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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Introduction and aim

- The ESSENCE trial is evaluating once-weekly semaglutide 2.4 mg versus placebo in participants with biopsy-defined metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis stage 2–3: 87% (694/800) met regulatory guidance thresholds for obesity pharmacotherapy (body mass index [BMI] ≥30 kg/m^2 or BMI ≥27 kg/m^2 with ≥1 cardiometabolic risk factor).[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.
- This analysis evaluated the efficacy and safety of semaglutide across baseline BMI strata in participants with BMI ≥27 kg/m^2.

Methods

- *Post hoc* analysis evaluating 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.
  - Enhanced Liver Fibrosis (ELF) score decrease of ≥0.5 units.
  - Liver stiffness measurement by vibration-controlled transient elastography (VCTE) decrease of ≥30%.
- Continuous non-invasive test endpoints included alanine aminotransferase (ALT), ELF score, FibroScan-AST (FAST) score and VCTE, with treatment effects for semaglutide versus placebo expressed as estimated treatment differences or ratios.
- Endpoints, including safety, were evaluated 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).

Results

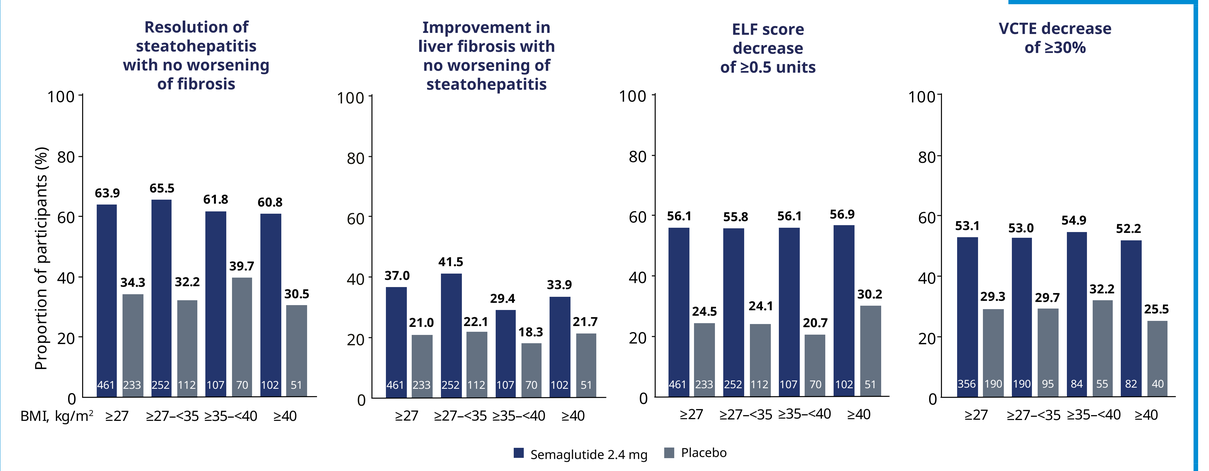
- Baseline characteristics were generally balanced across treatment arms within each BMI category, with participants exhibiting a high prevalence of type 2 diabetes (51.0–62.5%) and advanced fibrosis (stage 3: 60.8–71.4%) (**Table 1**).
- Semaglutide 2.4 mg increased histological response rates versus placebo across all baseline BMI categories at week 72 (**Figure 1**).
  - Response rates were consistently higher with semaglutide than with placebo for both resolution of steatohepatitis with no worsening of fibrosis and improvement in fibrosis with no worsening of steatohepatitis.
- Semaglutide 2.4 mg also increased the proportions of participants with an ELF score decrease of ≥0.5 units and a VCTE decrease of ≥30%, irrespective of baseline BMI (**Figure 1**).

Table 1. Baseline characteristics

	BMI ≥27–<35 kg/m^2		BMI ≥35–<40 kg/m^2		BMI ≥40 kg/m^2	
	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)
HbA_{1c} (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/m^2	31.2 (2.2)	31.4 (2.2)	37.3 (1.4)	37.4 (1.4)	45.7 (5.6)	46.1 (4.3)
Waist circumference, cm	106.0 (8.0)	106.7 (9.7)	119.9 (8.4)	119.2 (9.0)	132.0 (12.8)	133.2 (11.6)
Fibrosis stage 2, n (%)	79 (31.3)	34 (30.4)	34 (31.8)	20 (28.6)	37 (36.3)	20 (39.2)
Fibrosis stage 3, n (%)	173 (68.7)	78 (69.6)	73 (68.2)	50 (71.4)	65 (63.7)	31 (60.8)

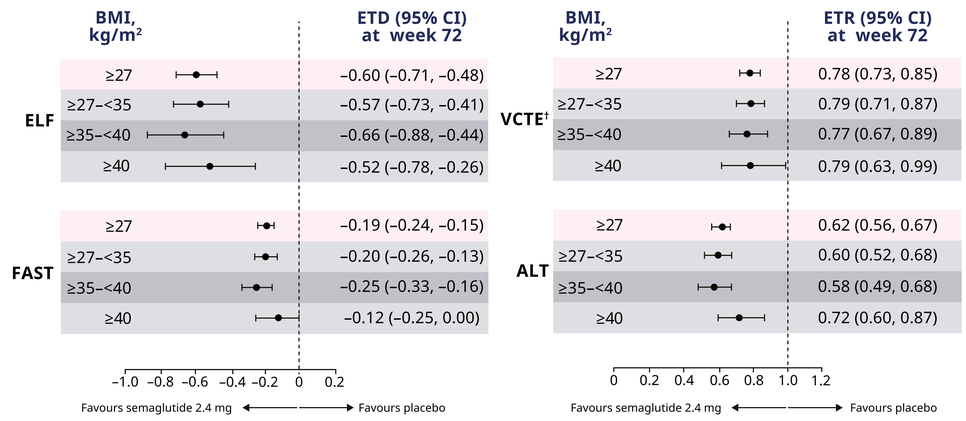
Data shown are mean (SD) unless otherwise stated.
BMI, body mass index; HbA_{1c}, glycated haemoglobin; SD, standard deviation; T2D, type 2 diabetes.

Figure 1. Semaglutide improved histological and fibrosis-related NIT response rates versus placebo



Data shown are the proportion of participants with histological and fibrosis-related 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.

Figure 2. Treatment effects on NITs favoured semaglutide across all BMI categories



†Evaluated at sites with available FibroScan® equipment.
Data are based on ANCOVA analysis 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.

Key results

- Continuous analyses similarly favoured semaglutide across BMI categories for ELF, FAST, VCTE and ALT, with generally consistent treatment effects (**Figure 2**).
- Mean body weight decreased by 10.4% with semaglutide 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.

Conclusions

- Semaglutide 2.4 mg increased rates of MASH resolution and fibrosis improvement versus placebo across baseline BMI categories (≥27–<35, ≥35–<40 and ≥40 kg/m^2), including participants with class III obesity (≥40 kg/m^2).
- Consistent improvements in non-invasive fibrosis measures, including ELF score and VCTE liver stiffness, and a consistent safety profile were observed with semaglutide across baseline BMI categories.
- Participants with BMI <27 kg/m^2 are being evaluated in a separate analysis.

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(**1**) Sanyal AJ et al. *N Engl J Med* 2025;392:2089–2099.