STATISTICAL ANALYSIS PLAN

PROTOCOL № CLAF237ARU05 / NCT02670928

Study title:

Interventional study of active weight management in patients with type 2 diabetes and obesity in routine clinical practice during 12 months

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Approval page

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
CRF	Case Report Form
DBP	Diastolic blood pressure
FAS	Full analysis set
FBG	Fasting blood glucose
GEE	Generalized Estimating Equations
HbA1c	Glycosylated hemoglobin
LLT	Lowest Level Term
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
PP	Per Protocol
SAE	Serious adverse event
SBP	Systolic blood pressure
T2DM	Type 2 Diabetes mellitus

Content

1 Purpose of the study

This study is aimed to achieve long-term weight loss in T2DM patients by use of comprehensive lifestyle change program, providing patients with structured diet, a physical exercise plan, group behavioral support and group education. Additionally the study was designed to establish that reduction of the body weight leads to the improvement of glycemic and lipid metabolism, and also to the reduction in blood pressure level. The study was also directed to show that lifestyle changes in T2DM patients can lead to a decrease in hospitalization rate and healthcare consumption. In order to demonstrate a change from standard of care, data will be collected from a parallel cohort in the same centers.

Study Objectives

Primary objective

The primary objective of the study is to demonstrate that comprehensive lifestyle changes program for patients with T2DM can lead to clinically significant weight reduction (≥5%) compared with baseline in 12 months of observation.

Secondary objectives

The secondary objectives are to show that intensive lifestyle changes program for patients with T2DM can lead to:

- weight reduction compared with baseline in 3, 6, 9 months of observation
- improved glycemic control: HbA1c and FPG
- improved blood pressure level
- improved lipid profile
- improved QoL (assessment of changes by Hypoglycemia Perspectives Questionnaire and by perceived exertion rate using Borg scale)

Other secondary objectives are:

- investigation of anthropometric parameters (waist circumference, waist-to-hip ratio, BMI)
- pharmacoeconomic analysis of T2DM therapy in active and control groups.

2 Study design and investigational plan

Study design

This is interventional, multicenter, non-randomized, parallel-group, open design study lasting during 12 months. Approximately 130 patients with type 2 diabetes and obesity were planned to be enrolled.
In spite of interventional study status, the drug therapy administration is carried out strictly in accordance with the approved instructions for medical use, only with the registered indications and in accordance with appropriate clinical practice. The decision on the drug therapy administration should be based only on the medical indications and on the judgment of a physician, but should not be dependent on the decision to include the patient in the study. The project includes unique method of weight management, specifically designed for the patients with type 2 diabetes. It includes five components:
1) Structured modified diet change;
2) Balanced and personalized physical exercises;
3) Cognitive behavioral support;
4) Intensive interactive medical assistance;
5) Group education.

The total duration of the study for each patient is 12 months (1 month is equal to 4 weeks or 28 days). Patients from active group will be monitored intensively during the first three months (weekly, with allowed visit window of +/- 1 day) and then will continue to participate in the study for the remaining 9 months. After the first 13 weeks, monthly (+/- 3 days) assessments of weight and health status of patients from the active group will be performed. Key laboratory parameters will be measured and the physician will make a decision on whether the diabetes therapy should be adjusted as the patient's weight is reduced.

3 Sample size determination

The primary objective of this study is to assess the change of weight from baseline, in patients with T2DM at 12 months in comparison to the change in weight from baseline in the parallel cohort. Sample size was calculated based on weight changes observed in Why Wait study conducted at the Joslin center. The average weight loss observed at the end of 12 months was 8%. Given that baseline criteria and translation of the program can be different in its implementation in Russia, we have assumed an achievable change in weight as 5%. Significant reduction of body weight in the control group is not anticipated. The sample size (with the possible dropout of 20%) of 100 patients in active group and 30 patients in parallel cohort is sufficient to provide 80% power to detect a significant difference (significance level is α=0.05) between values in the two groups.

4 Randomization and blinding

Not applicable.

5 Efficacy assessment

5.1 Primary endpoint

Number (proportion) of patients in active and control group that achieved weight loss of at least 5% in comparison with baseline at 12 months of observation.

5.2 Secondary endpoints

- Body weight decrease expressed in percents and in absolute values in comparison with baseline at 3, 6, 9, 12 months of observation;
- Number (proportion) of patients achieved weight loss of at least 5% in comparison with baseline at 3, 6, 9 months of observation;
- Number (proportion) of patients achieved weight loss of at least 10% in comparison with baseline at 3, 6, 9, 12 months of observation;
- Changes of HbA1c and FPG levels expressed in percents and in absolute values;
- Number (proportion) of patients achieved decrease of HbA1c by at least 0.5% in comparison with baseline;
- Number (proportion) of patients achieved HbA1c $\leq$ 7 % at 12 months of observation;
- Blood pressure changes in absolute values in comparison with baseline;
- Number (proportion) of patients achieved decreasing of systolic and diastolic blood pressure levels by at least 5 mmHg in comparison with baseline;
- Changes of lipid profile (cholesterol, triglycerides, LDL, HDL) expressed in percents and in absolute values in comparison with baseline;
- Changes of waist circumference, waist-to-hip ratio;
- Changes of BMI;
- Assessment of changes by Hypoglycemia Perspectives Questionnaire for active group patients, as well as by perceived exertion rate with Borg scale.

6 Patients enrolled in the study

The study planned to include 130 patients with type 2 diabetes and obesity. In the active group, it was planned to recruit 100 patients, who will actively participate in lifestyle correction program; the control group will consist of 30 patients with T2DM, matching the active group patients by main parameters, who will to be managed in accordance with routine clinical practice for T2DM patients. The control group should be comparable to the active group with regard to the core baseline parameters.

When forming the control group, the following criteria should be taken into account (inclusion criteria in the study): BMI (<30; ≥30) and baseline HbA1c (<7.5; ≥ 7.5). The decision about inclusion of a patient in the active or control group is left at the discretion of the treating physician.

Dropout of 20% from initially enrolled population was considered by the study design. The patient's dropout from the study is defined as three consecutively missed classes within the first 12 weeks of observation in the active group. No dropout in the control group is assumed.

Patients are distributed between two sites participating in the study.

The study is conducted on the basis of two clinical sites: [redacted], Moscow, and Kazan [redacted]. Adult patients with type 2 diabetes (men and women of 18 years and older) are chosen for body weight reduction program if the doctor decides that the active approach is justified in this case.

6.1 Inclusion Criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Signed Informed Consent. Written informed consent must be obtained before any assessment is performed.
2. Signed informed consent of ophthalmologist and cardiologist about inclusion of patient in the study*
3. Men and women at the age of 18 years and older
4. Confirmed diagnosis of Type 2 diabetes
5. The Body Mass Index is from 27 to 40 kg/m2

* - the criterion is applicable only for the active group.

6.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
2. Type 1 diabetes
3. Proliferative retinopathy, hemorrhage and disinsertion of retina
4. Renal impairment: serum creatinine >1.5 mg/dL, creatinine clearance < 40 ml/min and/or proteinuria.
5. The lack of ability to perform the physical exercises due to the orthopedic or cardiovascular disorders *
6. Chronic alcoholism, acute alcoholic intoxication

* - the criterion is applicable only for the active group.

7 Population determination for statistical analysis

- All enrolled patients: all patients who signed informed consent for inclusion in the study. The population will be used for the disposition data summaries and listings.
- Safety Population: all patients of the active group included in the study, who started participating in the lifestyle correction program, and all patients of the

control group for whom the observation was started. The population will be used to summarize adverse events and other safety parameters.

- Full Analysis Set (FAS): all patients who provided baseline data and data to evaluate at least one efficacy parameter after the onset of observation. The population will be used for efficacy analyses.
- Per Protocol Set (PP): all FAS patients who did not have any major protocol deviations. The population was used to analyze the primary endpoint (sensitivity analysis).

  The patient can be excluded from the Per Protocol Set for the following reasons:
  - did not attend more than 3 consecutive classes in the active group;
  - missed at least 50% classes of the program;
  - did not provide data for the estimation of the primary endpoint.

8 General considerations

The latest available estimates before the start of the program for the active group and data from the Visit 1 for the control group will used as the baseline values for the analysis of quantitative efficacy and safety parameters. The baseline visit is Visit 2 (Week 1) for the active group and Visit 1 for the control group.

The Last observation carried forward (LOCF) approach will be used in FAS population (primary analysis) to impute missing values of the efficacy parameters using the last available measurement after the initiation of the studied program for active group and after the start of observation for the control group.

Descriptive statistics for quantitative variables will include mean, standard deviation, median, quartiles, minimum and maximum, and the number of observations. The maximum number of decimal places reported shall be 4 for any summary statistic.

Qualitative data will be presented in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be calculated using n as denominator and will be presented to one decimal place.

9 Patient disposition

The following data on patient disposition will be provided for the All enrolled patients set:

- Number and proportion of patients in each population for statistical analysis;
- The number and proportion of patients enrolled in the study, as well as attended each study visit;
- Number and proportion of patients who discontinued prematurely (indicating the reasons for the discontinuation), as well as those who completed the study;
- Number and proportion of eligible patients.

10 Demographic and other baseline characteristics

The following demographic and other baseline characteristics will be tabulated and presented descriptively:

- Demographic characteristics (age, sex, race);
- Medical history (number (proportion) of patients with concomitant diseases);
- Duration of type 2 diabetes (months);
- Clinical manifestations of diabetes at the time of diagnosis and at the time of enrollment (the number (proportion) of patients with each of the clinicalmanifestations);
- Concomitant complications of diabetes (number (proportion) of patients with concomitant complications);
- Baseline body weight, height, body mass index;
- Baseline HbA1c% and fasting blood glucose (mmol/l).

Age will be calculated as the number of complete years between the date of birth of the patient and the date of signing the informed consent.

The body mass index (kg/m2) at each visit will be calculated as the ratio of body weight (kg) to the square of height (m) (Visit 1).

The duration of the disease will be calculated in years as (the date of the primary diagnosis of type II diabetes - the date of the informed consent + 1) / 365.25.

If the date of the primary diagnosis is partial, the following imputation rules will be used to calculate the duration of the disease:

- If year is missing - no imputation (missing value);
- If month and day are missing, 1st of January will be used;
- If only day is missing, 1st day of the corresponding month will be used.

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0). Prior and concomitant therapy will be coded using the WHO DDE Dictionary (1st December 2016), including the ATC class and LLT (Lowest Level Term).

All demographic data, concomitant therapy, and medical history data will also be listed.

11 Treatment

Patients participating in this study will receive drug therapy for diabetes according to routine clinical practice, and there are no restrictions for the therapy because of patient's participation in this study.

The drugs are used in accordance with the instruction for medical use, only for registered indications and in accordance with routine clinical practice.

The duration of treatment will be calculated as the length of participation in the study (the date of study completion or date of the last visit - the date of the baseline visit + 1) / 7 (weeks).

The program duration will be calculated for the active group as the length of participation in the program (the date of the last visit during the program sessions - the date of the initial visit + 1) / 7 (weeks).

Information on the intake of hypoglycemic therapy during the study will be presented in the frequency tables by ATC class and Lowest Level Term.

The duration of treatment within the study and the length of the program in weeks will be tabulated using descriptive statistics for continuous variables. The number and percent of classes attended will be summarized.

The number and percentage of patients taking concomitant medications will also be presented in frequency tables by ATC class and Lowest Level Term.

12 Efficacy analysis

12.1 Treatment response variables

Descriptive statistics for body weight (kg), body mass index (kg/m2), waist circumference (WC, cm) and waist to hip ratio (WHR), HbA1c%, fasting blood glucose (mmol/L), lipid profile (cholesterol, triglycerides, LDL, HDL) values together with absolute and relative (%) changes from baseline, as well as systolic and diastolic blood pressure (mmHg) values together with absolute changes, will be tabulated by visit for the FAS population. In addition, descriptive statistics for the above variables and their changes will be tabulated for visits corresponding to Weeks 12, 24, 36, 48, after the imputation of missing values using LOCF approach.

The primary endpoint - the number (proportion) of patients for whom body weight decreased by at least 5% compared to baseline values at 12 months of observation - will be analyzed in FAS (LOCF), additionally the primary endpoint analysis will be repeated in the Per Protocol Set (PP).

The number and proportion of patients with a decrease in body weight of at least 5% compared to the baseline values at 12 months of observation will be tabulated based on available measurements and based on imputed (LOCF) values in the FAS population. The results for the primary endpoint will also be presented by centers.

To compare proportions between groups, the main analysis of the primary endpoint will be carried out using logistic regression with the calculation of the odds ratio with 95% CI. In order to adjust for the potential confounding factors, potentially influencing factors such as age, gender, baseline value of the body mass index, the duration of the disease, baseline level of HbA1c will be included in the regression model.

As part of the sensitivity analysis, the primary endpoint will be analyzed without imputation of missing values using the GEE (Generalized Estimating Equations) method, taking into account the correlation of the repeated measurements at different visits for each patient.

The model will include group, time (visit) and group*time interaction. In addition to group, time and interaction term, only significant influencing factors (age, gender, baseline body mass index, disease duration, baseline HbA1c) ($p < 0.1$) will be included in the model. A first order autoregressive covariance structure [AR (1)] will be used in the model. If convergence is not achieved, other covariance structures (Independent, unstructured covariance structure (Unstructured)) will be tested as possible alternatives. Differences between groups (active group - control group) will be assessed using interaction term group*time, calculating the adjusted means and corresponding 95% confidence intervals for the group*time interaction.
Secondary dichotomous variables - a decrease in body weight by at least 5% at 3, 6, 9 months of observation and at least 10% of the baseline values at 3, 6, 9, 12 months of observation will be analyzed in a similar manner.

Secondary dichotomous endpoints – a decrease of HbA1c level by at least 0.5% from baseline, achievement of HbA1c $\leq$ 7% by 12 months of observation, a decrease in SBP and DBP by at least 5 mmHg at 3, 6, 9, 12 months of observation - will be analyzed using GEE with the imputation of missing values.

After the imputation of missing values, the endpoints representing the absolute and relative (%) changes in the quantitative variables for 3, 6, 9 and 12 months will be analyzed using the GEE method. The initial values of the relevant variable, age, sex, baseline body mass index, duration of the disease, and the initial value of HbA1c% will be used as factors and covariates. 95% confidence intervals for mean values of the parameters in both groups will be presented, as well as for the difference in the mean values between the compared groups adjusted for the influence of these factors.

In case of significant deviations from the normal distribution (verified using graphical methods), the logarithmic transformation or nonparametric Mann-Whitney U-test will be used as possible alternatives.

All data on primary and secondary endpoints will also be presented in the form of listings.

12.2 Safety assessment

The safety variables will be analyzed in the Safety Populations, missing measurements will not be imputed.

Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19).

Data on adverse events will be presented in terms of the number and proportion of patients with any adverse events overall, by system organ class (SOC) and preferred term (PT).

The number (proportion) of patients with AE and the number of AE will be tabulated by system organ class and preferred term, as well as by relationship to study treatment and severity. Within each system organ class and preferred term, each patient will be counted only once with the closest relationship to the study treatment or maximum severity. In the case of missing value of severity or relationship, the AE will be considered in the table as "severe" and "related", respectively.
The following tables will be provided:

- The number (proportion) of patients with AE and the number of AEs by system organ class and preferred term;
- The number (proportion) of patients with AE and the number of AEs related to study treatment by system organ class and preferred term;
- Number (proportion) of patients with AE and the number of AEs by severity, by system organ class and preferred term;
- The number (proportion) of patients with AE and the number of AEs that led to discontinuation of the program (for the active group), by system organ class and preferred term;
- The number (proportion) of patients with AE and the number of AEs that are fatal, by system organ class and preferred term;
- The number (proportion) of patients with SAE and the number of SAE, by system organ class and preferred term;

The analysis will not include AEs that started before the start of a lifestyle change program for patients in the active group. In the case of a partial start date for AE, it will be compared as far as possible with the program start date to determine if it occurred prior to the start of the program. If the available information is not sufficient, the AE will be considered to have started after the beginning of the program.

The analysis of the SAE will include all registered SAE. Data on all AE / SAE will be presented in the form of listings.

Laboratory data

Laboratory investigations were conducted on Visit 1, Week 12 and 48 and included the following parameters:

Biochemistry: total protein (g/l), cholesterol, LDL, HDL (mmol/L), triglycerides (mmol/L), ALT (U/l), AST (U/l), CPK (U/l) , creatinine (μmol/L), GFR.

Haematology: hemoglobin (g/l), leukocytes (10^9/l) (+ formula), erythrocytes (10^12/l), platelets (10^9/l), ESR.

Urinalysis: color, transparency, relative density, protein, glucose, ketones.

Descriptive statistics will be used to analyze the laboratory data. Hematology and biochemistry lab parameters values and their absolute changes from baseline will be presented by groups and study visits. Tables of shifts relative to normal ranges (low / normal / high) will be tabulated by visit. For the urinalysis parameters, the number and proportion of the normal / non-clinically significant deviations / clinically significant deviations will be tabulated. All laboratory data will be presented in listings.

Vital signs

Systolic and diastolic pressure (mmHg), heart rate and respiratory rate will be recorded at each visit of the study. For the analysis of vital signs, descriptive statistics will be used. Parameters of blood pressure, heart rate and respiratory rate and their absolute changes in from baseline values will be tabulated by visit. All vital signs data will be presented in listings.

ECG

ECG was performed on Visit 1, Week 12 and 48. The ECG results (normal / non-clinically significant deviations / clinically significant deviations) will be tabulated as the number and percentage of patients with each of the assessments from the number of patients present at the visit.

Physical examination

The results of the physical examination, including an overall assessment of the basic parameters of the vital activity of the organism, will be recorded on Visit 1 and on all visits, beginning from Week 12 in both groups, and also 4 and 8 weeks after inclusion in the study for active group patients. The results of the physical examination will be tabulated as the number and percentage of patients with each of the assessments (normal / non- clinically significant deviations / clinically significant deviations) from the number of patients present at the visit.

13 Other variables

The scale of individual perception of physical activity (the Borg scale) was filled on Visit 1 and at the end of the program in the active group. The score on the scale will be presented using descriptive statistics as the number and proportion of patients for each category. Changes will be presented as cross-tabulation of estimates at the beginning and after the program.

The questionnaire for hypoglycemia evaluation was filled on Visits 1, 24 and 48 weeks of observation. For each patient, the result for subscales 4, 5, 6, 7, 8, 9 will be calculated as the mean value of answers to subscale questions. The results for all subscales and changes from baseline will be presented descriptively by groups and visits.

14 Interim analysis

Not planned.

15 Presentation of results

Statistical analysis will be performed using IBM® SPSS® Statistics Version 19.0 or later. All results will be presented in the form of tables, listings and figures.

16 Changes in the statistical analysis plan

The analysis of the quantitative efficacy endpoints at each individual assessment visit using ANCOVA was replaced with an analysis based on a similar model, which takes into account the correlation between the repeated measurements, using the GEE method (Generalized Estimating Equations).

Secondary dichotomous endpoints - a decrease of HbA1c level by at least 0.5% from baseline, achievement of HbA1c $\leq$ 7% by 12 months of observation, a decrease in SBP and DBP by at least 5 mmHg at 3, 6, 9, 12 months of observation - will also be analyzed using GEE (logistic regression of repeated changes) instead of logistic regression for individual evaluation visits.

17 References

1. ICH (1998). International Conference on Harmonization. Guideline E9 on Statistical Principles for Clinical Trials.

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