7.1 (1.6)	7.3 (1.1)
Without T2D	5.8 (0.4)	5.8 (0.4)	5.8 (0.5)	5.9 (0.6)	5.9 (0.6)	6.0 (0.4)
Body weight, kg	86.2 (12.4)	86.3 (12.6)	107.5 (13.8)	105.4 (15.0)	126.9 (22.1)	131.1 (18.5)
BMI, kg/m²	31.2 (2.2)	31.4 (2.2)	37.3 (1.4)	37.4 (1.4)	45.7 (5.6)	46.1 (4.3)
Fibrosis stage, n (%)						
2	79 (31.3)	34 (30.4)	34 (31.8)	20 (28.6)	37 (36.3)	20 (39.2)
3	173 (68.7)	78 (69.6)	73 (68.2)	50 (71.4)	65 (63.7)	31 (60.8)

Data shown are mean (SD), unless otherwise stated.
BMI, body mass index; HbA_{1c}, glycated haemoglobin; SD, standard deviation; T2D, type 2 diabetes.

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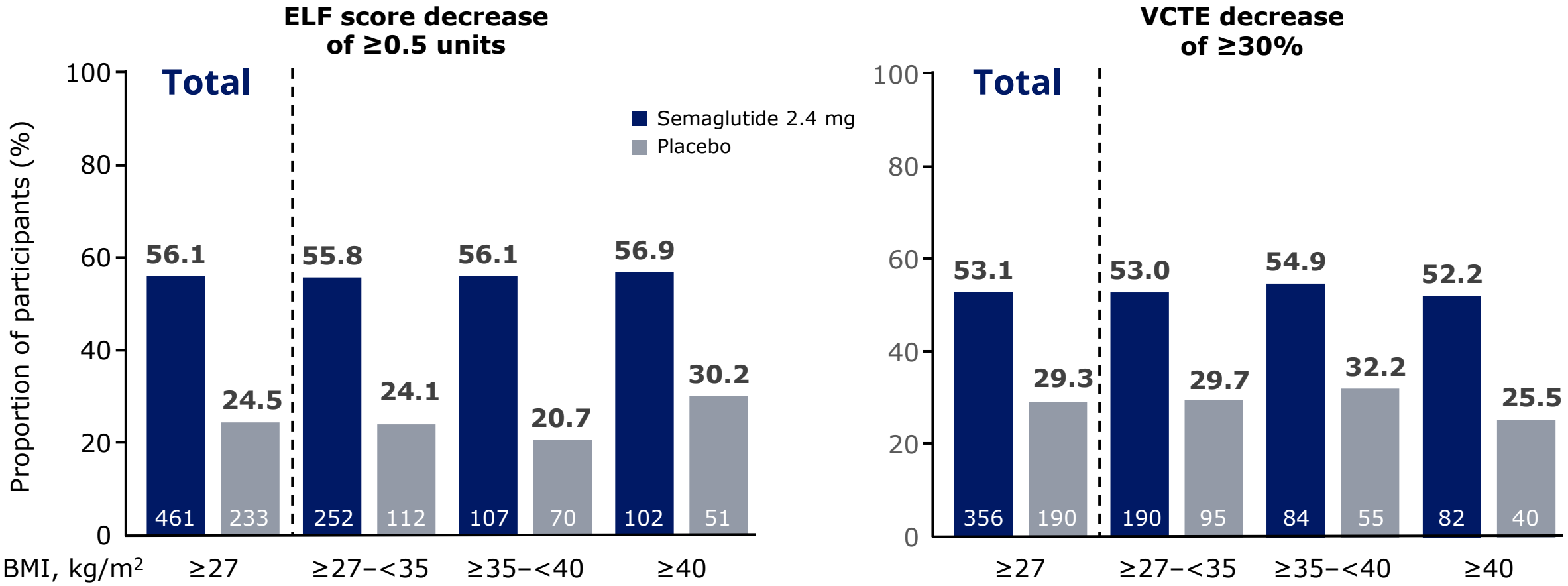
Semaglutide improved histological response rates versus placebo regardless of baseline BMI



Cochran-Mantel-Haenszel test stratified by baseline diabetes status and baseline fibrosis stage.
Data shown are the proportion of participants with histological response at week 72. Response rates are model-based estimates incorporating multiple imputation for missing data.
Number of participants in each group are indicated at the base of each bar.
BMI, body mass index.

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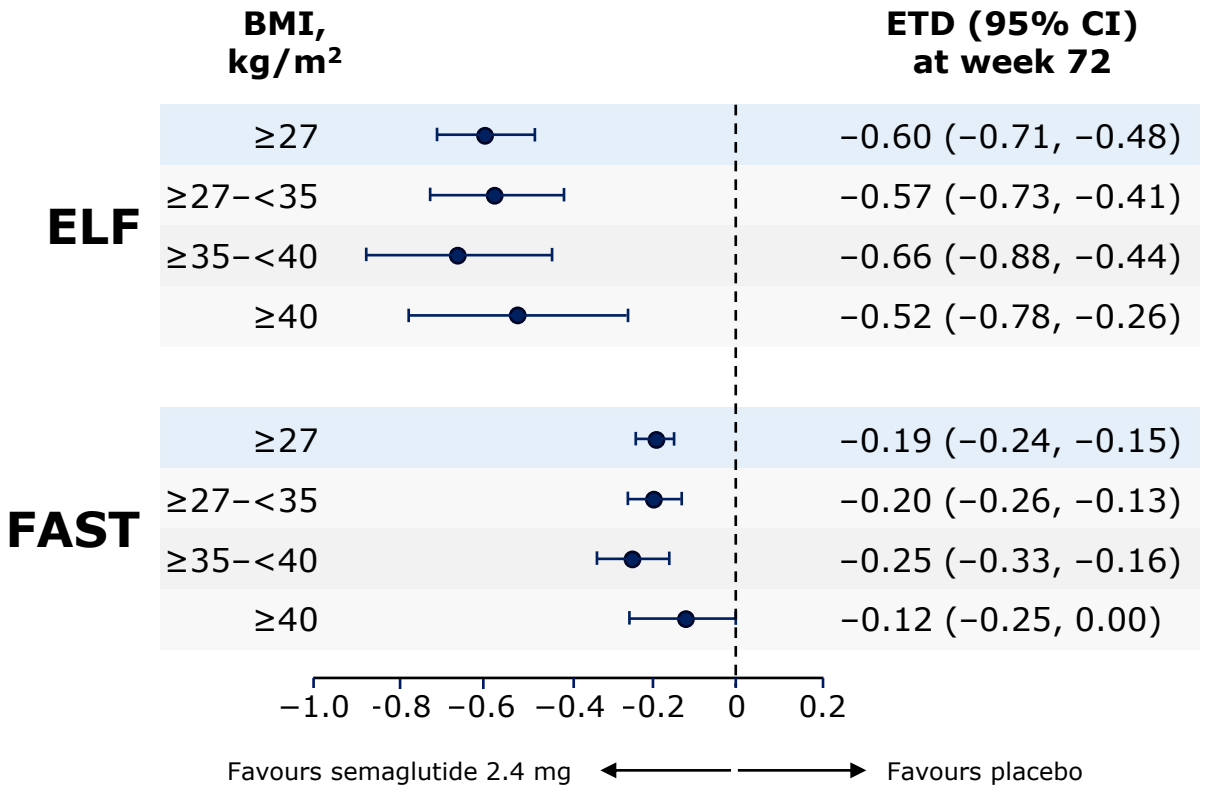
Semaglutide improved fibrosis-related NIT results versus placebo regardless of baseline BMI

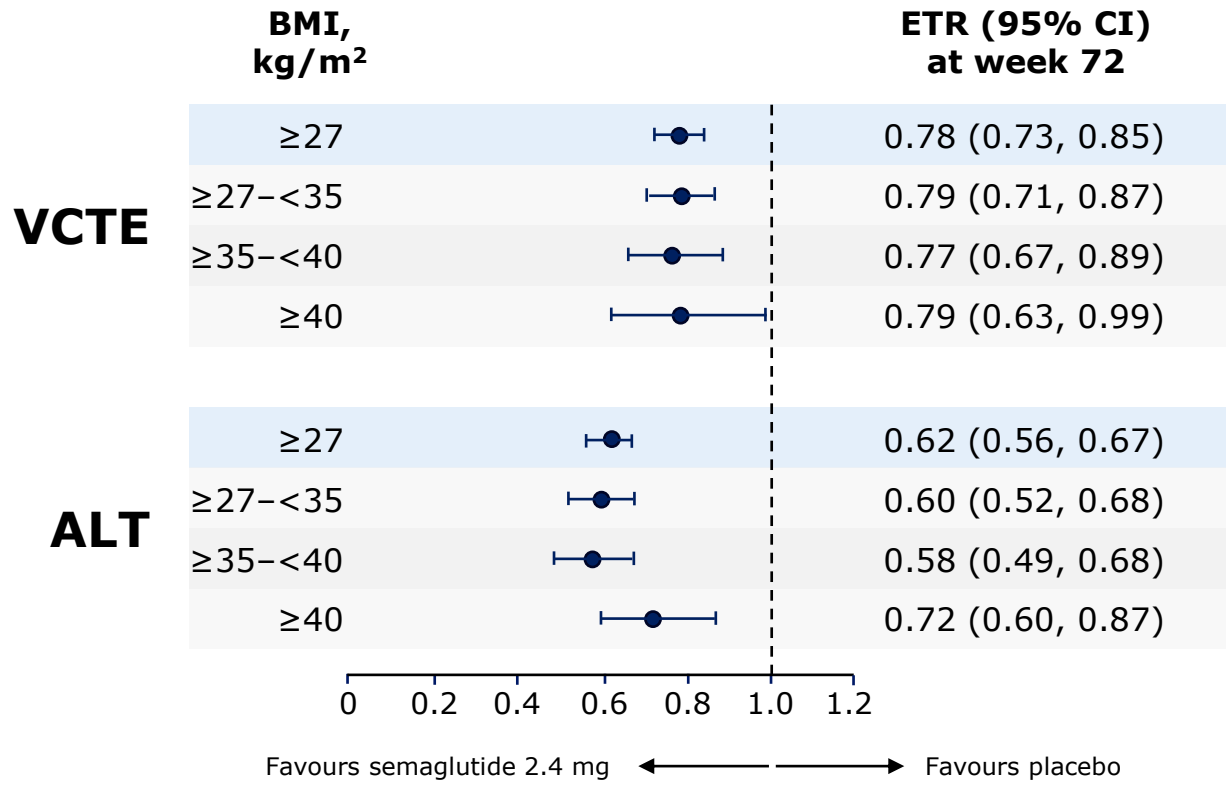


Data shown are the proportion of participants with NIT response at week 72. Response rates are model-based estimates incorporating multiple imputation for missing data.
Number of participants in each group are indicated at the base of each bar.
BMI, body mass index; ELF, Enhanced Liver Fibrosis; NIT, non-invasive test; VCTE, vibration-controlled transient elastography.

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Effects of treatment on NITs favoured semaglutide across all BMI categories

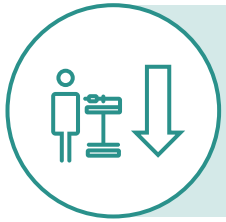




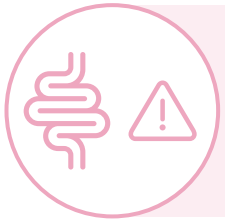
VCTE was evaluated at sites with available FibroScan® equipment.
Data are based on ANCOVA with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors and baseline parameter as covariates.
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; ELF, Enhanced Liver Fibrosis; ETD, estimated treatment difference; ETR, estimated treatment ratio; FAST, FibroScan-AST; NIT, non-invasive test; VCTE, vibration-controlled transient elastography.

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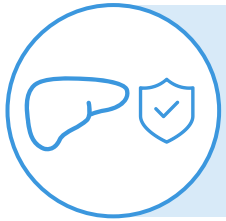
Semaglutide provided substantial weight reduction with a consistent safety profile across BMI categories



Mean body weight decreased by 10.4% with semaglutide treatment versus 2.2% with placebo in participants with BMI ≥27 kg/m^2, consistent with the total ESSENCE population



The safety profile of semaglutide was generally consistent across baseline BMI categories; the most frequent adverse events were gastrointestinal



Liver-related adverse events were uncommon with semaglutide irrespective of baseline BMI

BMI, body mass index.

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Conclusions



Semaglutide 2.4 mg treatment increased rates of MASH resolution and fibrosis improvement versus placebo across baseline BMI categories (≥27–<35, ≥35–<40 and ≥40 kg/m^2), including in participants with class III obesity (≥40 kg/m^2)



Consistent improvements in non-invasive fibrosis measures, including ELF score and VCTE-measured liver stiffness, and a consistent safety profile were observed with semaglutide treatment across the baseline BMI categories



Participants with BMI <27 kg/m^2 are being evaluated in a separate analysis

BMI, body mass index; ELF, Enhanced Liver Fibrosis; MASH, metabolic dysfunction-associated steatohepatitis; VCTE, vibration-controlled transient elastography.

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