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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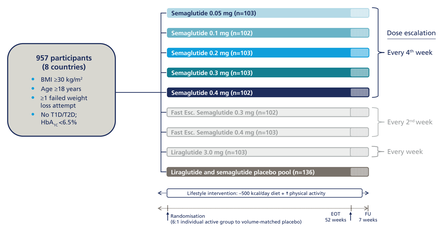
Aim

- 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: Trial design (NCT02453711)

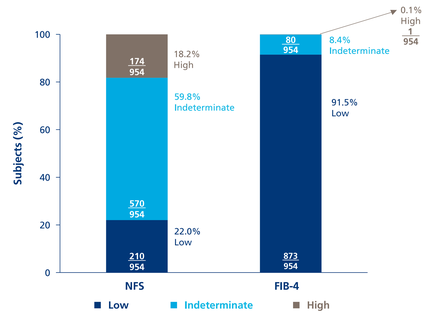


BMI, body mass index; EOT, end of treatment; FU, follow-up; T1D/T2D, type 1 or type 2 diabetes.

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 in ALT, 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 fibrosis scores (all subjects)



NFS:	≤–1.455	>–1.455 to ≤0.676	>0.676
FIB-4:	≤1.45	>1.45 to ≤3.25	>3.25

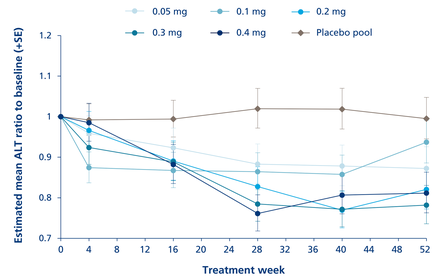
FIB-4, Fibrosis-4 Index; NFS, Non-alcoholic fatty liver disease Fibrosis Score.

Table 1: Baseline characteristics of subjects with elevated and normal baseline ALT

All median (range) unless otherwise indicated	Subjects with elevated baseline ALT (N=499)	Subjects with normal baseline ALT (N=458)
Age, years	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.

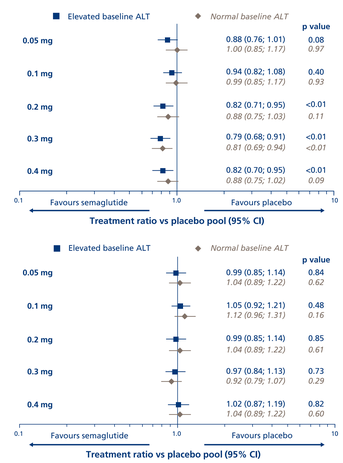
Figure 3: Ratio of on-treatment vs baseline ALT by semaglutide treatment group (subjects with elevated baseline ALT)



ALT, alanine aminotransferase; SE, standard error.

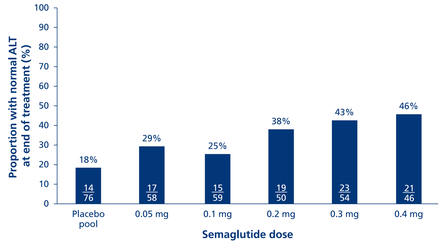
Figure 4: Treatment vs placebo ratio for change in ALT from baseline to week 52, unadjusted (A) or adjusted (B) for change in body weight from baseline

Key result



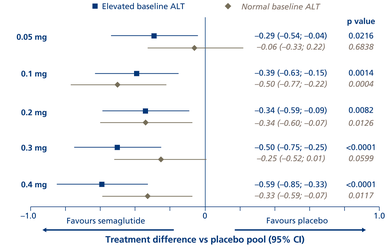
ALT, alanine aminotransferase; CI, confidence interval.

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.

Conclusion

- 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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References: (**1**) Armstrong MJ, et al. Lancet 2016;387:679–90. (**2**) Sorli C, et al. Lancet Diabetes Endocrinol 2017;5:51–60. (**3**) Ahren B, et al. Lancet Diabetes Endocrinol 2017;5:341–54. (**4**) Aroda VR, et al. Lancet Diabetes Endocrinol 2017;5:355–66. (**5**) Sanyal AJ, et al. Hepatology 2017; 66(suppl 1):1175A. (**6**) O'Neil PM, et al. Lancet 2018;392:637–49. (**7**) Angulo P, et al. Hepatology 2007;45:846–54. (**8**) Sterling RK, et al. Hepatology 2006; 43:1317–25. (**9**) Prati D, et al. Ann Intern Med 2002;137:1–10.