Cover Page for Statistical Analysis Plan

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16.1.9. Documentation of statistical methods

Real world effectiveness of combining an employer-based weight management program with medication for chronic weight management in employees with obesity – a pragmatic randomized trial

Statistical Analysis Plan

Protocol No. NN8022-4432

Novo Nordisk

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Version 2.0

Signature Page for Statistical Analysis Plan
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1.0 INTRODUCTION

This document describes the Statistical Analysis Plan (SAP) for Protocol Number NN8022-4432, Real world effectiveness of combining an employer-based weight management program with medication for chronic weight management in employees with obesity – a pragmatic randomized trial. This is a one-year, single-center, randomized, open label, parallel-group, pragmatic clinical trial (PCT) comparing Cleveland Clinic's existing Integrated Medical Weight Management Program (WMP) combined with medication for chronic weight management versus Cleveland Clinic's existing Integrated Medical WMP with no medication for weight management in subjects with obesity.

This SAP is based on the most recent version of the protocol: Version 1.0, October 10, 2018.

Protocol History:

Number	Version	Date
1.0	Original Protocol	October 10, 2018

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate superior effect of treatment with an employer-based weight management program in combination with medication for chronic weight management (WMP + Rx) compared to an employer-based weight management program alone (WMP) in subjects with obesity on weight loss.

2.2 Secondary Objectives

The secondary objectives are to compare the effects of treatment with an employer-based weight management program in combination with medication for chronic weight management to an employer-based weight management program alone in subjects with obesity with regards to:

- Categorical weight loss
- Adherence to the weight management program
- Patient-reported outcomes (PROs) on work productivity and work limitations

Furthermore, the secondary objectives will assess adherence to medication for chronic weight management (only in the treatment arm randomized to an employer-based chronic weight management program with medication for chronic weight management).

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

- Change from baseline (month 0) to month 12 (visit 13) in body weight (%)

3.2 Secondary Endpoints

All secondary study endpoints are to be considered supportive in nature. There are no pre-specified confirmatory secondary endpoints.

Supportive secondary endpoints of this study include:

- Subjects who after 12 months achieve (yes/no):
  - ≥5% reduction in body weight from baseline
  - ≥10% reduction in body weight from baseline
- Adherence to Cleveland Clinic's Integrated Medical WMP from baseline (month 0) to month 12 (visit 13), as:
  - Number of shared medical appointments (SMA) attended
  - Subjects attending ≥9 SMAs (yes/no)
- Adherence to medication for chronic weight management from baseline (month 0) to month 12 (visit 13) in the treatment arm randomized to the WMP in combination with medication for chronic weight management, as:
  - Proportion of days covered (PDC) by prescription claims for medication for chronic weight management
  - Subjects covered by prescription claims for medication for chronic weight management for at least 80% of days (yes/no)
- Change in PROs from baseline (month 0) to month 12 (visit 13) in
  - Work limitation as measured by Work Limitations Questionnaire Self-administered Short-Form (WLQ-8)
    - At-Work Productivity Loss Index (point)
    - Time Management (point)
    - Physical Tasks (point)
    - Mental/Interpersonal Tasks (point)

- Output Tasks (point)

- Work productivity as measured by Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0 (WPAI:SHP)
  - Work time missed due to excess weight (%)
  - Impairment while working due to excess weight (%)
  - Overall work impairment due to excess weight (%)
  - Activity impairment due to excess weight (%)

4.0 STATISTICAL METHODOLOGY

4.1 General Considerations

Statistical analyses will be performed using SAS® version 9.4 or higher computer software. Analyses will utilize prospectively collected data from study site at study visits as well as secondary data collection utilizing pharmacy dispensing data. Data from both sources will be integrated into one dataset for analysis.

Patient flow, patient characteristics, treatments, and outcomes will be tabulated and summarized with descriptive statistics based on observed values only. All descriptive data summaries will include means, medians, standard deviation (SD), and ranges for continuous variables and absolute/relative frequencies for categorical data. In addition, for each variable the number (count) of values that are missing will also be reported for dedicated study visit data. Missing data are data that are planned and can be collected but are absent. Statistics will be summarized for the study population overall and by treatment arm. Two sets of descriptive summaries will be produced: one based on the primary estimand ("intention-to-treat" (ITT)) and one based on the secondary estimand ("if all patients had adhered").

Raw data (i.e., minimum and maximum values presented for range in continuous variables) will be reported out to the precision with which it was collected. Means will be reported to 1 decimal place more than the raw data. SD will be reported to 1 decimal place more than the mean. Percentages will be reported to 1 decimal place. Trailing zeros will be presented to maintain a consistent level of precision, e.g. 2.0 rather than 2.

Inferential tests will be performed at the 5% level of significance (two-sided). All p-values will be rounded to 3 decimal places. If a rounded p-value is 0.000 (i.e., the actual p-value is less than 0.0005), then the p-value will be presented as '$p< 0.001$.'

4.2 Estimands

The estimand informs choices about data foundation and statistical analysis including possible imputation of missing data, hereby ensuring that randomization is preserved as a sound basis for

statistical inference; i.e. estimation of effect size, associated uncertainty and statistical testing. Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of an employer-based WMP combined with obesity medication compared to an employer-based WMP alone.

4.2.1 Primary Estimand

The primary estimand for all endpoints is an ITT estimand (also known as an "effectiveness" or a "treatment policy" estimand). This estimand will quantify the average treatment effect of an employer-based WMP combined with medication for chronic weight management compared to the employer-based WMP alone after 12 months, in all randomized subjects and regardless of adherence to randomized treatment.

4.2.2 Secondary Estimand

The secondary estimand for body weight loss, categorical weight loss, and PROs is an "if all subjects had adhered" estimand (also known as an "efficacy" estimand). This estimand will quantify the average treatment effect of an employer-based WMP combined with medication for chronic weight management compared to the employer-based WMP alone after 12 months, in all randomized subjects had they adhered to their randomized treatment for the entire planned study duration as defined in Section 5.6.2.

4.3 Study Populations

4.3.1 Trial Population

Planned number of subjects to be screened: 240

Planned number of subjects to be randomized: 200

Expected number of subjects to complete (defined as end of trial on-site weight measurement) the trial: 150

4.3.2 Analysis Population

The following analysis set will be defined:

Full analysis set (FAS): Includes all randomized patients analyzed according to the treatment group to which they were assigned at randomization.

4.4 Evaluation Schedule and Definitions

Study visits include an individual screening and randomization visit (visit 1, month 0), followed by twelve once-monthly visits set up in the context of SMAs (visit 2 to visit 13). End of Study (EOS) is visit 13 (month 12 (-14 days, +28 days)). The complete study visit schedule and data collection are summarized in the Time and Events Schedule (Protocol Appendix 1-1). For analysis, baseline refers to assessments conducted and patient data collected at or prior to the screening and randomization visit.

4.5 Primary Endpoint and Confirmatory Hypothesis

The primary endpoint is percent change in body weight from baseline (month 0) to month 12 (visit 13), as defined:

$$\% \text{ weight change} = \frac{\text{body weight at visit 13} - \text{body weight at baseline}}{\text{body weight at baseline}} \times 100\%$$

where a negative value indicates a body weight loss from baseline (month 0) to month 12 (visit 13).

One confirmatory hypothesis will be tested:

- Superiority of WMP + Rx versus WMP alone on % weight change from baseline (month 0) to month 12 (visit 13).

The test will be evaluated as a two-sided test of the null hypothesis that the mean weight change (%) in the two treatment arms is the same (H_0: % weight change [WMP + Rx] = % weight change [WMP]). Superiority will be claimed if the two-sided p-value is less than 5% and the estimated difference in mean weight change favors WMP + Rx (H_a: % weight change [WMP + Rx] < % weight change [WMP]).

4.6 Interim Analysis

There is no interim analysis planned for this study.

4.7 Missing Data

Except where noted in Section 5.5 for body weight and PRO endpoints, missing data will not be imputed and will be excluded from calculations.

4.8 Data Definitions and Calculations

4.8.1 General

Absolute change from baseline variables will be calculated as:

Change = Endpoint – Baseline

Percent (relative) change from baseline variables will be calculated as:

Percent Change = [(Endpoint– Baseline)/Baseline] x 100

If day and/or month is missing from dates, the first day of the month and/or the first month of the year will be assumed when calculating duration between dates. If imputation of an incomplete date associated with a post-randomization data element results in a date prior to randomization, the following assumptions will be made:

- For subject in the WMP + Rx arm, the date of first prescription fill will be used.

- For subject in the WMP arm, the first day of the month immediately following randomization will be used. E.g., if the randomization date is 08/15/18 (mm/dd/yy) and the unknown date is 08/UNK/18 or UNK/10/18 or UNK/UNK/18, the imputed date would be 09/01/18.

The data sources for each endpoint and variables used in analysis are summarized in Section 8.0.

4.8.2 Demographics and Baseline Characteristics

For this study, demographics will include age, sex, ethnicity, and race. Baseline characteristics will include height, weight, BMI, medical history, concomitant illnesses, and concomitant medication use.

Age will be presented in years, based on the patient's birth date and informed consent date, and will be automatically calculated via the Electronic Data Capture (EDC) system.

BMI will be presented in kg/m^2, based on the patient's height and weight, and will also be automatically calculated via the EDC.

4.8.3 Planned Study Duration

For this study, planned study duration will be defined as duration of time in days from an individual's screening and randomization visit (visit 1, month 0) to month 12 (visit 13). For subjects that drop out early, the expected visit 13 date (derived from the subjects' planned SMA group visit) will be used to calculate planned study duration.

4.8.4 Proportion of Days Covered (PDC)

Subjects randomized to the WMP + Rx arm will receive their first medication prescription at the time of randomization (visit 1). The proportion of days covered (PDC) by prescription claims for medication for chronic weight management will be calculated as the total number of days covered by prescription claims for obesity medication (obtained from the pharmacy dispensing database, collected as "days supply" on the Pharmacy card) divided by the total planned study duration, multiplied by 100.

For this study, the PDC will be used along with SMA attendance to derive the secondary estimand of the primary endpoint and assess the secondary endpoint of adherence to obesity medication.

4.8.5 Last Study Assessment Prior to Exceeding 20% of Planned Study Duration with No Prescription Claims

The last study assessment prior to exceeding 20% of planned study duration with no prescription claims for each subject will be used to derive the secondary estimand of the primary endpoint. Based on the medication fill date and days supply data collected on the Pharmacy card (obtained from the pharmacy dispensing database), a cumulative tally of time during the study with and without medication supply will be determined for each subject. Days supply from overlapping

prescription fills will contribute to the total amount of time with medication supply. E.g., if a patient refills a prescription before the days supply of the prior prescription is finished, the days supply from that latest prescription fill would not start until the days supply from the prior prescription was finished. With planned study duration as the denominator, the percent time without medication supply will be calculated for each subject, and the date when the cumulative percentage reaches 20% will be determined and used to identify the last study assessment for each individual.

4.8.6 Patient Reported Outcomes (PROs)

4.8.6.1 Work Limitations Questionnaire 8-Item (WLQ-8) Self-administered Short Form

The WLQ-8 questionnaire (Protocol Appendix 2-2) is an 8-item instrument used to assess the degree to which subjects have difficulty related to time management, physical tasks, mental/interpersonal tasks, and output tasks due to their physical and/or emotional health. The WLQ-8 produces 4 subscale scores as well as an index of overall at-work productivity loss. Subjects will self-administer these instruments on paper at visit 1, visit 7, and visit 13.

WLQ-8 Scoring Information

General Information:

Scale response options are as follows: “all of the time (100%)”; “most of the time”; “some of the time (approximately 50%)”; “a slight bit of the time”; “none of the time (0%)”; and “does not apply to my job”. The time management, mental-interpersonal, and output subscale items address the amount of time that physical or emotional health problems made the performance of specific demands difficult. The physical scale refers to the amount of time the employee was able to perform a demand without difficulty due to health problems. The recall period is the past 2 weeks.

Questions:

Q1 = get going easily at the beginning of the workday

Q2 = start on your job as soon as you arrived at work

Q3 = sit, stand, or stay in one position for longer than 15 minutes while working

Q4 = repeat the same motions over and over again while working

Q5 = concentrate on your work

Q6 = speak with people in-person, in meetings or on the phone

Q7 = handle the workload

Q8 = finish work on time

Scores:

In general, WLQ-8 outcomes are expressed as index scores, with higher numbers indicating greater limitations, i.e., worse outcomes. The WLQ-8 questionnaire includes two questions for each subscale. Each of the four subscale scores are computed as the mean of the non-missing responses from both questions. With the exception of data evaluating physical tasks (Q3 & Q4), data will be recoded so that 1 represents "none of the time (0%)" and 5 represents "all of the time (100%)". Values of "does not apply to my job" will be set to missing for the calculation of subscale scores. The at-work productivity loss score is computed as the mean of the non-missing responses from all 8 questions.

1. Time management: Q1 & Q2
2. Physical tasks: Q3 & Q4
3. Mental/Interpersonal tasks: Q5 & Q6
4. Output tasks: Q7 & Q8
5. At-Work Productivity Loss: Q1 - Q8

The four subscales and the overall at-work productivity loss will be calculated at baseline, month 6 (visit 7), and month 12 (visit 13). Change from baseline will be calculated for each score at month 6 (visit 7) and month 12 (visit 13).

4.8.6.2 Work Productivity and Activity Impairment: Specific Health Problems Questionnaire v2.0 (WPAI:SHP)

The Work Productivity and Activity Impairment: Specific Health Problems (WPAI:SHP) questionnaire is a 6-item instrument that measures absenteeism (work time missed), presenteeism (impairment while working), work productivity loss (overall work impairment), and activity impairment due to a target health problem, namely excess body weight, in the past seven days. Subjects will self-administer these instruments on paper at visit 1, visit 7, and visit 13. (Protocol Appendix 2-1).

WPAI:SHP Scoring Information

General Information:

In general, WPAI:SHP outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. The recall period is the past seven days, excluding the current day.

Questions:

Q1 = currently employed (Yes=works full-/part-time; self-employed; works in family business; on vacation from paid employment/No=does not work for pay; only does volunteer work; usually works, but has been laid-off or unemployed during the past seven days; retired; seasonal workers not currently working)

Q2 = hours missed due to specified problem
Q3 = hours missed for other reasons
Q4 = hours actually worked
Q5 = degree problem affected productivity while working
Q6 = degree problem affected regular activities

Scores:

Multiply scores by 100 to express in percentages

1. Percent work time missed due to health (Absenteeism): Q2/(Q2 + Q4)
2. Percent impairment while working due to health (Presenteeism): Q5 /10
3. Percent overall work impairment due to health (Work Productivity Loss): Q2/(Q2 + Q4) + [(1 – (Q2/(Q2 + Q4))) x (Q5/10)]
4. Percent activity impairment due to health (Activity Impairment): Q6/10

Absenteeism, presenteeism, work productivity loss, and activity impairment will be calculated at baseline, month 6 (visit 7), and month 12 (visit 13). Change from baseline will be calculated for each score at month 6 (visit 7) and month 12 (visit 13).

4.9 Examination of Subgroups

There are no subgroup analyses planned for this study.

5.0 STATISTICAL ANALYSES

5.1 Overview

Once data collection of the last subject visit and data management activities have been completed, database lock will occur and all analyses outlined in this SAP will be performed. Analyses results will be presented in a clinical study report and at an internal results meeting.

Descriptive summaries will be produced for both the primary (ITT) and secondary ("if all patients adhered") estimands. All statistical analyses will be conducted under both the primary estimand (ITT) and secondary estimand ("if all patients had adhered"), with the exception of the secondary endpoints for adherence to treatment, which will be based on the primary estimand only.

5.2 Patient Disposition and Accountability

Patient disposition will be descriptively summarized for all randomized patients overall and by treatment group, including the number and percentage patients in the FAS population, patients who completed study (defined as subjects with month 12 (visit 13) body weight data), and the primary reason for not completing the study for patients who terminated participation in the

study early. Summary metrics for number of screen failures will also be presented. A flow diagram (e.g.: Consort flow diagram) of patient disposition will also be created.

5.3 Demographics and Baseline Clinical Characteristics

Demographic and baseline clinical characteristics will be descriptively summarized for the FAS overall and by treatment group. For baseline comorbid conditions (medical history and concomitant illnesses), the number and percentage of patients with at least one of the comorbid conditions collected in the study will also be summarized along with the relative frequencies of type of comorbid condition. For baseline concomitant medications, the relative frequencies of the types of concomitant medications at the time of enrollment categorized by indication will be summarized.

5.4 Protocol Deviations

Major protocol deviations will be summarized by type (e.g.: informed consent, randomization error, inclusion/exclusion criteria error, unreported serious adverse events (SAEs), treatment violation, study visit not per protocol, other).

5.5 Missing Value Imputation Methodology

5.5.1 Body Weight

Missing endpoint data will be imputed for body weight at month 12 (visit 13). These data will be used for the analysis of the primary estimand for the primary endpoint and the analysis of the primary estimand for the secondary endpoint of categorical weight loss.

The primary approach for imputation of missing values of body weight at visit 13 is imputations by sampling among all available assessments at visit 13 in the WMP arm (including values from retrieved subjects). This approach is also known as “jump to reference” and makes the assumption that subjects instantly after discontinuation lose any effect of randomized treatment beyond what can be expected from the WMP. Body weight measurements at visits between baseline and visit 13 are not used for this imputation approach.

The multiple imputation approach is done in three steps.

1. **Imputation:** Step 1 defines an imputation model based on WMP arm subjects, which is used to impute missing body weight values at visit 13 in both arms. This will be done 100 times.
2. **Analysis:** Step 2 analyses each of the 100 complete data sets, using the statistical model described above and saves the 100 estimation results.
3. **Pooling:** Step 3 integrates the 100 estimation results into a final result using Rubin’s formula [5].

The imputation model in step 1 uses WMP arm subjects from FAS with non-missing body weight measurements at baseline and visit 13 (including values from retrieved subjects). The

imputation model is a linear regression of body weight (kg) at visit 13 with gender (male/female), BMI (kg/m2) in categories 30-<35, 35-<40, ≥40 as factors and baseline body weight (kg) as covariate. No interactions will be included. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model is then used to impute missing visit 13 body weight values for both randomized treatment arms.

If 100 copies are not sufficient to establish stable results, a higher number will be used. The multiple imputations will be generated using Novo Nordisk trial number 80224432 as seed number, and will be executed using the PROC MI and PROC MIANALYZE procedures in SAS.

5.5.2 Patient Reported Outcomes

Missing endpoint data will be imputed for each of the WLQ-8 and WPAI:SHP summary scores at month 12 (visit 13). These data will be used for the analysis of the primary estimand for the secondary PRO endpoints.

The primary approach for imputation of the missing PRO summary scores at visit 13 will be similar to that described for body weight (Section 5.5.1). The imputation model is a linear regression of the PRO summary score at visit 13 with gender (male/female), BMI (kg/m2) in categories 30-<35, 35-<40, ≥40 as factors and baseline PRO summary score as covariate. The imputation approach will be repeated separately for each of the five WLQ-8 summary scores and four WPAI:SHP summary scores, as warranted.

5.6 Primary Endpoint

5.6.1 Statistical Analysis for the Primary Estimand

The primary effectiveness analysis is the primary estimand of the primary endpoint. This analysis will be based on the FAS with missing data imputation as described in the Section 5.5.1. Percent change in body weight from baseline (month 0) to month 12 (visit 13) will be calculated for each study subject within the FAS per Section 4.5 and will be modeled using linear regression (Analysis of Covariance (ANCOVA)) with randomized treatment as a factor and baseline body weight (kg) as a covariate. The treatment difference between WMP + Rx and WMP alone will be estimated and reported together with the associated 95% confidence interval (CI) and corresponding p-value testing the null-hypothesis of no difference between treatment arms. Superiority for the primary endpoint will be considered established if the two-sided p-value is less than 5% and the estimated difference in mean weight change favors WMP + Rx.

5.6.1.1 Sensitivity Analysis of the Primary Estimand

A sensitivity analysis will be conducted using the multiple imputation approach as described by McEvoy [6] to impute missing body weight data at month 12 (visit 13). In this approach, month 12 measurements at visit 13 for non-retrieved drop outs will be imputed by sampling from values obtained from retrieved drop outs in the corresponding treatment arm and according to the timing of last available body weight. Multiple imputation will be performed separately for each

treatment arm following the three steps detailed in Section 5.5.1. The imputation model for this approach is a linear regression of body weight (kg) at visit 13 with gender (male/female), BMI (kg/m2) in categories 30-<35, 35-<40, ≥40 as factors and baseline body weight (kg), last available body weight prior to drop out, and month of last available body weight measurement prior to drop out as covariates. If timing by month is too restrictive, quarters (13 weeks), half-years (26 weeks), or excluding timing from the imputation model altogether will be used.

Analysis of percent change in body weight from baseline (month 0) and month 12 (visit 13) will be repeated and results summarized per the method outlined in Section 5.6.1. If this multiple imputation approach is not feasible, no sensitivity analysis will be done.

5.6.2 Statistical Analysis for the Secondary Estimand

The secondary estimand of the primary endpoint will address the efficacy of medication for chronic weight management if all subjects adhere to their randomized treatment (WMP + Rx or WMP). For the secondary estimand, the primary endpoint will be analyzed using a mixed model for repeated measurements (MMRM) including all subjects, but for subjects considered non-adherent to randomized treatment, only data prior to non-adherence will be used. Month 12 (visit 13) assessments for retrieved drop outs will not be used in this analysis. The MMRM for efficacy will only use assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment. Subjects in the WMP arm will be considered non-adherent if/when criterion 1 below is met. Subjects in the WMP + Rx arm will be considered non-adherent if/when criterion 1 or 2 is met:

1. Missing 4 SMA visits. In this case, the last assessment made prior to the 4th missed SMA visit will be used as the last assessment. This is also the case if, e.g., 4 SMA visits in a row are missed.
2. Period with no coverage of prescription claims according to PDC exceeds 20% of planned medication duration, or number of days from visit 1 to visit 13. For subjects that drop out early, the expected visit 13 date (derived from the subjects' planned SMA group visit) will be used to calculate planned study duration. The last assessment made prior to exceeding 20% of planned study duration with no prescription claims will be used as last assessment (as defined in Section 4.8.5).

The MMRM for efficacy will be fitted using % weight change with randomized treatment as factor and baseline body weight (kg) as covariate, all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent. From the model, treatment effect will be estimated and reported along with the associated 95% CI and corresponding p-value testing the null-hypothesis of no difference between treatment arms.

5.6.3 Supplementary Analyses

The analysis of % weight change will be complemented with the following supplementary analyses. Analyses #3 and #4 will assess the potential impact of altering the mode of administering the SMAs, from on-site to virtual, during the trial in response to the COVID-19 outbreak.

Supplementary Analysis #1 (Completer analysis)

In the context of this first supplementary analysis, the analysis population will be defined as subjects in the FAS with month 12 (visit 13) body weight data who adhered to randomized treatment up to and including visit 13. Adherence is defined as for the secondary estimand for the primary endpoint in Section 5.6.2, i.e., subjects in the WMP arm will be considered non-adherent if/when criterion 1 above is met and subjects in the WMP + Rx arm will be considered non-adherent if/when either criterion 1 or 2 above is met. As an example, a subject in the WMP + Rx arm that misses visit 10, 11, and 12, but attends all other visits and is covered by prescription claims for at least 80% of the planned study duration, is considered a completer in this context if month 12 (visit 13) weight data are available. This analysis will use the same ANCOVA model described for the primary estimand analysis of the primary endpoint (Section 5.6.1).

Supplementary Analysis #2

For the second supplementary analysis, the analysis population will be defined as subjects in the FAS who remain in the CC EHP for the entirety of their study participation. Subjects who leave the Cleveland Clinic Employee Health Plan (CC EHP) and end study participation or leave the CC EHP but continue to attend SMAs and take study medication if in the WMP + Rx arm will be excluded from the analysis. Analysis of this subset of subjects will include missing body weight data imputation as described in the Section 5.5.1. Change in percent body weight will be analyzed and presented as described for the primary estimand analysis of the primary endpoint (Section 5.6.1).

Supplementary Analysis #3

For the third supplementary analysis, a subgroup analysis will be performed based on the FAS and using the imputed weight data derived for the analysis of the primary estimand for the primary endpoint (Section 5.5.1). This analysis will use the same ANCOVA model described for the primary estimand analysis of the primary endpoint (Section 5.6.1), but with the addition of an interaction term composed of randomized treatment and mode of MN12 SMA administration (on-site or virtual) to the regression model. This interaction term will serve as a test for whether or not the observed treatment effect was consistent between those subjects who had an on-site MN12 SMA and those subjects who had a virtual MN12 SMA (H_0: treatment effect [on-site MN12 SMA] = treatment effect [virtual MN12 SMA]). In the event of a significant interaction effect, the treatment difference between WMP + Rx and WMP alone will be presented as

described for the primary estimand analysis of the primary endpoint but stratified by mode of MN12 SMA administration.

Supplementary Analysis #4

In the context of this fourth supplementary analysis, the analysis of the secondary estimand of the primary endpoint will be repeated and results summarized per the method outlined in Section 5.6.2, but with the additional exclusion of body weight data collected after the transition to virtual SMAs. This analysis will use a MMRM and all body weight assessments from subjects who were adherent to the randomized treatment until end of treatment or until the transition to virtual SMAs (whichever occurred first), or up until the subject was considered non-adherent to the randomized treatment prior to the transition to virtual SMAs per the adherence criteria noted in Section 5.6.2.

5.7 Secondary Endpoints

5.7.1 Statistical Analysis for the Primary Estimand

The following analyses are planned to further support the primary objective to compare weight loss of WMP + Rx versus WMP. They will also address the secondary objectives of this study to compare WMP + Rx versus WMP with respect to categorical weight loss, WMP adherence, and PROs, as well as adherence to obesity medication within the WMP + Rx cohort.

All secondary analyses described in this section will be the primary estimand based on the FAS. No sensitivity analyses are planned for the secondary endpoints.

5.7.1.1 Categorical Weight Loss

For the categorical weight loss endpoints, subjects will be dichotomized based on body weight loss at month 12 (visit 13) compared to baseline. Analysis will use the imputed weight data derived for the analysis of the primary estimand for the primary endpoint (Section 5.5.1). For the first categorical weight loss endpoint, subjects will be grouped as those with 5% or more body weight loss and those with less than 5% loss. The proportion of subjects achieving the endpoint will be analyzed using a logistic regression model with treatment as categorical effect and baseline weight (kg) as covariate. From the model, the estimated odds ratio (OR) (WMP + Rx / WMP) will be presented, along with the two-sided 95% CI and corresponding p-value. An OR above 1.0 will be interpreted as favoring WMP + Rx. In addition, the predicted probability of achieving at least 5% body weight loss for an average trial subject in each treatment arm will be estimated from the model.

For the second categorical weight loss endpoint, subjects will be dichotomized as those with 10% or more body weight loss and those with less than 10% loss. The analysis will utilize the same approach described for the first categorical weight loss endpoint.

5.7.1.2 Adherence to Weight Management Program (WMP)

The WMP adherence endpoints will be assessed through SMA attendance during the course of the study. For the first WMP adherence endpoint, SMA attendance will be calculated for each subject as the percentage planned SMAs attended between baseline (month 0) and month 12 (visit 13), i.e., number of SMAs attended/12 planned SMAs. Attendance will be descriptively summarized by treatment arm.

For the second WMP adherence endpoint, the proportion of subjects attending ≥9 SMAs will be descriptively summarized as percentage of number of subjects in each treatment arm.

No formal statistical testing will be conducted for either endpoint.

5.7.1.3 Adherence to Obesity Medication

Adherence to obesity medication will be assessed through PDC (as defined in Section 4.8.4) for the WMP + Rx treatment arm only. The PDC and the proportion of subjects with at least 80% PDC will be descriptively summarized for the WMP + Rx treatment arm. No formal statistical testing will be conducted.

5.7.1.4 Patient Reported Outcome (PRO) Analysis

PROs will be measured with the instruments described in Section 4.8.6. Analysis of these measures will address the secondary objective of this study to compare WMP + Rx versus WMP in the study's patient population as is relates to PROs, i.e., work productivity and work limitations, over one-year observation period. PRO analysis will descriptively summarize these measures at baseline and month 12 , as well as compare treatment arms for change from baseline.

The primary estimand for the PRO analysis will be based on the FAS with missing data imputation as described in the Section 5.5.2. Analysis of change for each instrument scale will follow the method described for the primary estimand for the primary endpoint: ANCOVA model with randomized treatment as a factor and baseline value of the endpoint variable as covariate. Estimated difference (WMP + Rx minus WMP) in change from baseline (month 0) to month 12 (visit 13) for each scale will be presented with 95% CI and corresponding p-value. If examination of the data indicate that it is not justifiable to model data based on assumptions of normality, e.g., many responses of 0% or close to 0%, alternative statistical modeling will be used (e.g. logistic regression after definition of a responder limit).

Change in PRO instrument scales will include:

- Change in WLQ-8: At-Work Productivity Loss index from baseline to month 12
- Change in WLQ-8: Time Management index from baseline to month 12
- Change in WLQ-8: Physical Tasks index from baseline to month 12
- Change in WLQ-8: Mental/Interpersonal Tasks index from baseline to month 12
- Change in WLQ-8: Output Tasks index from baseline to month 12

- Change in WPAI:SHP: Work time missed due to excess weight from baseline to month 12
- Change in WPAI:SHP: Impairment while working due to excess weight from baseline to month 12
- Change in WPAI:SHP: Overall work impairment due to excess weight from baseline to month 12
- Change in WPAI:SHP: Activity impairment due to excess weight from baseline to month 12

5.7.2 Statistical Analysis for the Secondary Estimand

5.7.2.1 Categorical Weight Loss

The secondary estimand for the categorical weight endpoint of ≥ 5% reduction in body weight from baseline (5% responder) will be assessed using the MMRM for efficacy as described for the secondary estimand for the primary endpoint in Section 5.6.2. Analysis will only use assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment. From the MMRM, individually predicted values for % weight change at month 12 will be used to classify each subject as 5% responder or not. This classification will then be analyzed using a logistic regression model with treatment as the only factor. From the model, the estimated OR (WMP + Rx / WMP) will be presented with the 95% CI and p-value. In addition, the predicted probability of achieving at least 5% body weight loss for an average trial subject in each treatment arm will be estimated from the model.

The secondary estimand for the categorical weight endpoint of ≥ 10% reduction of body weight from baseline (10% responder) will follow the same approach outlined for the 5% responder. The estimated OR (WMP + Rx / WMP), 95% CI and p-value will be presented, along with the predicted probability of achieving at least 10% body weight loss for an average trial subject in each treatment arm.

5.7.2.2 PRO Analysis

The secondary estimand for change from baseline (month 0) to month 12 (visit 13) in work productivity and work limitation endpoints (Section 3.2) will be assessed using the MMRM for efficacy as described for the secondary estimand for the primary endpoint in Section 5.6.2. The MMRM for efficacy will only use PRO assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment. The MMRM for efficacy will be fitted using change in PRO endpoint with randomized treatment as factor and baseline value of the endpoint variable as covariate, all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

5.7.3 Supplementary Analyses

The PRO analyses outlined for the primary and secondary estimands for the secondary PRO endpoints described above will be complemented with two supplementary PRO analyses.

- The analysis described in Section 5.7.1.4 will be repeated but evaluating change from baseline (month 0) to month 6 (visit 7) in work productivity and work limitation endpoints.
- The analysis described in Section 5.7.2.2 will be repeated but evaluating change from baseline (month 0) to month 6 (visit 7) in work productivity and work limitation endpoints. In place of the MMRM analysis, an ANCOVA model with randomized treatment as a factor and baseline value of the endpoint variable as covariate will be used. Analysis will only include month 6 (visit 7) PRO assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment.

5.8 PRO Analysis

In addition to the PRO endpoint analyses described under Section 5.7, data regarding all PROs will be reported for the entire sample by treatment group. Percentages of completed PROs will be reported as well. Descriptive statistics will be reported for aggregate scores for all appropriate measures by total score and subscale score(s) if applicable.

5.9 Excluded Medications

The number and percentages of patients reporting pre-specified excluded medication use during the study will be summarized for the population overall and by treatment group. Disallowed medications include GLP-1 RAs or SGLT-2 inhibitors for diabetes and any medication on- or off-label prescribed for weight loss other than the medication prescribed by the study clinician for chronic weight management.

6.0 SAFETY

6.1 AEs

For the purpose of this study, AEs will only be required to be collected if they meet the definition of an SAE (Protocol Section 7.2).

6.2 SAEs

All AEs meeting the definition of an SAE (Protocol Section 7.2) will be collected in the eCRF.

6.3 Pregnancy

Any abnormal pregnancy outcome (e.g., spontaneous miscarriage, fetal death, congenital anomaly/birth defect, etc.) is considered an SAE. For the purposes of this study, any pregnancies in participating female patients will be reported, along with pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age.

6.4 Technical Complaints

All SAEs resulting from a technical complaint will be collected in the eCRF.

6.5 Analysis

No formal safety analyses are planned for this study. SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarized by System Organ Class (SOC) and Preferred Term (PT). Pregnancies and technical complaints occurring during the study will be also be descriptively summarized.

7.0 SAP CHANGE LOG

Summary of SAP Changes since First Patient First Visit

SAP Version	Section/Page	Change	Rationale
2	Section 5.6.3 / Page 17-18	Addition of two supplemental analyses for primary endpoint	To assess the impact of altering SMA administration (on-site to virtual) in response to COVID-19 on study findings for primary endpoint.

8.0 STUDY ENDPOINTS AND OTHER VARIABLES BY DATA SOURCE

Endpoint/Variable	Data Source	
	eCRF	Pharmacy card
Primary Endpoint		
Change from baseline (month 0) to month 12 (visit 13) in body weight (%)	X	
Supportive Secondary Endpoint Assessment		
Subjects who after 12 months achieve ≥5% reduction in body weight from baseline	X	
Subjects who after 12 months achieve ≥10% reduction in body weight from baseline	X	
Adherence to Cleveland Clinic's Integrated Medical WMP from baseline (month 0) to month 12 (visit 13), as number of SMAs attended	X	
Adherence to Cleveland Clinic's Integrated Medical WMP from baseline (month 0) to month 12 (visit 13), as subject attending ≥9 SMAs	X	
Adherence to medication for chronic weight management from baseline (month 0) to month 12 (visit 13) in the treatment arm randomized to the WMP in combination with medication for chronic weight management, as proportion of days covered (PDC) by prescription claims for medication for chronic weight management	X	X
Adherence to medication for chronic weight management from baseline (month 0) to month 12 (visit 13) in the treatment arm randomized to the WMP in combination with medication for chronic weight management, as subjects covered by prescription claims for medication for chronic weight management for at least 80% of days	X	X
Change in WLQ-8: At-Work Productivity Loss index from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WLQ-8: Time Management index from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WLQ-8: Physical Tasks index from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WLQ-8: Mental/Interpersonal Tasks index from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WLQ-8: Output Tasks index from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WPAI:SHP: Work time missed due to excess weight from baseline (visit 1, month 0) to month 12 (visit 13)	X	

Change in WPAI:SHP: Impairment while working due to excess weight from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WPAI:SHP: Overall work impairment due to excess weight from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Change in WPAI:SHP: Activity impairment due to excess weight from baseline (visit 1, month 0) to month 12 (visit 13)	X	
Additional Derived Outcome Variables for Supplementary Analyses		
Change in WLQ-8: At-Work Productivity Loss index from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WLQ-8: Time Management index from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WLQ-8: Physical Tasks index from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WLQ-8: Mental/Interpersonal Tasks index from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WLQ-8: Output Tasks index from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WPAI:SHP: Work time missed due to excess weight from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WPAI:SHP: Impairment while working due to excess weight from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WPAI:SHP: Overall work impairment due to excess weight from baseline (visit 1, month 0) to month 6 (visit 7)	X	
Change in WPAI:SHP: Activity impairment due to excess weight from baseline (visit 1, month 0) to month 6 (visit 7)	X	

9.0 REFERENCES

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