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 ≥ 5% body weight and ≥ 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 ± 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

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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/m^2) 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 ≥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