

Effect of semaglutide on liver measures and indices: Pooled analysis from the STEP UP trials

Eric Lawitz¹, W. Timothy Garvey², Christine Sofie Fuchs Jacobsen³, María Quiroga³,
Lauren Wilson⁴, Philip N. Newsome⁵

¹Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, USA; ²University of Alabama at Birmingham, Birmingham, AL, USA;

³Novo Nordisk A/S, Søborg, Denmark; ⁴Novo Nordisk Inc., Plainsboro, NJ, USA; ⁵King's College Hospital, London, UK.

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Background, aim, and baseline characteristics

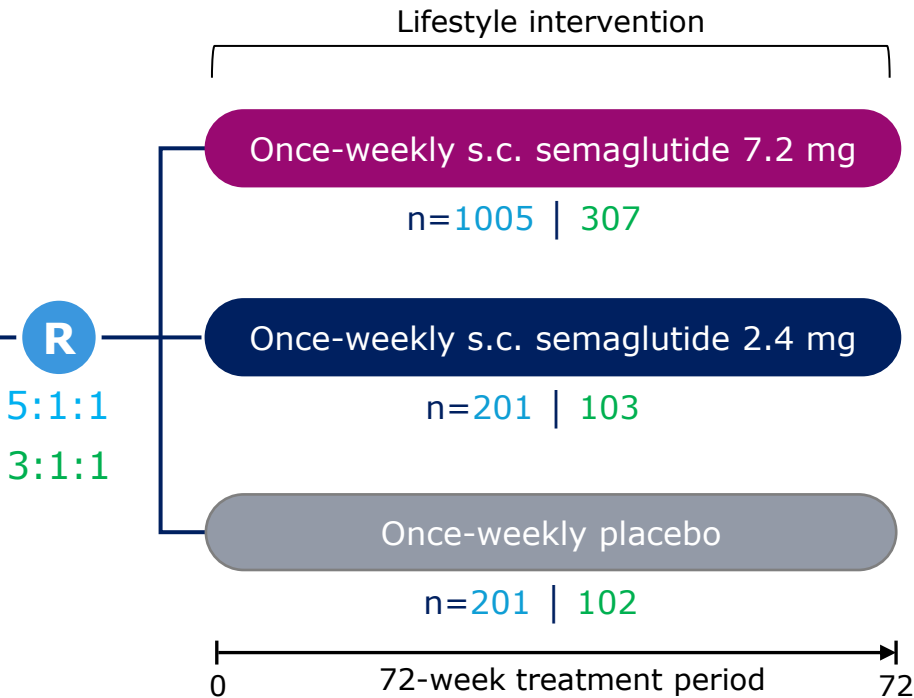
Trial designs

STEP UP¹ | STEP UP T2D²

Phase 3b, randomised, controlled, multinational, double-blind trials
(NCT05646706)
(NCT05649137)

1407 | 512 participants

- Adults with BMI ≥30 kg/m².
- Without diabetes | T2D (HbA_{1c} 7.0–10.0%).
- Evaluate the efficacy and safety of semaglutide 7.2 mg vs semaglutide 2.4 mg and placebo.

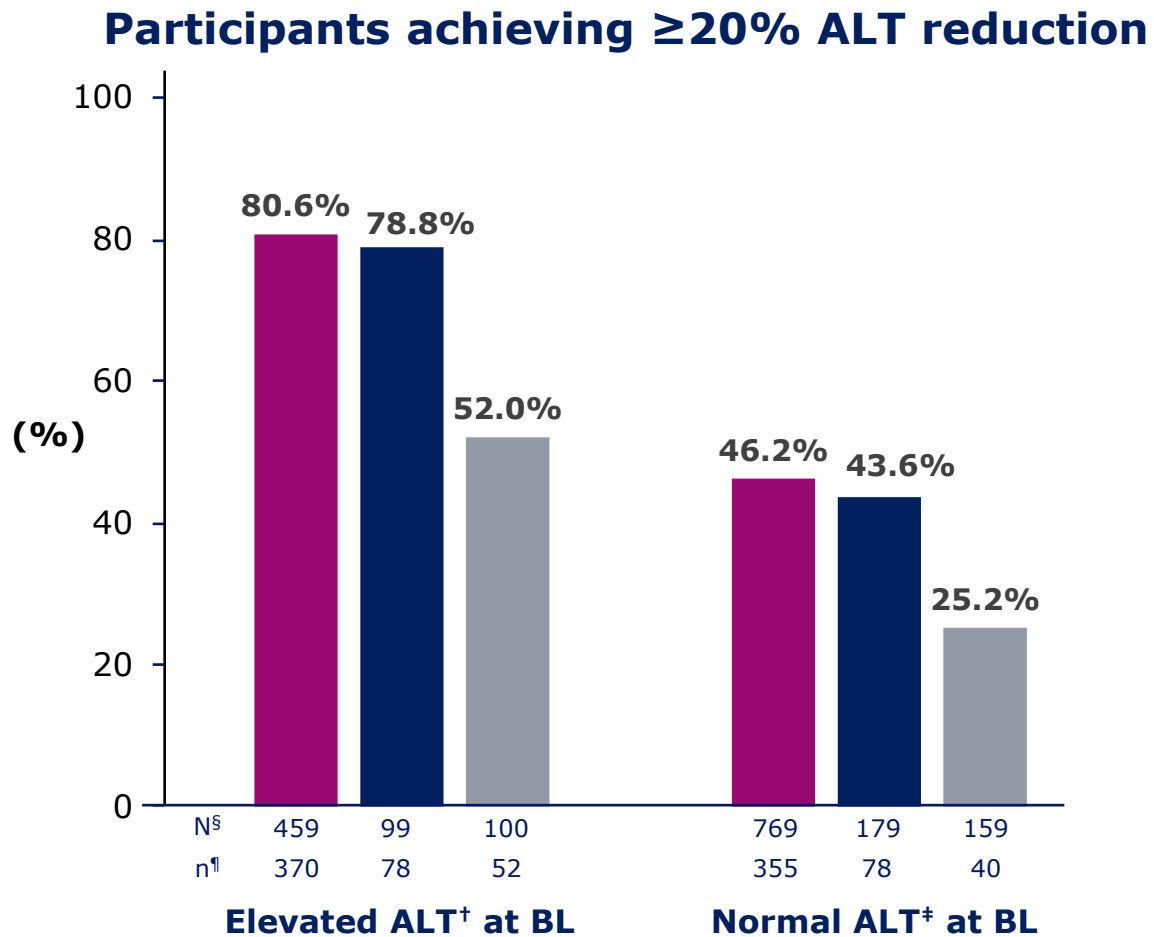
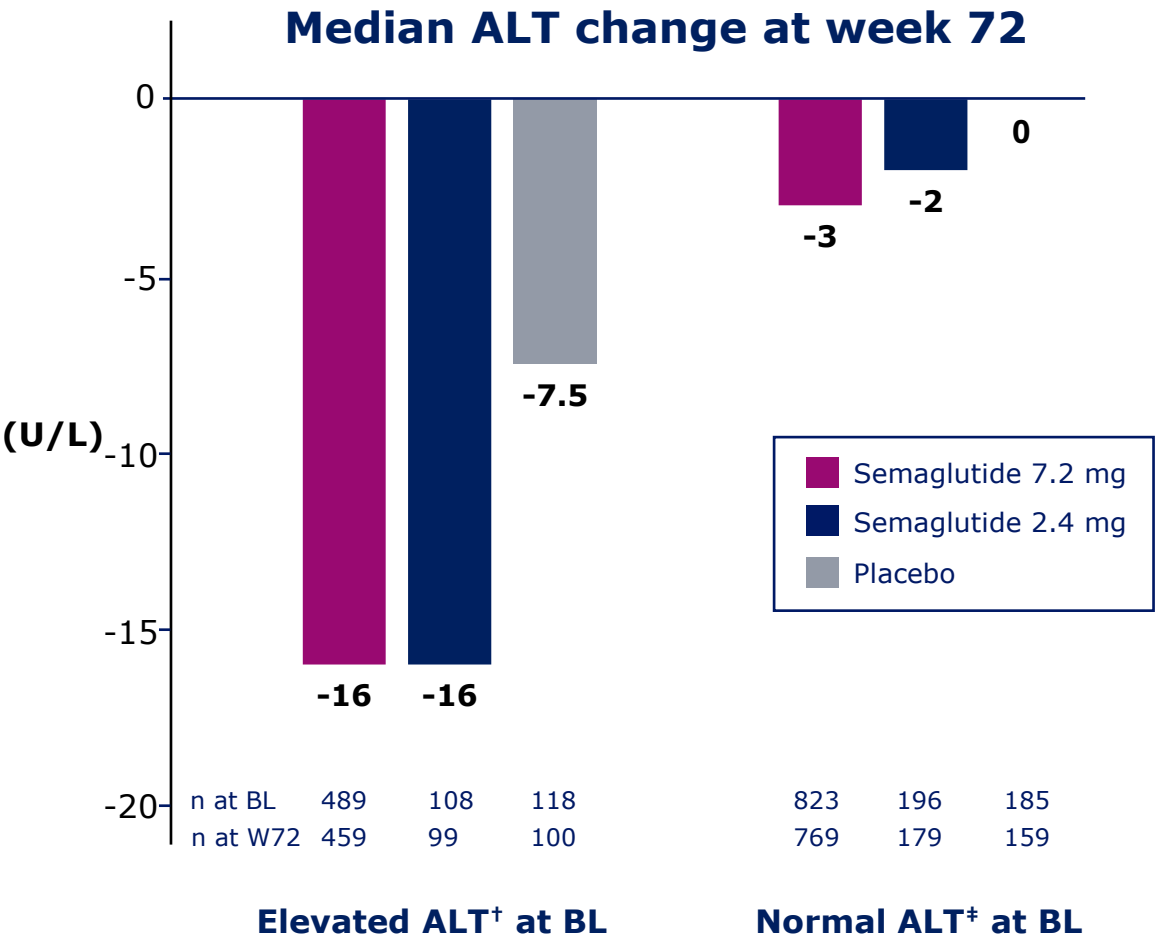


Aim: *Post hoc* analysis of pooled STEP UP and STEP UP T2D data to assess the effect of semaglutide on liver-related measures, including steatosis, across both trials

Baseline characteristics	Semaglutide 7.2 mg (n=1312)	Semaglutide 2.4 mg (n=304)	Placebo (n=303)
High risk of hepatic steatosis (FLI >60), n (%)	1239 (94.4)	289 (95.1)	294 (97.0)
High risk of advanced fibrosis (FIB-4 >2.67), n (%)	11 (0.8)	2 (0.7)	2 (0.7)

BMI, body mass index; FIB-4, fibrosis-4 index; FLI, fatty liver index; HbA_{1c}, glycated haemoglobin; R, randomisation; s.c., subcutaneous; T2D, type 2 diabetes.
1. Wharton S, et al. Lancet Diabetes Endocrinol 2025;13:949–963; 2. Lingvay I, et al. Lancet Diabetes Endocrinol 2025;13:935–948.

ALT improvements were greatest among participants with elevated baseline ALT, and rates of $\geq 20\%$ ALT reduction were higher with semaglutide versus placebo in both ALT strata



[†]Defined as ALT >35 U/L for males or >25 U/L for females; [‡]Defined as ALT $\leq$ 35 U/L for males or $\leq$ 25 U/L for females; [§]Participants with BL and W72 ALT measurements; [¶]Responders at week 72 ALT, alanine aminotransferase; BL, baseline; n/N, number; W, week.

Conclusions

- In this pooled, *post hoc* analysis of STEP UP and STEP UP T2D, semaglutide 7.2 mg and 2.4 mg reduced ALT and hepatic steatosis burden more than placebo over the 72-week treatment period.
- In STEP UP, liver fat measure by MRI was significantly reduced.
- These findings suggest a favourable impact of semaglutide on liver health, even in a population with a relatively low baseline burden of metabolic dysfunction-associated steatotic liver disease.

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Aim

- This analysis assessed the effect of semaglutide on liver-related measures, including steatosis, across both trials.

Introduction

- In STEP UP and STEP UP T2D, semaglutide 7.2 mg treatment led to greater weight reductions than semaglutide 2.4 mg and placebo; 20.7% versus 17.5% and 2.4% in participants with obesity (body mass index [BMI] ≥ 30 kg/m²) without diabetes,¹ and 14.1% versus 10.7% and 3.6% in those with obesity and type 2 diabetes,² respectively, based on the trial product estimand.

Methods

- In this post hoc analysis, observed in-trial data from STEP UP and STEP UP T2D were pooled.
- Pre-specified outcomes included change from baseline to week 72 in alanine aminotransferase (ALT), analysed overall and by baseline ALT status.
- Elevated ALT was defined as >35 U/L for male participants and >25 U/L for female participants; values at or below these thresholds were classified as normal ALT.
- ALT response was defined as a $\geq 20\%$ reduction in ALT from baseline to week 72.
- Additional outcomes included:
 - The proportion of participants achieving improvement in fatty liver index (FLI) risk category.
 - Change in percentage of liver fat determined by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) in a STEP UP subpopulation, with semaglutide groups pooled.
- All analyses were descriptive.

Results

- Across both trials, 1312, 304 and 303 participants received semaglutide 7.2 mg, semaglutide 2.4 mg and placebo, respectively (Figure 1).
- Baseline characteristics were comparable (female: 70.0%, 60.5% and 65.7%; mean body weight: 112.0, 113.3 and 112.3 kg; mean waist circumference: 119.2, 119.9 and 120.4 cm; mean BMI: 39.5 kg/m² in each group).
- At baseline, participants had similar liver enzyme values for ALT (29.3, 29.4, 29.3 U/L), most participants were classified as high risk of hepatic steatosis (FLI >60 ; 94.4%, 95.1%, 97.0%) and $<1\%$ met criteria for high risk of advanced fibrosis (fibrosis-4 index >2.67).
- At week 72, among participants with elevated baseline ALT, median ALT decreased by 16.0 U/L with semaglutide (7.2 mg and 2.4 mg) versus 7.5 U/L with placebo; a $\geq 20\%$ ALT reduction was achieved by 80.6% (7.2 mg), 78.8% (2.4 mg) and 52.0% (placebo) of participants (Figure 2).
- Among participants with FLI >60 at baseline, high-risk status improved to low or moderate risk in 42.9% with semaglutide 7.2 mg and 32.3% with 2.4 mg versus 10.7% with placebo (Figure 3).
- In the MRI-PDFF subpopulation ($n=40$), mean liver fat decreased from 8.8% to 3.1% by week 72; 88.5% of participants with hepatic steatosis ($>5\%$ liver fat) at baseline reached liver fat normalisation by week 72 (Figure 4).

Conclusions

- Semaglutide improved liver-related measures and steatosis in adults with obesity, with and without T2D, suggesting a favourable impact of semaglutide on liver health, even in a population with a relatively low baseline burden of metabolic dysfunction-associated steatotic liver disease.

Figure 1. Trial designs

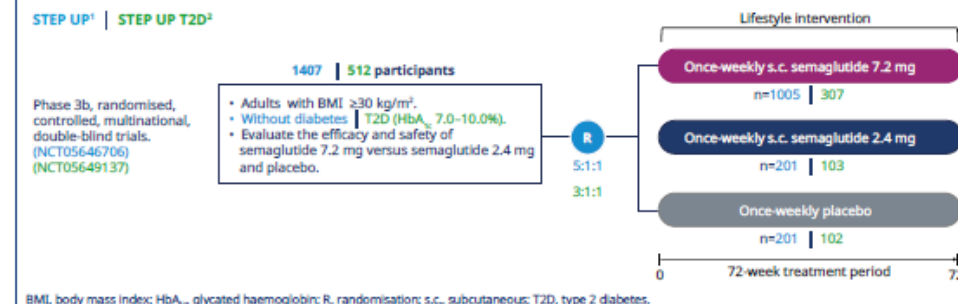
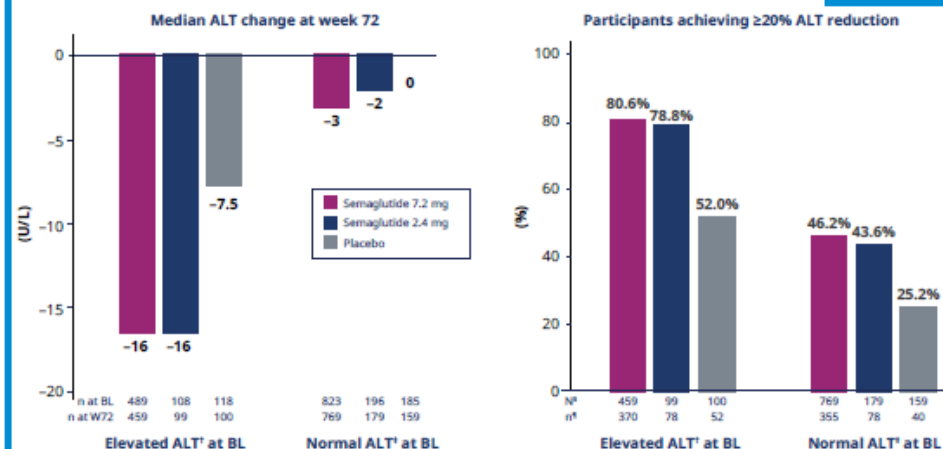


Figure 2. Median ALT reductions and response rates with semaglutide versus placebo by baseline ALT status



Key results

¹Defined as ALT ≥ 35 U/L for male participants or ≥ 25 U/L for female participants; ²Defined as ALT ≥ 35 U/L for male participants or ≥ 25 U/L for female participants; ³Participants with BL and W72 ALT measurements; ⁴Responders at week 72.

Figure 3. FLI risk category transitions among participants with FLI >60 at baseline

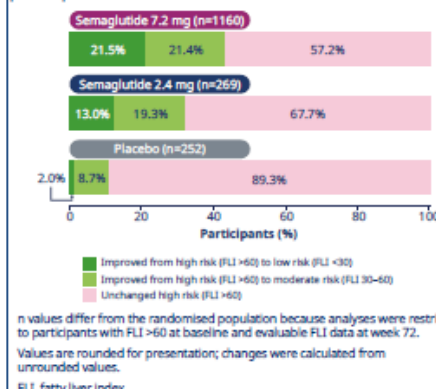


Figure 4. Mean change in liver fat percentage measured by MRI-PDFF

