Weight loss with liraglutide 3.0 mg vs. placebo for individuals who adhere to the trial drug: a secondary analysis from SCALE IBT

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Background

- The International Conference On Harmonisation (ICH) regulatory guidelines on quantifying treatment effects of medications have recently been updated with the introduction of estimands, with the aim of improving the planning, conduct, analysis and interpretation of clinical trials.[1]
- The objective of the SCALE IBT trial (ClinicalTrials.gov: NCT02963935) was to compare weight loss with liraglutide 3.0 mg to placebo, both in combination with intensive behaviour therapy (IBT).
- In SCALE IBT, the primary estimand was a 'treatment policy' estimand ('intention-to-treat' principle) and the secondary a 'hypothetical' estimand ('if all adhered' principle). A description of both is presented in Figure 1.

Aim

- In this pre-specified secondary analysis, based on the 'hypothetical' estimand, we sought to determine the expected effect of liraglutide 3.0 mg on weight loss, as compared to placebo, if all randomised individuals had adhered to trial product for 56 weeks.

Methods

- 282 individuals with obesity (body mass index ≥30 kg/m^2) were randomised (1:1) to 56 weeks of IBT (i.e. reduced caloric intake, increased physical activity [max target: 250 min/week], and 23 counselling sessions) combined with liraglutide 3.0 mg or placebo.
- Evaluation of treatment effect on body weight was based on the 'treatment policy' and 'hypothetical' estimands.
- Efficacy (if-all-adhered principle) was evaluated with two different approaches:
  - » The first approach (mixed model repeated measures [MMRM]) estimated the weight loss that would have been achieved if all individuals adhered to the trial product using information from individuals still on drug after the point of first discontinuation.
  - » The second approach (covariate) used a regression model to calculate the weight change of individuals with full adherence to trial product by including adherence as a moderator of the effect of trial product on weight change.

Results

- Over the trial period, of the 282 individuals randomised, 65 discontinued the trial product (28 liraglutide; 37 placebo). Of those 65, 16 resumed treatment (eight liraglutide; eight placebo) and completed the trial (Table 1).
  - » Time to first treatment discontinuation is shown in Figure 2.
- Based on the 'treatment policy' estimand, placebo-subtracted weight loss was 3.5% (95% confidence interval [CI]: –5.3;–1.6; *p*=0.0003), favouring liraglutide (Figure 3).
- With regard to the 'hypothetical' estimand, the MMRM approach yielded a placebo-subtracted weight loss of 4.59% (95% CI: –6.54;–2.64; *p*<0.0001) (Figure 3) and the covariate approach yielded a placebo-subtracted weight loss of 4.63% (95% CI: –6.45;–2.81) (*p*<0.0001), with both estimates favouring liraglutide 3.0 mg (Figure 4).

Discussion

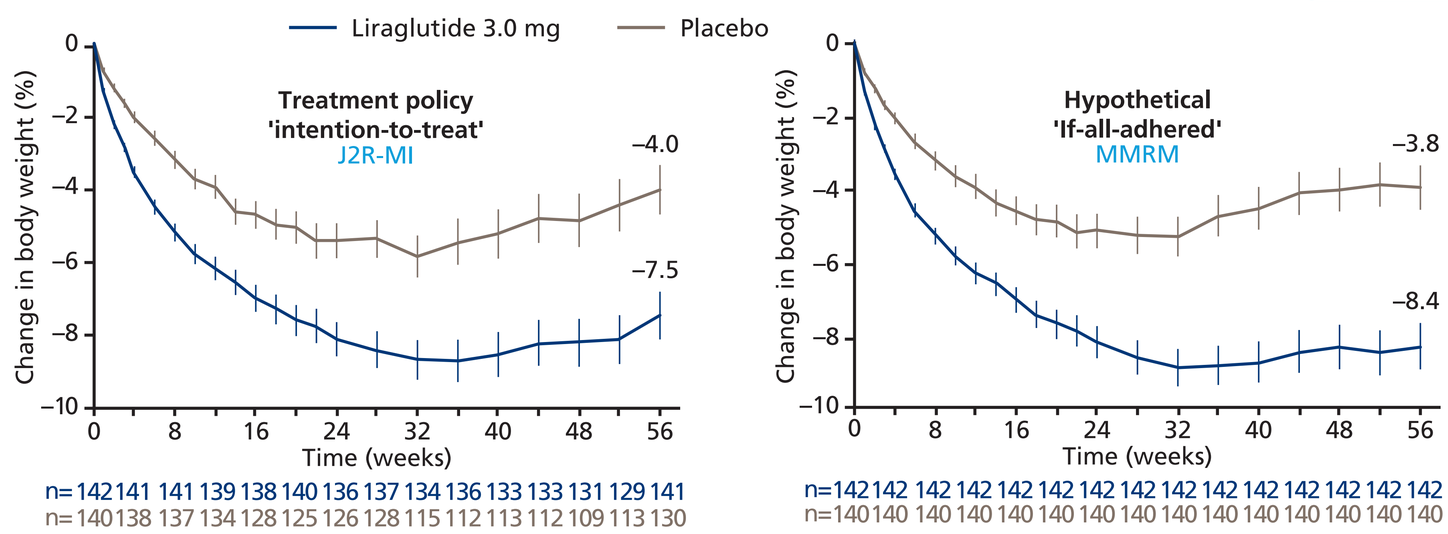
- There was good agreement between the two statistical approaches for estimating the efficacy of liraglutide 3.0 mg vs. placebo for individuals who adhered to trial product for 56 weeks, indicating that underlying assumptions are robust.
- The findings of this analysis can provide regulators and physicians with an understanding of how adherence to liraglutide 3.0 mg can impact weight loss.

Figure 1: Description of the primary and secondary estimands

Treatment policy	Hypothetical
'Intention-to-treat'	**'If all adhered'**
Evaluates the treatment effect for all randomised subjects regardless of premature discontinuation of trial product	Evaluates the treatment effect for all randomised subjects assuming that all subjects remained on trial product
Relevant to those involved in deciding the treatment policy for the indicated patient population (e.g. regulatory authorities)	Relevant to those who base patient-specific decisions on the anticipated treatment effect (e.g. physicians)

Figure 3: Change in body weight for the 'treatment policy' and 'hypothetical' estimands

Key result



J2R-MI n= number of observations available at each visit before imputation. MMRM n= number of subjects contributing to the model fit.
CI, confidence interval; J2-MRI, jump-to-reference missing data imputation; MMRM, mixed model repeated measures.

Table 1: SCALE IBT trial disposition

Individuals	Liraglutide 3.0 mg	Placebo	Total
Randomised, n	142	140	282
Exposed, n	142	140	282
On drug at week 56 visit, n (%)	114 (80.3)	103 (73.6)	217 (77.0)
Discontinued trial product, n (%)	28 (19.7)	37 (26.4)	65 (23.0)
Retrieved, n (%)	27 (19.0)	27 (19.3)	54 (19.1)
Withdrawals, n (%)	1 (0.7)	10 (7.1)	11 (3.9)
Subjects who discontinued treatment at least once, n (% of randomised)	36 (25.4)	45 (32.1)	81 (28.7)
Subjects who resumed treatment having discontinued at least once, n (% of discontinued)	13 (36.1)	16 (35.6)	29 (35.8)
Subjects who are treatment completers having discontinued at least once and then resumed treatment, n (% of resumed)	8 (61.5)	8 (50.0)	16 (55.2)

Figure 2: Time to first trial product discontinuation

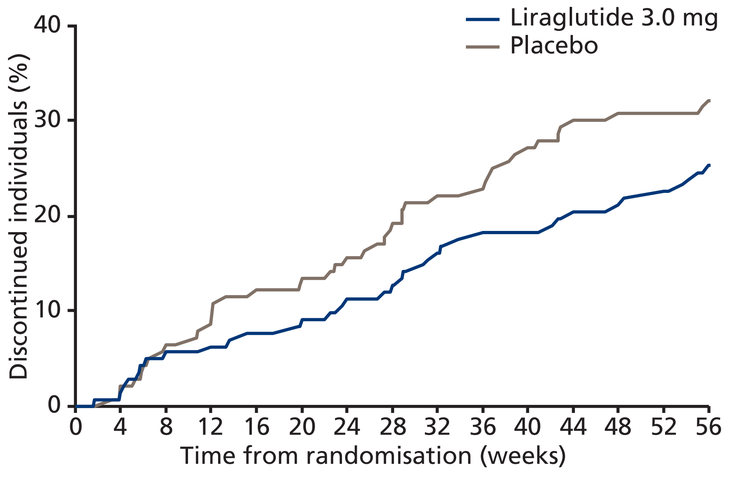
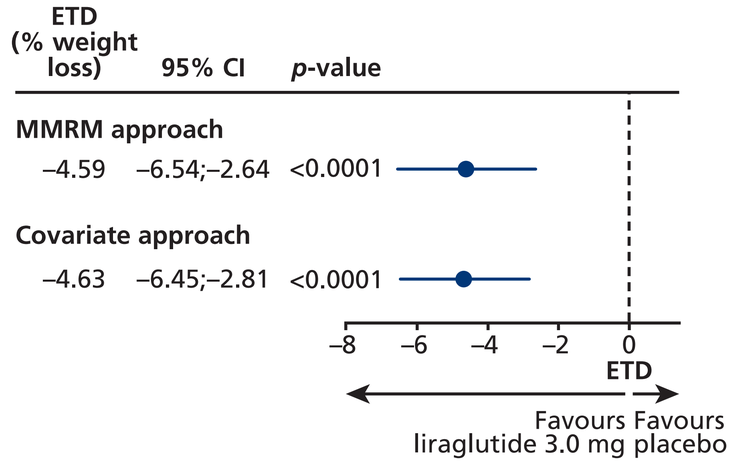


Figure 4: Sensitivity analysis of the placebo-subtracted change in body weight for the secondary hypothetical estimand



CI, confidence interval; ETD, estimated treatment difference; MMRM, mixed model repeated measures.

Conclusion

- The estimated weight loss in medication-adherent individuals is an important supplement to the study's primary outcome ('treatment policy' estimand) and can inform physicians' expectations when prescribing liraglutide 3.0 mg in combination with IBT for 56 weeks.

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Footnote: For more information on SCALE IBT please see posters P02.192, P02.194, P02.197.

Reference: (**1**) ICH. ICH Harmonised Guideline: Estimands and Sensitivity Analysis in Clinical Trials. E9(R1). www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf.