**Weight-independent benefits of semaglutide on histology and non-invasive tests in participants with biopsy-defined MASH: *Post hoc* analysis of the ESSENCE trial part 1**

**Aim**: In this *post hoc* analysis of the phase 3 ESSENCE trial (NCT04822181), we assessed the weight dependency of the effects of semaglutide 2.4 mg on study endpoints (non-invasive tests (NIT)s and histology) after 72 weeks, using weight loss-independent and -dependent pathways as covariates.

**Methods:** NITs and biopsies were assessed at baseline and week 72. MASH-related NIT responder endpoints were change in alanine aminotransferase (ALT; ≥17-unit reduction) and FibroScan-aspartate aminotransferase (FAST) score (≥0.22 reduction). Fibrosis-related NIT responder endpoints were change in vibration-controlled transient elastography (VCTE) liver stiffness measurement (30% reduction) and Enhanced Liver Fibrosis (ELF) score (≥0.5-unit reduction). Histologic endpoints included resolution of MASH and improvement in fibrosis. All endpoints were assessed using logistic regression at week 72 with treatment as exposure, % weight loss from baseline to week 72 as mediator, and baseline T2D status, fibrosis stage, and body weight as covariates. The total and weight loss-independent and -dependent effect sizes were calculated as odds ratios (ORs), and missing data were omitted. All data are based on the full analysis set from the on-treatment observation period.

**Results:** For MASH-related endpoints, the total effect (OR [95% confidence interval (CI)]) for ALT, FAST score and resolution of MASH without worsening of fibrosis was 4.7 (3.3, 6.6), 6.9 (4.3, 10.9) and 3.9 (2.8, 5.5), respectively. ORs (95% CI) for the weight loss-independent effect were 3.0 (2.0, 4.6), 2.8 (1.7, 4.7) and 2.0 (1.4, 3.0), respectively, and for the weight loss-dependent effect, the ORs (95% CI) were 1.5 (1.2, 2.0), 2.5 (1.8, 3.4) and 1.9 (1.6, 2.4), respectively. Overall, 71.9%, 53.3% and 51.9% of the total effect for ALT, FAST score and resolution of MASH, respectively, were not mediated by weight loss. For the fibrosis-related endpoints, the total effect (OR [95% CI]) for VCTE, ELF score and improvement in fibrosis without worsening of MASH were 3.0 (2.0, 4.4), 4.5 (3.1, 6.4) and 2.1 (1.5, 3.1), respectively. ORs (95% CI) for the weight loss-independent effect were 1.7 (1.1, 2.7), 2.4 (1.6, 3.7) and 1.5 (1.0, 2.4), respectively, and for the weight loss-dependent effect, the ORs (95% CI) were 1.7 (1.4, 2.2), 1.9 (1.5, 2.3) and 1.4 (1.1, 1.8), respectively. This shows that 48.9%, 58.5% and 55.5% of the total effect for VCTE, ELF score and fibrosis improvement, respectively, were not mediated by weight loss.

**Conclusion:** Semaglutide 2.4 mg improved MASH-related histological and NIT endpoints and fibrosis-related NIT endpoints through equal contributions of weight loss-independent and -dependent metabolic mechanisms, with effects beyond weight loss.

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