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Interventional Study Protocol

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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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1 List of abbreviations

AE	Adverse Event
BMI	Body Mass Index
BP	Blood pressure
CAD	Coronary artery disease
CI	Confidence interval
CRF	Case Record Form
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiography
eCRF	Electronic Case Record Form
FPG	Fasting plasma glucose
HbA_{1c}	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
HDL	High Density Lipoprotein
HE	Health economic
LDL	Low Density Lipoprotein
LEC	Local Ethic Committee
PhA	Physical activity
PPG	Postprandial Glucose
RAE	Russian Association of Endocrinologists
QoL	Quality of Life
SAE	Serious Adverse Event
SBP	Systolic blood pressure
T2DM	Type 2 Diabetes mellitus
TE	Therapeutic exercise
TG	Triglycerides

2 Responsible parties

Table 2-1. Main responsible parties

Role	Person
Main protocol author	[redacted]
Principal investigator (PI)	[redacted]
Scientific support	[redacted]
Medical Safety Expert	[redacted]

3 Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Study discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

4 Protocol synopsis

Protocol number	
Title	Interventional study of active weight management in patients with type 2 diabetes and obesity in routine clinical practice during 12 months
Brief title	Feeling better together
Sponsor	Novartis
Investigation type	Non drug
Study type	Interventional study
Purpose and rationale	This study is aimed to achieve of long-term weight loss in T2DM patients by use of comprehensive lifestyle changes program, providing patients with structured diet, exercise plan, group behavioral support and group education. Additionally the study is designed to establish reduction of the body weight leads to the improvement of glycemic and lipid metabolism, and can also reduce blood pressure level. The study is also directed to show that lifestyle changes program in T2DM patients can lead to decreasing of hospitalization rate and healthcare consumption. In order to demonstrate a change from standard of care, data will be collected from a parallel cohort from the same centers.
Primary Objective(s) and Key Secondary 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 ($\geq$5%) compared with baseline in 12 months of observation.
Secondary Objectives	The secondary objective is 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
Study design	This is a interventional, multicenter, non-randomized, parallel-group, opened designed study lasting during 12 months for approximately 130 patients with type 2 diabetes and obesity.
Population	The study is expected to include approximately 100 patients with T2DM and obesity who will be on active management and another 30 patients whose case records will be collected from routine clinical practice for comparison purposes.
Inclusion criteria	• Signed Informed Consent. Written informed consent must be obtained before any assessment is

	performed. • ≥ 18 years • Type 2 diabetes • The Body Mass Index is from 28 to 40 kg/m^2
Exclusion criteria	• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. • Type 1 diabetes • Proliferative retinopathy • Renal impairment: serum creatinine >1.5 mg/dL, creatinine clearance < 40 ml/min and/or proteinuria • The lack of ability to perform the physical exercises due to the orthopedic or cardiovascular disorders • Chronic alcoholism, acute alcoholic intoxication
Investigational and reference therapy	No drugs will be supplied during the study. Hypoglycemic drug therapy will be provided according routine standard practice without any special changes.
Efficacy assessments	• Weight reduction • Control of glycemic in HbA1C and FPG • Blood pressure • Lipid profile indicators
Safety assessments	• Adverse events • Vital signs • Laboratory assessments • ECG
Other assessments	• HE supply form • Survey for hypoglycemic assessment • Scale of individual perception of physical exercises (Borg scale)
Data analysis	Descriptive statistics will be applied in the study to describe the sample size of the patients at baseline and at follow-up visits, demographic data recorded during the examination of the study parameters, as well as their changes. The primary analysis of the proportion of the patients with response on the treatment will be performed using multivariate logistic regression and calculating odds ratios with corresponding 95% CI. To control the potential confounding factors, age, sex, BMI, disease duration, the baseline values of HbA1c will be taken into account in the regression model.
Key words	Type 2 Diabetes mellitus, obesity, life changes

Amendment 1

Changes in Protocol

Changes in Protocol are indicated in track changes in the following mode: deleted paragraphs are marked as text deleted, new paragraphs are marked in bold.

Background for the Addendum.

This Addendum is made to optimize the schedule of tests and visits for patients, i.e.:

- Results of physical examinations, indications of BMI, waist circumference and waist/hip circumference ratio in patients of active groups in the first three months will be registered in four and eight weeks after inclusion into the study.
- Analysis of HbA1c will be conducted at the Visit 1 and then after 12, 24, 36 and 48 weeks after the patient is included in the study.
- Complete blood count and biochemical blood tests, general urine test and ECG will be conducted at Visit 1 and then after 12 and 48 weeks after the patient is included in the study.
- HE supply form will be conducted at the 1st visit and then at the end of study (week 48).

Another changes/corrections were made to ensure the text is cohesive and consistent and is stylistically viable.

Approval by the Independent Ethical Committee

Before this Protocol version with incorporated Addendum 1 becomes active it should be verified and approved by the Independent Ethical Committee. Additionally, above mentioned changes also relate to the Consent form that should also be approved by the Research centers. Signed Certificate should be at Sponsor's disposal once approved by the Independent Ethical Committee.

Summary of the previous Addendums

Not applicable.

5 Introduction

5.1 Background

Type 2 Diabetes mellitus (T2DM) is a chronic, progressive disease characterized by hyperglycemia due to multiple metabolic disorders, including the resistance of peripheral tissues to insulin, inappropriate secretion of insulin, increased glucose production in the liver and hyperglucagonemia [1].

Most part of the patients with T2DM has obesity. Global data indicates that 80% of patients with diabetes mellitus are overweight, and in patients with type 2 diabetes, this proportion is higher. In Russia about 50% of the patients with T2DM are suffering from obesity (body mass index [BMI] > 30 kg/m2) and 45% of patients are overweight (BMI 25-29 kg/m2). In the process of body weight management in patients with T2DM, there are certain problems: unwillingness of the physicians and the patients to modify the lifestyle, the diet and the habits, as well as use of the drug (insulin, sulphonylurea) leading to increase in body weight. Surveys confirm that one third of the physicians do not give to the patients with obesity any recommendations for lifestyle modification in obesity. It indicates that the physicians do not have the tools to long-term change of these parameters [2].

The adipose tissue is the basis for the development of insulin resistance; therefore, obesity is a significant aggravating factor for achievement of the carbohydrate metabolism compensation and is associated with cardiovascular risk factors [3].

The adipose tissue is the potent endocrine organ synthesizing hormones and adipokines, most of which negatively influence on the cardiovascular risk profile (increase in BP, activation of pro-inflammatory and pro-thrombotic processes, atherogenic effects) [4].

According to the one of the largest studies in the diabetes history - Look AHEAD (follow-up for 13.5 years), it was evidenced that in patients with reduced body weight and with the maintenance the result in the course of the study, the parameters of the cardiovascular diseases and mortality, the incidence of the strokes and heart attacks decreased [5].

This study complies with the guidelines for medical care provision for the patients with T2DM in the Russian Federation. The algorithms for specialized medical care of patients with T2DM [6] recommend as the based therapy the combination of the following approaches:

- Diet therapy
- Physical activity
- Antidiabetic drugs
- Education and self-control.

This study provides the personalized approach to the lifestyle changes in the patients, the development of an optimal exercise and nutrition plan, the change in the behavioral habits of the patient in order to adopt the corrections and to the improve the adaptation, as well as to adjust a drug treatment plan in order to use the agents, indifferent to the body weight.

5.2 Purpose

This study is aimed to achieve of long-term weight loss in T2DM patients by use of comprehensive lifestyle changes study, providing patients with structured diet, exercise plan,

group behavioral support and group education. Additionally the study is designed to establish that reduction of the body weight leads to the improvement of glycemic and lipid metabolism, and can also reduce blood pressure level. The study is also directed to show that lifestyle changes study in T2DM patients can lead to decreasing of hospitalization rate and healthcare consumption. In order to demonstrate a change from standard of care, data will be collected from a parallel cohort from the same centers.

6 Study objectives

6.1 Primary objective(s)

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

6.2 Secondary objectives

The secondary objective is 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 based on Nvs survey in hypoglycemia and scale of individual perception of PhA (scale of Borg)
- assess changes of another anthropometric indicators (waist circle, proportion of waist circle and circle of hips, BMI)
- HE assessment of drug therapy in patients with T2D in active and control groups.

6.3 Primary end point

Number of patients in active and control groups who presented a weight reduction in 12 months and not less than 5% compared with the baseline.

6.4 Secondary end points

- Weight reduction in % and in absolute numbers compared with baseline in 3rd, 6th, 9th and 12th months of observation;
- Number (proportion) of patients who showed weight reduction not less than 5% compared with the baseline in 3rd, 6th, 9th and 12th months of observation;
- Number (proportion) of patients who showed weight reduction not less than 10% compared with the baseline in 3rd, 6th, 9th and 12th months of observation;

- Change of HbA1c and FPG in % and absolute numbers;
- Number (proportion) of patients who reached reduction of HbA1c at least of 0,5% compared with the baseline;
- Number (proportion) of patients who reached reduction of HbA1c of ≤7% in 12 months of observation;
- Change of arterial blood pressure in absolute numbers compared with the baseline;
- Number (proportion) of patients who reached reduction of SBP and DBP at least at 5 mm Hg;
- Change in lipid profile (cholesterol, triglycerides, lipid protein of high and low density) compared with the baseline in % and absolute numbers;
- Change in waist circle, proportion of waist circle and circle of hips;
- Change in BMI;
- Assessment of change in hypoglycemia based on Nvs survey for the patients in active group – also based on Borg scale (individual perception of PhA).

7 Investigational plan

7.1 Study design

This is a interventional, multicenter, non-randomized, parallel-group, opened designed study lasting during 12 months for approximately 130 patients with type 2 diabetes and obesity.

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;

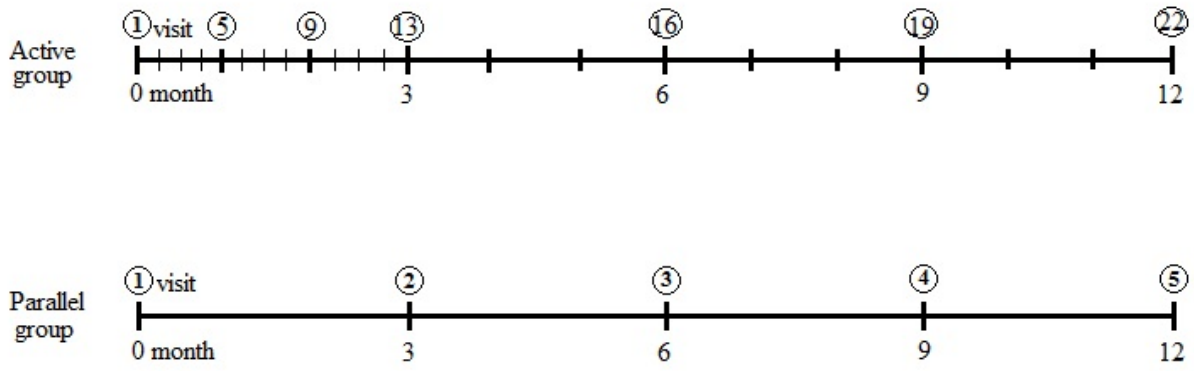
4) Intensive interactive medical assistance;

5) Group education.

An outline of the study design is presented in Figure 7-1. The full study lasts 12 months (1 month constitutes 4 weeks or 28 days). Patients from active group are monitored intensely during the first three months (on a weekly basis with acceptable window of visits +/- 1 day)

and then maintained on the study for the remaining 9 months. Plan of activities with the step of one week is described in the **Appendix 1.**

Figure 7-1 Study design



Information materials will be handed out to patients in active group during the group classes (Appendix 8, 9, 10, 11, 12, 13, 1):

- Diary of self-control
- Information card
- Diabetes practicum
- Practicum on nutrition (Hurmanica)
- Practicum on physical activity (PhizcultUra)
- Psychological practicum (fly of bumblebee)

After the first 13 weeks, monthly assessments are made on weight and health status for active group. Key biomarkers are measured (Please see Table 6-1) and the physician makes a decision on whether the diabetes medicines need to be adjusted as the patient reduces weight.

Table 7-1. Assessment visit schedule in active group

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Week*		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Obtain informed consent	X																					
Inclusion/exclusion criteria	X																					
Consultation of cardiologist	X																					
Consultation of ophtalmologist	X																					
Hypoglycemic therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concominant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Consultation of a psychologist	X																					

Nutritionist consultaition	X																				
TE doctor/fitness trainer consultation	X																				
Demographic data[1]	X																				
Diabetes history[2]	X																				
Relevant medical history / current medical condition[3]	X																				
Group classes with endocrinologist		X	X	X	X	X	X	X	X	X	X	X	X								
Group classes with psychologist		X	X	X	X	X	X	X	X	X	X	X	X								
Group classes of nutrition		X	X	X	X	X	X	X	X	X	X	X	X								
Group classes of medical physical culture		X	X	X	X	X	X	X	X	X	X	X	X								
Physical examination	X					X				X			X	X	X	X	X	X	X	X	X
HbA_{1c}	X												X			X			X		X
FPG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X				X				X				X	X	X	X	X	X	X	X	X
Waist circumference	X				X				X				X	X	X	X	X	X	X	X	X
Waist/hip ratio	X				X				X				X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (standard 12-lead)	X												X								X
General blood pressure[4]	X												X								X
Clinical blood chemistry[5]	X												X								X
Urinalysis[6]	X												X								X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diaries of self-control	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemia questionnaires	X															X					X
Scale of Borg[7]		X																			X
HE supply form	X				X				X				X	X	X	X	X	X	X	X	X

*Acceptable deviation for weekly planned visits (visits 2-13) is +/-1 day from the planned date, monthly visits (visits 14-22) is +/- 3 days from the planned date.

[1] Demographic indicators: age, gender, race.

[2] Date of diagnosis of diabetes, clinical symptoms.
Therapy for diabetes: insulin (type, dosage), insulin+oral hypoglycemic therapy (type, dosage), sulphonylurea (type, dosage), glinide (type, dosage), metformin (dosage), TZD (dosage), DPP4 (type, dosage), GLP1 (type, dosage), other type of treatment.
Complications of diabetes: cardio-vascular diseases, strokes, retinopathy, neuropathy, nephropathy, diabetic foot, other.

[3] Concomitant diseases (cardio-vascular diseases, hypertension, eye diseases, vascular diseases of the brain, gastrointestinal tract diseases, respiratory diseases, liver and bile ducts diseases, kidney diseases, blood diseases, etc.)

[4] General blood test: hemoglobin, leukocytes (+formula), erythrocytes, thrombocytes, ESR.

[5] Clinical blood test: crude protein, cholesterol, lipids of low and high density, triglycerides, ALT, AST, KPhK, creatinine, GFR.

[6] Urine analysis: color, transparency, relative density, traces of protein, sugar in urine, ketone bodies.

[7] Scale of Borg (scale of individual perception of physical training) is part of Information card (Appendix 8).

Study completion																					X

The parallel group will be examined for all criteria at the beginning of the study and invited for physician examination at months 3, 6, 9 and 12 to collect data on primary and secondary endpoints (Please see Table 7-2).

Table 6-2. Assessment visit schedule in control group

Visit	**1**	**2**	**3**	**4**	**5**
Week		**12**	**24**	**36**	**48**
Obtain informed consent	X				
Inclusion/exclusion criteria	X				
Hypoglycemic therapy	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
Endocrinologist consultation	X	X	X	X	X
Demographic data	X				
Diabetes history	X				
Relevant medical history / current medical condition	X				
Physical examination	X	X	X	X	X
HbA_{1c}	X	X	X	X	X
FPG	X	X	X	X	X
Weight	X	X	X	X	X
BMI	X	X	X	X	X
Waist circumference	X	X	X	X	X
Waist/hip ratio	X	X	X	X	X
ECG (standard 12-lead)	X	X			X
General blood test*	X	X			X
Clinical chemistry*	X	X			X
Urinalysis*	X	X			X
AEs	X	X	X	X	X
Survey on hypoglycemia	X		X		X
HE supply form	X	X	X	X	X
Study completion					X

*All indicators are collected the same way as in active group (see the table 7-1 as a reference). Acceptable deviation from the planned date for visits is +/- 3 days.

7.2 Rationale of study design

This study focuses on a population of patients who present with T2DM and obesity. All patients are eligible for both active and parallel groups only in the case of fulfilling all inclusion criteria and not fulfilling all exclusion criteria (see chapter 4). Study design is aligned with previously published studies of lifestyle changes in such patients [2,5].
Study is non-randomized. Patients can be included in active or control groups only provided they meet all the inclusion and exclusion criteria. By doing this we ensure the effect of another influencing factors are minimized.

Study period and parallel group study design allows achieving of primary end point.

The control group indicators should be coordinated with the indicators of patients in active group. The following should be taken into account when active group is being formed: correspondence of BMI and baseline HbA1c. The decision on whether the patient is included in active or control group is made by the doctor.

7.3 Rationale of dose/regimen, route of administration and duration of treatment

Not applicable.

7.4 Rationale for choice of comparator

Not applicable.

7.5 Purpose and timing of interim analyses/design adaptations

No interim analyses will be performed. The primary endpoint analysis will be performed at the end of the study, after all patients have completed their study assessments and the database locked.

7.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring.

There are no therapy changes or innovations in this study. 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 study is designed to establish for patients with T2DM and obesity the reduction of the body weight, improvement of glycemic and lipid metabolism, and reducing blood pressure level. We expect that the study can improve a QoL and reduce diseases complications in the study populations. Nvs survey on hypoglycemia will be used to assess the quality of life in patients **(Appendix 2).**

8 Population

The study is expected to include approximately 100 patients with T2DM and obesity. It is planned to have 100 patients in the active group who will be on active life style management; the control group will be 30 patients who will be matched with active group in terms of their indicators. Both groups will receive standard drug therapy for diabetes.

The control group should match the active group. The following criteria should be taken into account (criteria of inclusion and exclusion): match in BMI (<30; ≥ 30) and baseline HbA1c (<7.5; ≥ 7.5). The decision to include a patient into active or control group should be made by a doctor.

Drop-out of patients is expected for about 20% of patients compared with the originally included population. The drop-out criteria is three in a row missed group classes in the first 12 weeks of the study in active group.

The drop-out in control group is not expected.

Patients will be distributed among two participating research centers.

The study will be executed in two sites, the [redacted] in Moscow and the [redacted] in Kazan. The adult patients with T2DM (men and women at the age of more than 18 years) will be under the observation if they need in the active weight loss according to the physician's decision and if a doctor decides that the active approach is necessary.

An investigator must ensure that the participation in the study will be offered only to the patients, which meet the criteria for the study participation. To ensure the representativeness of the sample size, an investigator should not use any additional exclusion criteria; in addition, he/she must provide equal access to the study participation for all patients suitable for inclusion criteria. Drug therapy administration should be based exceptionally on the medical indications and should not aim at the inclusion of the patient in the study.

8.1 Inclusion criteria

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

1. Signed Informed Consent Form **(Appendix 3 and 4).** Written informed consent must be obtained before any assessment is performed.
2. Signed Informed Consent Form of doctor-ophthalmologist **(Appendix 5)** and cardiologist **(Appendix 6)** about inclusion of the patient *.
3. Men and women at the age of 18 years and older
4. Type 2 diabetes
5. The Body Mass Index is from 28 to 40 kg/m2

The objective to have a signed consent form from ophthalmologist and cardiologist is to ensure the patient can practice physical exercises and the level of physical activity for a patient (active, with limitations and what particular limitations) based on the existing condition – if cardio-vascular diseases are present. Consultation of ophthalmologist and cardiologist should be conducted before patients are included in the study. Medical specialists will be selected from the existing research center staff (Moscow and Kazan) where he study will be conducted.

8.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

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 peeling of a 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 criteria is only applicable to the active group.

9 Treatment

Hypoglycemia drug therapy will be applied to the study participants according to the routine clinical practice, no limitations to correct the therapy (for the reason a patient takes part in the study) is implied.

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 investigator should inform the patients that in case the patient change their therapy or take new drugs the patients should inform the investigator. All drugs (including non-patterned name, dosage, first and end date of intake) and clinically significant non-medical therapy that are used by the patients to treat diabetes at the moment the patient enters the trial should be registered in eCRF.

10 Visit schedule and assessments

Patients will be subject to a comprehensive evaluation of health and functional status.

The main parameters, which should be measured in accordance with the periodicity adopted in routine practice:

- BMI and body weight
- Waist circumference, ratio between waist and hip
- HbA_1c, FPG
- BP (SBP, DBP)
- Lipid profile (cholesterol, triglycerides, LDL, HDL)
- The number of DM related hospitalizations
- QoL data via filling of questionnaires
- HE data **(Appendix 7)**

The full study lasts 12 months. Patients in active group are monitored intensely every 7 days. After first 13 weeks assessment of weight and health condition are conducted on a monthly basis (see Table 7.1 as reference). For patients in control group all examinations should be conducted every three months (see Table 7.2 as reference).

In order to collect data for the primary and secondary end points (6.3, 6.4) in control group assessment of all indicators will be conducted at trial' start and then the patients will be invited to the doctor by the end of 3rd, 6th, 9th and 12th months (see table 7-2).

Patients from active group fill out the Information card before they enter the study **(Appendix 8)** and Registration form **(Appendix 9).** Patients fill out the Information card at the end of the study as well (including assessment of individual perception of physical exercises using the scale of Borg).

It is necessary to discuss with a patient the patient's ability and readiness to make changes in his/her lifestyle when a doctor makes a decision to include a patient in the study.

The program of active weight reduction includes group classes with the team of doctors:

- Nutritionist in regards to healthy nutrition **(Appendix 10)**
- TE doctor/fitness trainer in regards to physical activity **(Appendix 11)**
- Psychologist in regards to motivation and education **(Appendix 12)** and self-control **(Appendix 13)**
- Endocrinologist **(Appendix 13).**

Classes for the patients in active group are conducted one time a week in the first 12 weeks with the following monitoring once a month in the next 36 weeks. Total period of observation is one year (48 weeks). Detailed classes description is in the **Appendix 1**.

Patients from control group do not take part in the group classes but their indicators are collected during the routine visits to doctors (a doctor will invite a patients following the plan of visits, table 7-2).

All prescribed procedures assigned by the doctors should meet the medical needs of the patients and should be conducted according to the recommendations of the Russia Association of Endocrinologists.

The specialists will use their professional skills in order to achieve the purposes and outcomes and they are responsible for taking into account the guidelines of the RAE.

Recommendations of the nutrition specialist should be within the framework specified by the Russian algorithms for the patients with type 2 DM (6th edition, 2013, chapter 6.1.1. Recommendations for diet), namely:

Diet therapy of the patients with type 2 DM which are overweight/obese, not receiving insulin

1.1. The basic principle - moderately hypocaloric diet with the caloric deficit of 500 - 1000 calories per day, but not less than 1500 kcal per day (men) and 1200 kcal per day (women).

1.2. More marked caloric restriction is used only for a short time and only under medical supervision. Fasting is absolutely contraindicated.

1.3. Calorie reduction is achieved by restriction of high-fat food, simple carbohydrates, as well as restriction of complex carbohydrates and protein by about fifty percent of the usual patient consumption. More strict carbohydrate restriction is not indicated.

1.4. It is not necessary to calculate the carbohydrates using carbohydrate units.

- Inclusion in the diet the food products enriched with plant fiber (fiber) (vegetables and herbs, cereals, flour, products of household flour), unsaturated fatty acids (vegetable oils in small quantities, fish);
- Moderate use of the noncaloric artificial sweeteners is admissible;
- Use of alcoholic beverages should be not more than 1 conventional unit per day for women and 2 conventional units for men,* in case of the absence of pancreatitis, severe neuropathy, hypertriglyceridemia, alcohol dependence.
- It is not recommended:

- Intake of vitamins (in case of the absence of clinical signs of vitamin deficiency) and antioxidants due to the insufficient knowledge of the long-term results of their use.

Recommendations of TE doctor/fitness instructor should be located within the framework provided by the Russian algorithms (6th edition, 2013, chapter 6.1.2. Recommendations on Physical Activity), namely:

- Regular physical activity (PhA) in type 2 DM improves the glycemic control, helps to reduce and maintain the body weight, reduces the degree of insulin resistance and abdominal obesity, facilitating the reduction of hypertriglyceridemia, and increase in cardiovascular fitness.
- PhA is selected individually, taking into account the patient's age, complications of type 2 DM, concomitant diseases, as well as the tolerability.
- The aerobic exercises with duration of 30-60 min are recommended, preferably daily, but at least 3 times a week. The total duration is at least 150 min per week.
- Contraindications and precautions for use are in general the same as for PhA and type 1 DM (see. Section 5.1.4. Recommendations), and are defined by DM complications and comorbidities.
- Additional factors limiting PhA in case of type 2 DM: coronary artery disease (CAD), diseases of the respiratory system, joints and others.
- The CAD risk requires mandatory electrocardiography (ECG) (according to the indications - stress tests, etc.) before starting PhA study.

In patients with type 2 DM, receiving insulin or oral hypoglycemic agents stimulating the insulin secretion (and very rarely - other hypoglycemic agents) PhA can cause hypoglycemia.

Education and self-control are carried out with the assistance of the clinical psychologist should be in compliance with the principles provided in the Russian algorithms (6th edition, 2013, Chapter 7, Education of the patients with DM).

Observation period is 12 months. The objective is to reduce weight no less than 5% compared with the baseline in the first three months and then to maintain the positive dynamics in the next 9 months.

Weight reduction will help to improve the metabolism of carbohydrates and lipids as well as to reduce the risk of complications.

10.1 Withdrawal of Consent form

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

The patient form active group will be considered as terminated the study provided he/she missed three group classes in a row in the first 12 weeks.

10.1.1 Early study termination

The study can be terminated at any time, for any reason, by Novartis. The investigator will be responsible for informing the Local Ethics Committee (LEC) of the early termination of the trial.

10.2 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

10.3 Patient demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study treatment administration. Patient demographic data to be collected on all patients include: date of birth, sex, race, ethnicity, and child-bearing potential (for females only), see the comments to the table 7-1.

10.4 Safety

Safety assessments will be performed as indicated in Table 6-1 and Table 6-2 and will be based on:

- Evaluation of all AEs and SAEs
- Physical examination, vital signs
- Laboratory tests analysis
- ECG results

10.4.1 Physical examination

A physical examination, including general appearance, will be performed as indicated in Table 7-1 and Table 7-2.

If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. Information for all physical examinations must be included in the source documentation at the study site.

10.4.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed as indicated in Table 7-1 and Table 7-2.

DBP and SBP are measured after the patient has been sitting for 5 minutes, with their back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured twice, 1-2 minutes apart, using a validated device, with an appropriately sized cuff. In the event that a sufficiently large cuff is not available, a sphygmomanometer with an appropriately sized cuff may be used. The average of the two measurements will be entered into the eCRF.

Normal blood pressure will be defined as a systolic pressure of 90 to <120 mmHg, and a diastolic blood pressure of 60 to <80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) or hypotension (systolic blood pressure of <90 mmHg and/or a diastolic blood pressure of <60 mmHg).

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rates are a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

Whether action needs to be taken to address notable vital signs will be decided by the investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

10.4.3 Height, weight, body mass index, waist circumference, waist/hip ratio

Height, body weight, body mass index, waist circumference, waist/hip ratio will be measured as indicated in Table 7-1 and Table 7-2. All parameters will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

10.4.4 Laboratory evaluations

A local laboratory will be used for analysis of all specimens unless noted otherwise.

10.4.4.1 General blood test

All indicators will be measured at planned visits according the Table 7-1 and Table 7-2.

10.4.4.2 Clinical blood chemistry

All indicators will be measured at planned visits according the Table 7-1 and Table 7-2.

10.4.4.3 Urinalysis

All indicators will be measured at planned visits according the Table 7-1 and Table 7-2.

10.4.4.4 Glycosylated hemoglobin

Glycosylated hemoglobin (HbA1c) assessment should be done at visit 1 and then after 12, 24, 36 and 48 weeks after the patient is included in the study, see Table 7-1 and Table 7-2.

10.4.4.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at visits according Table 7-1 and Table 7-2. At each visit when an ECG is done, the investigator must review, date and initial the tracing. The tracing must then be stored with the patient's source documents.

10.4.5 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for patients with T2DM.

10.5 Other assessments

These include:

- Health economic supply form
- Survey on hypoglycemia

10.5.1 Health economic supply form

Special designed health economic (HE) supply form should be completed by investigator at the visits according Table 7-1 and Table 7-2.

This form includes the following aspects:

- Medical services for diabetes and it’s complications over the last year
- T2DM drug therapy over the last year

- Related diseases drug therapy over the last year

Based on data from HE supply form health economic aspects will be analyzed. This analysis will be conducted separately after the final study report is completed.

10.5.2 Hypoglycemia Perspectives Questionnaire

The impact of T2DM on various aspects of patient's health-related quality of life will be assessed by the following validated instruments, each of which will be performed as indicated in Table 7-1 and Table 7-2.

• Health Questionnaire EQ-5D-3L
• Hypoglycemia Perspectives Questionnaire
• DTSQ

Doctor (investigator or acting as investigator) should fill out this survey based on what the patient says. The survey will be filled out in Russian before the patient attends the 1st visit of the study. The doctor should ask the patient to answer the questions and fill out the survey. The originals should be kept with other primary documents in the research center.

The patient should fill out the Diary of self-control in between the visits. The diary has teared-off pages where all data on food intake, the level of glucose before and 2 hours after the food intake and hypoglycemia therapy should be mentioned. Additionally, the patient should register in the Diary the change in glucose level, BP and pulse before and after physical exercises. Completed pages should be given to the doctor by the patient at each visit. In case of AEs or SAEs they should be registered according to the instructions of the Chapter 11. Reporting system is also described in Chapter 11.

11 Safety monitoring

Any serious adverse events will be reported to the Local Ethics Committee within 24 hours of the occurrence. All serious adverse events will also be reported to Novartis Drug Safety & Epidemiology (DS&E) within 24 hours of the investigator (or designee) being aware of the serious adverse event. Specific definitions of adverse events, and serious adverse events, are outlined below, along with reporting criteria required by Novartis.

Adverse events (AE)

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on an Adverse Event Case Report Form and will be followed up as appropriate.

An AE is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be part of lifestyle changes implied by this study.

Medical conditions/diseases present before starting study treatment will only be considered adverse events if they worsen after starting study treatment (any procedures specified in the

protocol). Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form will be recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

Serious Adverse Events (SAEs)

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event will also be reported to Novartis DS&E within 24 hours of the investigator learning of its occurrence.

An SAE is defined as an event which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Transmission of infectious agent via medicinal product

No specific SAEs exempt from this reporting process are planned in this protocol.

Any SAE occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation will be reported. Serious adverse events occurring more than 4 weeks after study discontinuation will be reported to Novartis DS&E only if a relationship with any Novartis study therapy is suspected by the investigator.

Local Department of Pharmacovigilance (Clinical Safety) of Novartis Pharma in Russia

Phone: [redacted]

Fax: [redacted]

Email: [redacted]

Specialists in drug safety: [redacted]

As far as possible, each SAE will also be described by (but not limited to):

- Its duration (onset date = date of 1st signs or symptoms, and end dates)
- The seriousness criteria and severity if applicable (mild, moderate, severe)
- Its relationship to current investigational regimen (suspected / not suspected as judged by the investigator)
- The action(s) taken and investigation results if applicable
- Concomitant medication details
- Outcome

Notification of serious adverse events to Novartis Pharmaceuticals Drug Safety & Epidemiology (DS&E)

Each Serious Adverse Event (SAE) will be reported by the investigator to Novartis DS&E within 24 hours of learning of its occurrence, even if it is not felt to be related to study procedures or Noivartis treatment. Follow-up information about a previously reported SAE will also be reported to Novartis DS&E within 24 hours of receiving it. If the SAE has not been previously documented (new occurrence) and it is thought to be related to study treatment, Novartis Drug Safety Department may contact the investigator to obtain further information.

If warranted, an Investigator Notification may be issued, to inform all investigators involved in any study with the same drug that this serious adverse event has been reported.

Reporting procedures

The investigator will complete the SAE Report Form, assess the relationship to study treatment\study procedures and send the completed and signed form by fax within 24 hours to Novartis DS&E. The original and the duplicate copies of the SAE Form, and the fax confirmation sheet will be kept with the case report forms at the study site.

Follow-up information will be sent to the same person to whom the original SAE Form was sent, re-stating the date of the original report. A new SAE Form will be used (stating that this is a "follow-up"). The follow-up report should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet will be retained by the study site.

It is necessary to use a new form for SAEs reporting (it will be indicated there that new data is presented). While new form is presented it is necessary to report whether the previos case was resolved, treatment conducted or the SAEs is still ongoing. This form and fax copy will be kept in the research center.

Reporting about pregnancy

To ensure patient safety, each pregnancy in a patient will be reported to Novartis within 24 hours of learning of its occurrence. Pregnancy will be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up will be recorded on the same form and will include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy will be reported on the SAE Report Form.

12 Data review and database management

12.1 Site monitoring

Before study initiation at a site initiation visit or at an investigator meeting, a Novartis representative will review the protocol and eCRF with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRF, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

The investigator/qualified site staff must maintain source documents for each patient in the study, consisting of, but not limited to, case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRF must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a dated and signed copy is given to the patient).

The investigator/qualified site staff must give the monitor access to all relevant source documents to confirm their consistency with eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRF are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12.2 Data collection

Designated investigator staff will enter the data required by the protocol into the EDC system. Designated investigator site staff will not be given access to the EDC system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The investigator must certify that the data entered into the eCRF are complete and accurate.

After database lock, the investigator/qualified site staff will receive copies of the patient data for archiving at the investigational site.

12.3 Database management and quality control

Novartis staff, or CRO working on behalf of Novartis, review the data entered into the eCRF by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions.

Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the World health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

13 Data analysis

Descriptive statistics will be applied in the study to describe the sample size of the patients at baseline and at follow-up visits, demographic data recorded during the examination of the study parameters, as well as their changes.

The choice of parametric or non-parametric criteria for testing statistical hypotheses will be determined on the basis of the Kolmogorov-Smirnov criteria (conclusion of the presence or absence of statistically significant differences between the distribution of the respective parameter and the normal one), as well as with the graphical methods.

AE data will be presented as an absolute number and as the proportion of the patients with any AE, according to the organ systems and specific AE with corresponding 95% confidence intervals (CI). The association between therapy duration and AE (SAE) risk will be analyzed on the base of the proportional-hazards regression model of the survival analysis. Age, sex, BMI, disease duration, baseline HbA1c. will be taken into account in the model for the control of potential confounding factors. Secondary indicators will be analyzed the same way.

The primary analysis of the proportion of the patients with response on the treatment will be performed using multivariate logistic regression and calculating odds ratios with

corresponding 95% CI. To control the potential confounding factors, age, sex, BMI, disease duration, the baseline values of HbA1c will be taken into account in the regression model.

The Last observation carried forward method (LOCF) will be used to restore the missing values of the efficacy indicators at the final visit according to the last available measurement after initiation of studied intervention. Sample size calculation

13.1 Sample size calculations

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 is calculated based on observed weight changes 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 executing this in Russia, we have assumed an achievable change in weight as 5%. The sample size (with the possible dropout of 20%) of 100 patients in active group and 30 patients in parallel cohort is required to provide 80% power to detect a significant difference (significance level is α=0.05) between values in two groups.

14 Ethical considerations

14.1 Council of Ethics

The study can be started only after written approval of Local Ethic Committee, which is in accordance with the international quidelines on Good Clinical Practice and with federal legislation.

14.2 Ethical support of the study

An investigator and all subjects and organizations involved in the study should conduct the present study in compliance with the Protocol, GCP standards.

The confidentiality of the records identifying the subject of the study should be ensured in compliance with the right on the private life and protection of the data confidentiality according to the normative requirements.

The rights, safety and welfare of the subject of the study are of a high priority and should be prevail over the interests of the science and society.

14.3 Patient Informed Consent

The Investigator and co-investigator, using the printing materials, should explain to the patient the purposes and the scope of the study, as well as the other issues related to the study and it should be clear, that the presented information has been completely recognized by the patient and the written consent on participation in the study has been the free expression of patient’s will.

Before the onset of the participation of the study the patient or his/her legal representative, made the expository conversation, personally sign and put the date on the written Informed Consent Form.

Investigator or other responsible personnel should handle directly to the patient the copy of the Informed Consent, an original copy of which will be archived by an investigator in accordance with the rules of Good Clinical Practice.

The Information card and Consent form for patients in active and control groups will be different according to the plan of visits for these groups.

The signed Informed Consent Form should be stored by the Investigator and be available (only for review) for the specialists on Clinical Monitoring and for an auditor, if required.

14.4 Confidentiality of the personal data of the patients

Personal clinical information, obtained in the course of the present study is considered as confidential and should not be disclosed to the third parties. Investigator must ensure the adherence to the anonymity of the patients and protection of this data, disclosing the patient personality, from the subjects not authorized to receive assess to this information. Data of the patient received by the Sponsor and/or by the Contract Research Organization, involved in the study conduction, can include only identification number of the patient and/or his/her initials. Initials of the sponsor confirms that the personal data of the patients will be protected with the complete compliance with the requirements of the Federal Law No. 152-FZ from July 27, 2006 “On the Personal Data”.

14.5 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

14.6 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient’s representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. Only those patients will be included in the study who understand all study related procedures and their obligations to complete the study. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by

the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

14.7 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

14.8 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

15 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research-related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

16 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in section 7 Safety Monitoring should be followed.

17 References

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