**Phase 3 ESSENCE Trial: Semaglutide in metabolic dysfunction-associated steatohepatitis (MASH)**

**Background:** Semaglutide is being investigated for its potential to treat metabolic dysfunction-associated steatohepatitis (MASH) in the phase 3 ESSENCE trial.

**Methods:** ESSENCE, an ongoing multi-center, phase 3 randomized, double-blind, placebo-controlled outcome trial involving 1200 participants with biopsy-defined MASH and fibrosis stage F2/F3, randomized participants 2:1 to once-weekly subcutaneous semaglutide 2.4 mg or placebo for 240 weeks. An interim analysis at week 72 of the first 800 randomized participants evaluated the trial’s primary endpoints: resolution of steatohepatitis with no worsening of liver fibrosis, and improvement in liver fibrosis with no worsening of steatohepatitis.

**Results:** Among participants (semaglutide [n=534] or placebo [n=266), mean (standard deviation [SD]) age was 56.0 (11.6) years and body mass index was 34.6 (7.2) kg/m2. Most participants were White (67.5%), female (57.1%) and 55.9% had type 2 diabetes at baseline; 31.3% had F2 and 68.8% had F3. Resolution of steatohepatitis with no worsening of fibrosis was achieved by 62.9% (semaglutide) vs 34.3% (placebo) of participants, with an estimated difference in responder proportions (EDP) of 28.7% (95% CI, 21.1 to 36.2; P<0.001). Improvement in liver fibrosis with no worsening of steatohepatitis was achieved by 36.8% (semaglutide) and 22.4% (placebo) (EDP, 14.4%; 95% CI, 7.5 to 21.3; P<0.001), while 32.7% (semaglutide) and 16.1% (placebo) achieved combined resolution of steatohepatitis with improvement in liver fibrosis (EDP, 16.5%; 95% CI, 10.2 to 22.8; P<0.001). There were improvements in liver enzymes, non-invasive fibrosis markers, body weight and cardiometabolic parameters. Incidence of serious adverse events in the safety analysis set was similar in both arms.

**Conclusions:** In participants with MASH and moderate to advanced liver fibrosis, semaglutide 2.4 mg demonstrated superiority vs placebo for improvement of histological activity and fibrosis markers, meeting both primary endpoints at 72 weeks. Semaglutide improved MASH injury and fibrosis biomarkers and cardiometabolic features.