

Impact of Liraglutide 3.0 on Body Fat Distribution—Statistical Analysis Plan

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Statistical Analysis Plan - Impact of Liraglutide 3.0 on Body Fat Distribution

Important points:

1. Modified intention-to-treat (mITT) which includes data from the full-analysis set of all participants who underwent randomization and had a follow-up endpoint assessment (full analysis set, FAS).
2. Secondary analyses will be performed using per-protocol approach which includes data from the full-analysis set of all participants who underwent randomization, received at least one dose of study drug, and completed a final imaging visit at the planned study end; this is termed a “completers analysis”.
3. Missing values will be imputed with the Monte Carlo Markov Chain method. Sensitivity analyses will be performed to determine the effect of missingness/imputation on the primary and secondary outcomes.

Descriptive:

1. Baseline characteristics of study population overall and stratified by treatment assignment
2. Mean medication adherence as a percentage of drug taken/drug dispensed after randomization through final outcomes assessment.
3. Proportion losing $\geq 5\%$ body weight and $\geq 10\%$ body weight in each group (and compared with p-value).
4. Adverse events: a) most frequent (%), b) serious (%), rate of withdrawal in each group for adverse events

Endpoints analysis:

Note: All to be reported as mean \pm standard deviation in each group with between group differences reported as placebo-adjusted difference with 95% confidence interval.

- 1. Primary endpoint:** Relative percent change in visceral adipose tissue volume
- 2. Secondary endpoints**
 - a. Absolute change in visceral adipose tissue volume
 - b. Relative percent change in body weight
 - c. Absolute change in body weight
 - d. Relative percent change in waist circumference
 - e. Absolute change in waist circumference
 - f. Relative percent change in total body adipose tissue volume
 - g. Absolute change in total body adipose tissue volume
 - h. Relative percent change in abdominal subcutaneous adipose tissue volume
 - i. Absolute change in abdominal subcutaneous adipose tissue volume

- j. Relative percent change in lower body subcutaneous adipose tissue volume
 - k. Absolute change in lower body subcutaneous adipose tissue volume
 - l. Relative percent change in liver fat percent
 - m. Absolute change in liver fat percent
 - n. Relative percent change in total body lean volume
 - o. Absolute change in total body lean volume
 - p. Relative percent change in total thigh muscle volume
 - q. Absolute change in total thigh muscle volume
 - r. Relative percent change in mean anterior thigh muscle fat infiltration percent
 - s. Absolute change in mean anterior thigh muscle fat infiltration percent
- 3. Subgroup analyses**
- a. To be performed for the primary endpoint as well as selected secondary endpoints as below:
 - i. Relative percent change in abdominal subcutaneous adipose tissue volume
 - ii. Relative percent change in lower body subcutaneous adipose tissue volume
 - iii. Relative percent change in liver fat percent
 - iv. Relative percent change in total thigh muscle volume
 - v. Relative percent change in mean anterior thigh muscle fat infiltration percent
 - b. Age (stratified by median)
 - c. Sex (M/F)
 - d. Race (non-Hispanic black, non-Hispanic white, Hispanic)
 - e. Body mass index (kg/m²) category (overweight 25-29.9, class I 30-34.9, class II/III ≥ 35)
 - f. Sex-specific tertiles of total body fat (T1, T2, T3)
 - g. Prediabetes (Y/N)
- 4. Correlation between change in body weight, BMI, total body fat, and change in fat distribution for:**
- a. Visceral adipose tissue
 - b. Abdominal subcutaneous adipose tissue
 - c. Lower body subcutaneous adipose tissue
 - d. Liver fat
 - e. Anterior thigh muscle fat infiltration
- 5. “Responders” analysis**
- a. Pre-specified analysis stratified by those who did vs. did not lose $\geq 4\%$ body weight at week 16 of treatment to determine differential outcomes among “responders” vs. “non-responders” as outlined in the Liraglutide package insert.
 - b. This analysis will be performed for the primary endpoint only.

Statistical approach:

- 1. For continuous endpoints, an analysis of covariance model will be used to analyze mean changes. The model will include treatment, sex, BMI stratification (<30 , ≥ 30),

- prediabetes status at baseline, interaction between BMI and prediabetes status strata as fixed effects, with the baseline value of the relevant variable as a covariate.
2. For categorical endpoints, logistic regression will be used with the same fixed effects and covariates as the analysis of covariance model.
 3. Sensitivity analyses for primary endpoint

| Endpoint | Type of analysis | Description |
|--|------------------|---|
| Relative percent change in visceral adipose tissue | mITT | Analysis of FAS with a valid non-imputed measurement at study end |
| Relative percent change in visceral adipose tissue | LOCF | Same analysis as the primary applied to all randomized patients allowing for baseline carried forward for those without a post-baseline measurement |
| Relative percent change in visceral adipose tissue | MCMC | Same analysis as the primary applied to all randomized patients allowing for imputation of missing observations using a modeling method |

FAS denotes full analysis set, defined as all participants who underwent randomization and had a follow-up endpoint assessment