The effect of semaglutide on liver enzymes in subjects with obesity and elevated alanine aminotransferase: data from a randomised phase 2 trial

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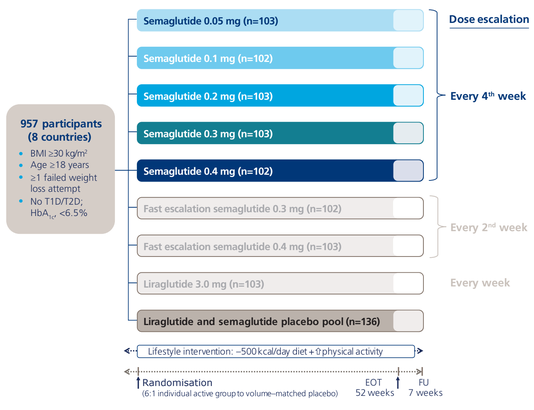
Background and Aims

- Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are a significant and increasing public health issue, linked with obesity, diabetes and the metabolic syndrome
- Glucagon-like peptide 1 (GLP-1) and its synthetic analogues exert multiple effects via a network of GLP-1 receptors in the brain, pancreas, gastrointestinal tract and elsewhere. GLP-1 analogues regulate glucose-dependent secretion of insulin and glucagon, and modulate satiety and appetite. They also have effects on the liver, inflammation and the heart via mechanisms that are still not fully understood
- Several GLP-1 analogues are approved for the treatment of type 2 diabetes (T2D) due to their effects on glucose homeostasis. One, liraglutide, is indicated both for T2D at a dose of 1.2 or 1.8 mg/day, and for weight management at 3.0 mg/day in combination with diet and exercise. At T2D dosing, liraglutide has been shown to promote histological resolution of NASH without worsening of fibrosis in a clinical study in subjects both with and without T2D[1]
- Semaglutide is a GLP-1 analogue with a significant beneficial effect on glycaemic control and cardiovascular events in T2D trials.[2–4] It is approved for T2D at doses up to 1.0 mg/week and is under clinical development for weight management at a higher dose
- Semaglutide has reduced elevated alanine aminotransferase (ALT) when used for T2D treatment in subjects with a high cardiovascular risk[5]
- A recent phase 2 dose-ranging study of semaglutide in subjects with obesity and without diabetes (NCT02453711) showed dose-dependent estimated mean weight losses between 6.0% and 13.8% after 52 weeks at semaglutide doses between 0.05 and 0.4 mg/day, versus 2.3% with placebo.[6] The effect of semaglutide treatment on high serum ALT in subjects from this study was evaluated in a *post-hoc* analysis

Methods

- The design of the study is shown in Figure 1. *Post-hoc* analyses are presented for the placebo pool and the five once-daily semaglutide dosing arms escalated every 4 weeks
- The baseline NAFLD Fibrosis Score (NFS)[7] and the Fibrosis-4 Index (FIB-4)[8] were calculated in the full cohort
- Subjects were categorised as having normal ALT or elevated ALT at baseline. Elevated ALT was defined as >30 U/L in men and >19 U/L in women[9]
- Changes from baseline in serum ALT were estimated by treatment group using a mixed model for repeated measurements (MMRM) on log-transformed data, with treatment, region and sex as fixed factors
  - Analyses were either adjusted or unadjusted for change from baseline body weight
  - Unadjusted analyses used log-transformed baseline ALT as the covariate, whereas adjusted analyses used log-transformed baseline ALT, body weight and change from baseline body weight as covariates. All parameters were nested within visit and subgroup of normal or elevated baseline ALT
- Changes from baseline in NFS were estimated by treatment group using the same MMRM model but on untransformed data and with baseline NFS as a covariate

Figure 1. NCT02453711 trial design.

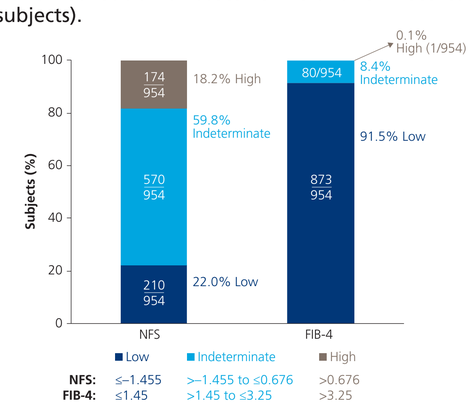


BMI, body mass index; EOT, end of treatment; FU, follow-up; T1D/T2D, type 1/type 2 diabetes.

Results

- Overall, 18% of subjects (174/954) with baseline data had a high NFS (>0.676), whereas only 0.1% (1/954) had a high FIB-4 index (>3.25) (Figure 2)
- Of 957 subjects enrolled and treated, 499 (52%) had elevated baseline ALT and 458 (48%) had normal ALT; their baseline characteristics are shown in Table 1
- Among those with elevated ALT at baseline, ALT reductions were seen over time on all doses of semaglutide but with no change seen in the placebo pool (Figure 3). There was an apparent trend towards dose dependent reductions, and the maximum reduction was generally achieved by week 28, which persisted for the remainder of the trial
- At week 52, subjects with elevated baseline ALT on semaglutide doses above 0.1 mg/day had statistically significant ALT reductions versus the placebo pool, while numerically lower reductions were seen for subjects with normal baseline ALT (Figure 4A). After adjusting for weight changes, the treatment ratios clustered around 1.0 (Figure 4B), indicating the contribution of weight reduction to the decline in ALT in a population with obesity without T2D
- Among those with high baseline ALT, between 25% and 46% of subjects across the five semaglutide dosing groups had normalised their ALT by week 52, versus 18% on placebo (Figure 5)
- Statistically significant decreases from baseline in mean NFS were observed at week 52 for semaglutide treatment versus placebo in both the elevated and normal ALT groups (Figure 6), whereas significant differences were not generally seen for changes in FIB-4 (data not shown)
- Semaglutide was generally well tolerated. Dose-related gastrointestinal events were the most common adverse events of therapy, as previously seen with GLP-1 receptor agonists

Figure 2. Distribution of baseline NFS and FIB-4 scores (all subjects).



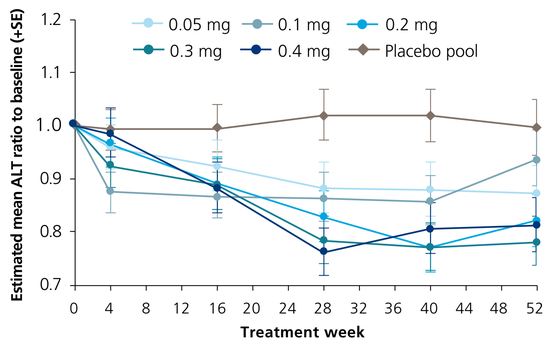
FIB-4, fibrosis-4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

Table 1. Baseline characteristics (all subjects).

All median (range) unless otherwise indicated	Subjects with elevated baseline ALT (n=499)	Subjects with normal baseline ALT (n=458)
Age, y	48 (18–76)	47 (19–86)
Male, n (%)	187 (37.5)	151 (33.0)
Weight, kg	106.9 (70.5–216.3)	107.8 (70.2–243.7)
BMI, kg/m²	37.4 (29.7–77.1)	37.9 (29.7–80.3)
HbA_{1c}, %	5.5 (4.3–6.6)	5.5 (4.2–7.0)
Total cholesterol, mmol/L	5.2 (2.7–9.7)	5.0 (2.6–10.3)
LDL-cholesterol, mmol/L	3.2 (1.1–6.2)	3.0 (0.8–7.2)
HDL-cholesterol, mmol/L	1.2 (0.5–2.4)	1.3 (0.7–2.9)
Triglycerides, mmol/L	1.6 (0.5–11.9)	1.4 (0.4–9.9)
ALT, IU/L	34 (20–313)	17 (3–30)
AST, IU/L	24 (12–272)	16 (8–62)
APRI	0.3 (0.1–3.4)	0.2 (0.1–0.9)
NFS	–0.71 (–4.70; 4.31)	–0.31 (–4.03; 4.66)
FIB-4	0.73 (0.14–3.31)	0.69 (0.19–2.52)

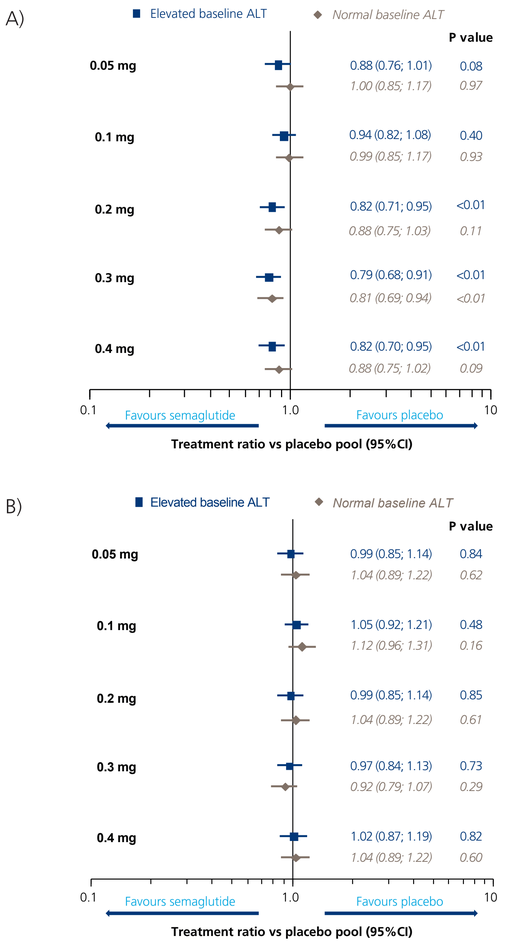
ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFS, Non-alcoholic fatty liver disease Fibrosis Score.

Figure 3. Ratio of on-treatment vs baseline ALT by semaglutide treatment group (subjects with elevated baseline ALT).



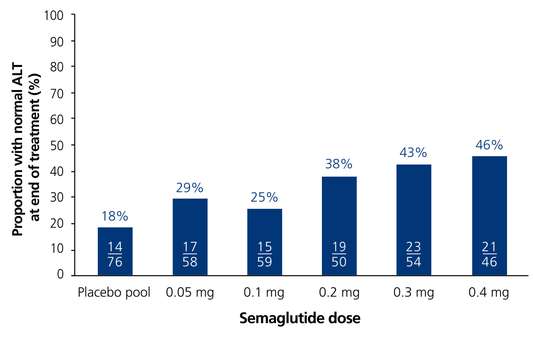
ALT, alanine aminotransferase; SE, standard error.

Figure 4. Treatment vs placebo ratio for change in ALT from baseline to week 52, unadjusted (panel A) or adjusted (panel B) for change in body weight from baseline.



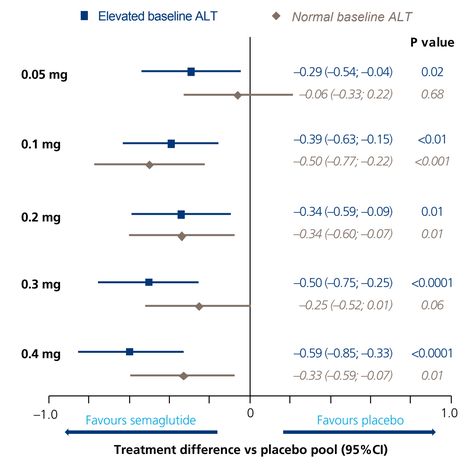
ALT, alanine aminotransferase; CI, confidence interval.

Figure 5. ALT normalisation at week 52 (end of treatment) among subjects with elevated baseline ALT.



ALT, alanine aminotransferase.

Figure 6. Treatment difference vs placebo pool for change in NFS from baseline to week 52.



CI, confidence interval; NFS, Non-alcoholic fatty liver disease Fibrosis Score.

Conclusions

- In this study of semaglutide for weight management, 52% of the subjects had elevated baseline ALT, and 18% were predicted to have or be at risk for NAFLD/NASH with advanced fibrosis by NFS result
- At week 52, semaglutide 0.2–0.4 mg/day reduced ALT vs placebo. Among those with elevated baseline ALT, 25–46% on semaglutide had normal ALT at week 52, vs 18% on placebo
- ALT reductions were associated with weight loss at week 52, although the data do not preclude the potential for a weight-independent effect. Further investigation is required
- Statistically significant reductions in NFS but not FIB-4 were noted on semaglutide. This may reflect the inclusion of body weight in the calculation of NFS but not FIB-4[7,8] The clinical significance of this NFS reduction is unknown
- These data suggest a potential role for semaglutide in the treatment of NAFLD/NASH. A development programme for semaglutide in NASH is currently underway

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