Cover Page

Protocol Title:	The role of proper insulin injection technique in the treatment of diabetes mellitus
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Clinical trial protocol

«The role of proper insulin injection technique in the treatment of diabetes mellitus».

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Sponsor	Becton, Dickinson and Company Dvintsev Str, No 12 Building 1 Moscow 127018 Russia
Sponsor's Medical Monitor	Stanislav Glezer, VP, Medical Affairs, Diabetes Care Email: Stanislav.Glezer@bd.com _____ (signature for protocol approval)

«Becton, Dickinson and Company», Russia confirms that the proposed clinical trial will be conducted in accordance with the ethical principles of the WMA Declaration of Helsinki, and will not be started until the receipt of the approval by the Ethics Committee of research center or Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Trials (where applicable). During the conduct of clinical trial, any additional comments by the Ethics Committee of the research center will be taken note of, should such comments be provided.

CONFIDENTIALITY AGREEMENT AND INVESTIGATOR SIGNATURE PAGE

I, the undersigned, NAME _____

_____,

agree to take personal responsibility for maintaining confidentiality with regard to the clinical trial protocol and any other related documents, and pledge not to disclose the documents to third parties bearing no relation to the Protocol. I accept the liability for conducting clinical trial procedures in accordance with the 1964 World Medical Association Declaration of Helsinki and its successive versions, also, in accordance with the National State Standard R ISO (GOST R ISO) 14155-2014. I affirm that the staff members of my research center understand and agree to comply with the protocol requirements, and are ready for participation in the clinical trial.

Date_____ Signature_____

Contents

List of abbreviations

ADE – adverse device effect
AE – adverse event
BD Micro-Fine Plus 4mm 32G pen needle – disposable BD Micro-Fine Plus 32G pen needle (0.23mm/32G x 4mm)
BG- blood glucose value
BGM – Blood Glucose Meter
BMI – body mass index
eCRF – electronic case report form
CT – clinical trial
DM – diabetes mellitus
FITTER - Forum for Injection Technique Therapy Expert Recommendations
GLP-1 – glucan-like peptide-1
HbA1c – glycated hemoglobin
ICF – informed consent form
LEC – local ethics committee
LH - Lipohypertrophy
QOL – Quality of Life
SAE – serious adverse event
TDD – total daily dose
USADE – unanticipated adverse device effect

List of terms

Hypoglycemia is defined as the occurrence of ≥ 1 symptoms of low blood sugar (e.g., fast heartbeat, tiredness, sweating, extreme hunger, dizziness, tremors) and a blood glucose meter-confirmed reading ≤ 3.9 mmol/L.

Hypoglycemia of unknown etiology is defined as hypoglycemia occurring in the absence of a certain provoking event, such as a change in the administration of medications, diet or physical activity.

Principal investigator is the qualified person responsible for the conduct of the clinical trial in the research center.

Monitoring is the activity related to the supervision of the course of the clinical trial, in order to make sure that a given investigation is carried out and recorded, and the report is produced in accordance with the trial protocol, documented procedures, set standards and applicable regulatory requirements.

Multicenter studies are clinical studies which are conducted according to a unique protocol in two or more research centers.

Commissioner (Sponsor): An individual or organization bearing responsibility and having duties regarding the initiation or conduct of the clinical trial. For this trial, the Sponsor is the «Becton Dickinson and Company», Russia.

Case report form, CRF: A set of documents in the form of a hard copy, electronic or optical data carrier recorded for each study subject, which, according to CT protocol, contains information that must be submitted to the study sponsor.

Investigator (same as physician-investigator): The individual member of a research team appointed by and subordinate to the Principal Investigator in the research center, who will carry out the major procedures related to the clinical trial or take important decisions pertaining to all aspects of the clinical trial.

Research center (Center): An institution or site where the clinical trial is conducted.

Clinical trial: Systemic study with participation of one or more individuals as study subjects, aiming at evaluating the safety or functional characteristics of a medical device.

Outcome measure (primary): The most important parameter(s) used to test the main hypothesis in the clinical trial.

Outcome measure (objectives) (secondary): Parameter(s) used to test additional hypotheses in the clinical trial.

Adverse Event (AE): : Any unfavorable medical manifestation, such as an unanticipated disease or trauma, as well as undesirable clinical signs, including abnormal laboratory values, in the subject, user, or any other individual who may not be associated with the studied medical device.

Unanticipated Adverse Device Effect (UADE): Undesirable effect associated with the use of studied medical device.

Serious Adverse Event (SAE)is

An SAE is any AE occurring during study participation that results in any of the following outcomes:

a) leads to a lethal outcome;

b) leads to the serious deterioration of the health of the subject, which, in turn, leads to either:
    1) disease or a life-threatening injury, or
    2) injury, or
    3) hospitalization or its extension, or
    4) medical or surgical intervention for the prevention of the life-threatening disease or injury;
c) fetal injury, fetal death or abnormalities or defects of fetal development.

Unanticipated Serious Adverse Device Effect (USADE): Serious unfavorable effect of the device, of which the character, extent of effect, severity or consequences of its use have not been identified in the current working version of the risk analysis report.
Deviation: Case(s) of departure, deliberate or accidental, from the protocol requirements.
Clinical trial design (study protocol): The document which states the substantiation, objectives, study proposal (plan) and prospective analysis, method, monitoring, management and maintenance of the records pertaining to the clinical trial.
Procedure of obtaining the informed consent: The process during which the subject is provided with complete information about the clinical trial, and he/she gives a voluntary consent for participation in the clinical trial.
Sensitive subject is an individual whose preparedness to participate in the clinical trial can be unduly affected by anticipation, reasonable or not, participation-related benefit or negative reaction of the administration in case of the subject's refusal to participate.
Objective means the main objective of the clinical trial.
Ethics committee; EC: An independent committee responsible for the analysis of the clinical trial aiming at protecting the rights and ensuring the safety and wellbeing of the subjects taking part in the clinical trial.

Brief description of the clinical trial

Title	The role of proper insulin injection technique in the treatment of diabetes mellitus
Type	A prospective, post-marketing, single-arm clinical study
Duration	Planned First patient in: end of June 2019 Enrolment period: approximately 1 month Study duration per patient: 6 months
Number and name of research centers	Total number of centers - 6: 1. Federal State-Funded Institution "National Medical Research Center of Endocrinology" of the Ministry of Healthcare of the Russian Federation. 2. State-Funded Healthcare Institution of the Moscow Region "Moscow regional clinical scientific research institute named after M.F. Vladimirsky (MONIKI)". 3. State-Funded Healthcare Institution "Endocrinology Dispensary of the Health Department of Moscow City". 4. Federal State-Funded Educational Institution of advanced professional education of the Russian Medical Academy of continuous professional education of the Ministry of Healthcare of the Russian Federation. 5. State-Funded Healthcare Institution of the Sverdlovsk region "Sverdlovsk regional clinical hospital №1". 6. Pavlov First Saint Petersburg State Medical University
Rationale	Insulin is the drug used in the treatment of diabetes mellitus, and it is administered via injection into subcutaneous adipose tissue. Proper technique of insulin injection in diabetic patients is a prerequisite for achieving good glycemic control, a reduction in the variability of insulin absorption, and reaching optimal efficacy of the anti-diabetic drugs [1].
Objective	The study aims at testing the effect of training in optimal technique of insulin injection using a multimodal individual approach supplemented with a platform for personalized distance education of diabetic patients who are on insulin therapy, with regard to clinical outcomes and essential skills necessary for managing diabetes.
Outcome measures	- Reduction in glycated hemoglobin (HbA1c) (in %); - Insulin total daily dose (TDD); - Incidence of hypoglycemia;

	- Incidence of severe hypoglycemia (which required assistance by others); - Change in Blood Glucose levels (measured by BGM) - Correct alternation of injection sites; - Cases of repeat needle use; - Changes in lipohypertrophy, its size (length and width, in mm) and localization (if applicable); - Cases of injection into lipohypertrophy areas (if applicable); - Quantitative experience with the use of distance-learning video lessons by patients. - Quality of Life assessments
Number of participants	At least 73, but not more than 90.
Length of time of patients' participation	Total time of patient participation in the study is 6 months, which includes: - Three personal visits - Two phone calls
Selection criteria	Selection of patients will not be influenced by race, religion, socio-economic and other factors. Approximately 50% of the subjects to be enrolled will have lipohypertrophy areas and 50% of the subjects will not. **Inclusion criteria:** 1. Type 1 or type 2 diabetes mellitus; 2. Patients (male and female) of 18 years of age and over; 3. At least 1 year of experience with insulin self-administration; 4. Use of insulin pen for insulin injections. 5. HbA1c > 7.5 % measured at study entry or maximally 30 days prior to screening. 6. BMI below 40 kg/m^2 at study entry. 7. Daily self-control of blood glucose level; 8. Access to the internet for watching video lessons. 9. Only outpatients are eligible for the study. 10. Availability of signed informed consent of the patient for inclusion in the study. **Exclusion criteria:** 1. Pregnant women or women planning to become pregnant during the time of study, breastfeeding women; 2. Subjects using an insulin pump; 3. Those using treatment with a GLP-1 receptor agonists alone; 4. Subjects not fluent in Russian (reading and writing). 5. Patients at high risk for ketoacidosis and/or hyperglycemia. 6. Psychic, physical or any other reasons hampering patient participation in the study (based on the reasonable opinion of the physician-investigator).
Name of medical	Disposable BD Micro-Fine Plus 32G pen needle (0.23 x 4 mm).

device and its manufacturer	Manufacturer: “Becton Dickinson and Company”, USA.
Ancillary Products	Blood Glucose Meter
Interim analysis	Will not be carried out.
Statistical analysis	The HbA1c and insulin total daily dose will be analyzed using linear models with mixed effects (with transformation or without it, whenever necessary) where lipohypertrophy will be a fixed effect. Analyses will be done overall and per lipohypertrophy sub-group (with or without LH) whenever the sub-group effect is significant. Generalized linear models with mixed effects will include logistic models for binomial responses or Poisson models for count responses. Fixed effect models can be used when models with mixed effects cannot be employed. The effect of different covariates will be studied (including, but not limited to these), such as site, age, BMI, gender and diabetes type, as well as their interaction. The threshold to keep covariates in a model will be p <0.05.

1. Identification and description of the medical device used in the trial.

Disposable BD Micro-Fine Plus 32G pen needles (0.23mm/32G x 4mm) will be used. The needles (Fig. 1) are made of stainless steel AISI 304, silicone, UV light curable adhesive, polypropylene, polyethylene and paper/copolymer film. The length of the needle is 4 mm, diameter 0.23 mm and weight 3 g.

BD Micro-Fine Plus 4 mm 32G needles are intended for parenteral (subcutaneous) injection of medicines (insulin, hormonal medications and other drugs supplied in cartridges which, in turn, are enclosed in pen injectors [pre-filled syringes]).

BD Micro-Fine Plus 4 mm 32G needles are intended for self-injection of medications by the patient at home, using special injectors (pen injectors or pre-filled syringes). The same needles can be used in the hospital by skilled medical staff, provided the cartridges and injectors are used individually for each patient.

The needles are manufactured by the «Becton Dickinson and Company», USA. The manufacturing sites include Pottery Road, Dun Laoghaire Co Dublin, Ireland, and Donore Road Drogheda, Co Louth, Ireland.

Fig. 1 Disposable BD Micro-Fine Plus 4 mm 32G needle (0.23mm/32G x 4mm): view of the open needle, individually packaged and in a carton box.

2. Study sponsor

The study is sponsored by the «Becton, Dickinson and Company», Russia. Becton, Dickinson and Company is a manufacturer of different medical devices, including needles for insulin pen injectors. The company provides all necessary educational, instructional and supporting materials and provides assistance with the monitoring of studies, the analysis of data, and the publication of results.

For the period of the clinical trial, BD supplies all participating patients with 4 mm 32G needles free of charge.

In the course of study, the required number of needles (depending on the number of insulin injections per patient and the number of patients in every center) will be supplied by the Sponsor to the research center. An entry will be made regarding the supplied needles (number of packages, date of receipt, batch №) by the investigator in a special log book (see Appendix A to the protocol). Upon study completion, the center must return all unused needles (if any) to the Sponsor and mark this in the needle log book.

The needles will be used for insulin injection by patients with type 1 and type 2 diabetes mellitus who have been using insulin injections for more than a year. The injections will be done using pen injectors.

BD will also supply, via the research center, a Blood Glucose Meter (BGM) as well as sufficient lancets and test strips to all study patients for use in the study. This BGM will need to be returned to the research center after the patient finished the study. This will also be documented in a log book. Upon study completion, the center must return all BGMs (used and unused) unused strips and lancets (if any) to the Sponsor and mark this in the corresponding log book.

3. Rationale of clinical trial plan (design)

To date, several clinical trials have been conducted [2,3,4] with the aim of evaluating the effect of proper insulin injection technique on such parameters as glycemic control, glycated hemoglobin, hypoglycemia, glycemic variability and TDD of insulin. The above mentioned studies attest to the fact that the use of proper injection technique yields tangible results, namely, a reduction in % of glycated hemoglobin, an improved control of blood glucose level and an overall improvement of patient satisfaction with treatment. A 6-month follow-up is considered a necessary and sufficient measure for the evaluation of the above parameters. In our study, we would also like to evaluate all the above mentioned parameters with regard to proper injection technique; in addition, physicians' explanations on the injection technique will be reinforced by on-line video lessons, which will be recommended by the attending physician to patients for their own viewing.

4. Summary about the training and experience of the medical staff needed to handle the device

The experienced medical staff participating in this trial are in a position to handle the insulin pen needles. However, the Sponsor will run training classes for the medical specialists involved

in the study to familiarize them with the study protocol, including a briefing on how to find lipohypertrophy areas (using training phantoms). Training will employ the "teach the teacher" method. Moreover, the Sponsor will run training classes on how to fill in the supporting documents required for the clinical trial, such as source worksheets, and the eCRF, the needle log book, etc. The site staff will also be instructed on how to deal with the subject diaries and how to administer the Quality of Life questionnaire EQ-5D.

5. Risks and benefits associated with the use of the device and the clinical trial

The risks associated with the use of disposable BD Micro-Fine Plus: 32G (0.23 x 4 mm) needles and the injection pen are the standard risks occurring during subcutaneous injections, which include the following:

1) *Hemorrhages and hematomas.* Sometimes during an injection, the needle may damage blood vessels, causing hemorrhages or hematomas. Changes in needle length or other injection parameters do not seem to influence the rate of occurrence of bleeding or hematomas, although, according to some data, these complications may occur less frequently when short needles are used. Pressing on the injection site for 5-10 seconds should stop the bleeding [1].

2) *Leakage of the medication from the injection site.* This can occur due to the following reasons:

a) a one-time injection of a large insulin dose. In some cases, it would be preferable to divide large insulin doses into two doses and inject them one after another [1].

b) individual skin properties (dermal structure) and its age-related changes may be the cause of medication leakage following an injection [1].

3) *Pain.* Injections of insulin and GLP-1 receptor agonists do not usually cause pain, except for cases when the needle damages nerve ending fibers, which is a fairly rare event. However, some patients respond to injections in a rather sensitive way and describe their sensations as painful ones. Patient discomfort during injections was carefully studied and is attributed to three key factors: needle length, needle diameter and injection setting [1].

The benefit provided by this study is the demonstration of the fact that proper insulin injection technique used by patients is a prerequisite for achieving good glycemic control of diabetes, reducing the variability in the absorption of insulin preparations, and obtaining the optimal effect of their use [1]. Also, we expect that the proper technique of insulin injections will help to reduce the risks of injections: hemorrhages, hematomas cases and pain.

6. Objectives of the clinical trial and the hypotheses to be tested

The study aims at verifying the effect of teaching the optimal technique of insulin injection using the multimodal individual approach, supplemented with a personalized remote platform for the education of diabetic patients who are on insulin therapy, with regard to the clinical outcomes and essential skills necessary for managing diabetes.

This is a prospective study conducted in Russia, with a subsequent progress review after a 6-month follow-up to assess the correctness of insulin injection technique. The study design represents a "before" and "after" comparison, where the patient is left under

his/her own control after the health worker-guided assessment of the existing technique, and is undergoing training in conjunction with the reinforcing video lessons. The study includes patients with and without lipohypertrophy. During the follow-up phase, the insulin total daily dose, extent of glycemic control (glycated hemoglobin, hypoglycemic episodes), repeat use of needles, insulin injection technique and practical use by patients of the taught hands-on skills will be reviewed and evaluated.

Hypothesis

- Proper insulin injection technique, which includes the single use of needles, alternating the injection sites, avoiding injection in lipohypertrophic areas and the use of short (4 mm-long) needles will allow us to improve glycemic control parameters (% glycated hemoglobin, hypoglycemia) and to reduce insulin TDD .

Primary objective

- Evaluation of the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G (0.23mm/32G x 4 mm) pen needles on the reduction in glycated hemoglobin (HbA1c in %) after 6 months follow up in patients with Type 1 or Type 2 diabetes .

Secondary objective

- Evaluation of the effect of optimal insulin injection technique on the total daily dose of insulin and clinical parameters of glycemic control (hypoglycemia and severe hypoglycemia requiring third party assistance).
- Evaluation of the effect of optimal insulin injection technique on glucose blood levels (measured by BGM).

Additional objective

- Evaluation of the effect of education (especially distanced learning) on patients' knowledge and their mastering insulin injection technique, including correctly alternating the injection sites, avoiding injecting the lipohypertrophy areas, and the single use of needles.

7. Clinical trial proposal (design)

This clinical trial is a prospective, post-marketing, single-arm clinical trial.

7.1. Standards for the clinical trial

To allow for 73 evaluable subjects at 6 months follow up, a total of up to 90 patients will be enrolled (the statistical power of the study is provided in a section below, dedicated to statistical analysis). Each center will be offered to supply a sufficient number of patients as study subjects (up to 15 patients). Approximately half of these patients will be with lipohypertrophy (LH), and half will be without. Ideally, each center should recruit half of their patients with and half of their patients without LH. The Sponsor will monitor if the overall balance of 50%/50% is maintained

and will advise study centers accordingly. The main goal is to have an equal distribution across the study, not necessarily per site, however, each study center should have at least a distribution of 1/3 versus 2/3 in each group. The optimal injection technique and choice of needle length is based on the Russian Procedural Guidelines on injection techniques and infusions used in the treatment of diabetes mellitus [1]. These Guidelines, in turn, are based on recently published international guidelines by the Forum for Injection Technique Therapy Expert Recommendations (FITTER) [5].

7.2. Outcome measures for the clinical trial

- Reduction in glycated hemoglobin (HbA1c, in %);
- Insulin total daily dose (TDD);
- Incidence of hypoglycemia;
- Incidence of severe hypoglycemia (which require assistance by others);
- Change in Blood Glucose levels (measured by BGM)
- Correct alternation of injection sites;
- Cases of repeat needle use;
- Change of lipohypertrophy, its size (length and width in mm) and localization (if applicable);
- Cases of injection into lipohypertrophy areas (if applicable);
- Patients' quantitative experience with the use of distant video lessons.
- Quality of Life assessments (EQ-5D)

7.3.Inclusion/exclusion criteria.

The selection of patients will not be influenced by race, religion, socio-economic and other factors. Approximately 50% of the subjects to be enrolled will have lipohypertrophy areas and 50% of the subjects will not.

Inclusion criteria:

1. Type 1 or type 2 diabetes mellitus;
2. Patients (male and female) of 18 years of age and over;
3. At least 1 year of experience with insulin self-administration;
4. Use of insulin pen for insulin injections.
5. HbA1c > 7.5% measured at study entry or maximally 30 days prior to study entry..
6. BMI below 40 kg/m^2 at study entry.
7. Daily self-control of blood glucose level;
8. Access to the internet for watching video lessons.
9. Only outpatients are eligible for the study.
10. Availability of the patient's signed informed consent for inclusion in the study.

Exclusion criteria:

1. Pregnant women or women planning to become pregnant during the time of study, breastfeeding women;
2. Subjects using an insulin pump;
3. Those using treatment with a GLP-1 receptor agonists alone;
4. Subjects not fluent in Russian (reading and writing).
5. Patients at high risk for ketoacidosis and/or hyperglycemia.
6. Psychic, physical or any other reasons hampering patient participation in the study (based on the reasonable opinion of the physician-investigator).

7.4. Patient information and obtaining informed consent

Before executing any study procedure, the informed consent of the patient must be obtained. The following steps must be taken in order to obtain the informed consent of the patient for participation in the study.

1. Physician-investigator must ascertain whether patients understand and read Russian.
2. Patient receives information about the study, its objectives, a brief description of the study design and the patient requirements in case he/she consents to participate in the study. Patients are informed that they meet the criteria required for study entry.
3. Patient takes his/her time to ask questions, discuss the study with family members and take a decision about study participation before the next visit to the medical center. If the patient gives his/her consent to participate in the study, the next visit is scheduled within 5 days from the moment of signing the inform consent form by the patient.
4. Patients are informed that they are entitled to change their mind and withdraw from participation at any time, and this will not affect their treatment in any way.

A patient is considered to be enrolled in the study when he/she signed the Informed Consent Form.

7.5. Stages of the clinical trial.

The enrolment period of the trial will be approximately 1 month, The follow-up period for each patient is 6 months. A total of maximally 90 patients will be included in the trial, to allow for 73 evaluable subjects at 6 months follow up, which is due to the statistical calculation of the required number of patients (see section 10 of this protocol).

The study design and calendar of events, including all the necessary visits, their order, appointment time and manipulations carried out during the visits, are presented in Fig. 2 (Study Flow) Table 1 (Study design) and Table 2 (Calendar of events).

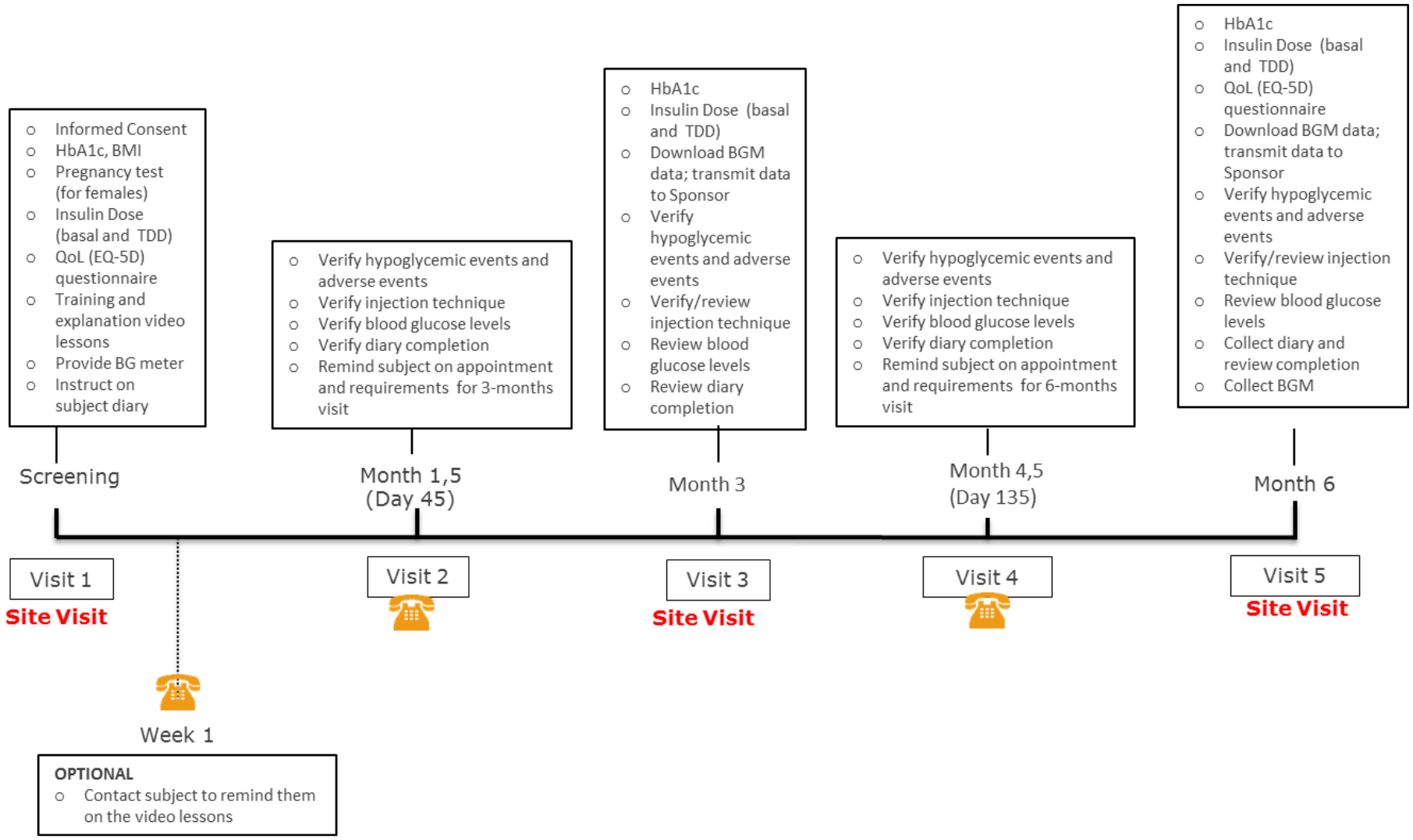

Fig. 2. Study Flow

Table 1. Trial design

Patient selection and start	Interim control (telephone)	Interim control (3 month FU visit)	Completion and evaluation
Visit 1 (Screening) duration - 5 working days)	Follow-up visits – visit №2,and 4 (by phone) in 45 and 135 days +/-10 days after visit 1	Follow-up visit – visit №3 (personal) in 90 days +/-10 days after visit 1	Visit 5 (personal, final) in 180 days +/-10 days after visit 1
1 Patient evaluation in terms of his/her possible participation in the study. For female patients: perform a pregnancy test	1 Make sure that patient follows study protocol: uses supplied needles only once, and watches recommended video lessons	1 Enter data regarding HbA1c and insulin TDD	1 Enter data regarding HbA1c and insulin TDD
2 Obtaining the informed consent	2 Evaluate current level of glycemic control and cases of hypoglycemia	2 Evaluate current level of glycemic control and cases of hypoglycemia.	2 Evaluate current level of glycemic control and cases of hypoglycemia.
3 Assignment of participant identification number (code)	3 Find out about current level and frequency of measuring blood glucose and insulin TDD.	3 Examine injection sites and injection technique, size and localization of lipohypertrophy	3 Examine injection sites and injection technique, size and localization of lipohypertrophy
4 Fill in the questionnaire, enter data regarding HbA1c and insulin TDD. Note: the HbA1c value may be measured at screening or the latest measured value (max. 30 days prior to screening) may be taken.	4 Make sure that the patient follows the recommended injection technique, correctly alternates injection sites and avoids injections into sites of lipohypertrophy. Remind the patient to use the BGM and complete the diary.	4 Enter data regarding possible AE	4 Collect diary and review completion
5 Examine injection sites and injection technique, size and localization of lipohypertrophy (if applicable).	5 Enter patient's answers in the interim control form	5 Review diary completion	5 Request patient to complete the EQ-5D questionnaire
6 Evaluate current level of blood glucose and cases of hypoglycemia.	6 Remind patient about next personal visit	6 Download the data from the BGM to a PC for further statistical analyses.	6 Arrange subsequent medical follow-up for the patient, if required
7 Carry out personalized training on correct injection technique	7 Enter data regarding possible AE	7 Provide new supply of BD Micro-Fine Plus 4 mm 32G needles (3 months' supply) and additional strips and lancets for BGM.	7 Release patient from participation in the study (fill in Exit from study form).

8 Familiarize patient with distance education resource and recommend independent studies using video lessons			8 Schedule the HbA1c test and next personal visit in 90 days. Schedule next telephone follow up (visit 4)	8 Download the data from the BGM to a PC for further statistical analyses.
9 Request patient to complete the EQ-5D questionnaire				9 Enter data regarding possible AE
10 Provide patient with required supply of BD Micro-Fine Plus 4 mm 32G needles (3 months' supply).				10 Collect the BGM from the patients. Complete the log forms
11 Schedule the HbA1c test and next personal visits in 90 and 180 days, and over-the-phone visits for interim control in 45 and 135 days.				
12 Provide patients the diary and a Blood Glucose Meter (BGM) with strips and lancets (3 months' supply). Explain how to complete the diary and use BGM.				
13 In a week +/-2 days after the screening visit, the investigator must ascertain if patient viewed recommended lessons.				

Visit № 1 – screening visit (personal visit).

1. For study purposes, prior to patient enrolment a physician will interview the patient about his/her condition in order to evaluate the effectiveness of current practices in terms of injection technique, the finding of gaps and possibilities for their improvement. Depending on the results of such an evaluation, the investigator will offer the patient familiarization with the corresponding distance learning modules.
2. Information about study participation is provided, and the informed consent form is signed.
3. Collection of the patient's demographic data and medical history data is carried out. The patient undergoes a physical examination to make sure that he/she meets the inclusion/exclusion criteria. A **urine** pregnancy test must be done for the childbearing potential female patients.
   Examination of injection sites and injection technique is performed. The presence of lipohypertrophy is determined, and lipohypertrophy areas are marked on the diagram, indicating their number and size.
4. A physician makes an arrangement for the glycated hemoglobin test (HbA1c), which is carried out in the laboratory of the center participating in a given clinical trial at investigator's place of work.. To verify the inclusion criteria, the HbA1c value may be measured at screening or the latest measured value (max. 30 days prior to screening) may be taken. The result should be entered in the eCRF.
5. The current level of blood glucose and cases of hypoglycemia will be evaluated during the visit and the patient will be asked about his/ her condition and data will be completed in the eCRF.
6. The insulin dose of the day prior to the visit (basal and boluses) will be captured in the eCRF.
7. A theoretical course is given on lipohypertrophy and the necessity of alternating the injection sites, followed by hands-on classes on insulin injection technique. Also, patients are familiarized with other aspects of insulin therapy. Patients are given instructions that, in case of necessity, they can change the insulin dose during the clinical trial. The patient is not recommended to change the long-acting and intermediate-acting insulins, and not to change insulin subgroups, i.e., short-acting and ultra short-acting insulins.
8. The patient is familiarized with the structure and scope of the distance learning program. The whole course of video lessons will be recommended to the all patients for individual studies independently from their insulin injection technique success.
9. Patients are requested to complete the EQ-5D questionnaire, see Appendix B for an example.
10. Patients are supplied with an information package – booklet with instructions how to practice the right injection technique, rotation grid, the information letter for a physician in a local outpatient hospital to inform the patient is participating in the clinical trial. The letter should be formalized on the formal paper of the site. Guidelines on video lessons and web access codes, if required.
11. Patients will also receive:
    a. disposable BD Micro-Fine 32G (0.23mm/32G x 4 mm) needles in the amount

required for 3 months (Table 3),

b. Blood Glucose Meter (BGM), strips and lancets in the amount enough for 400 measurements, which corresponds with 100 days (approx. 3 months) of 4 measurements per day,
c. a patient's diary. Patients are requested to record their insulin doses and if they experienced any adverse effects, including hypoglycemia's.

12. Patients must be informed to return the BGM back to the site after the study. Boxes of needles, boxes of strips and lancets will be marked: "BD property. Only for clinical trial. Not for sale". Glucometers will be marked: "BD property. Only for clinical trial. Not for sale. Must be returned".
13. Patients are instructed how to use the BGM and its accessories, how to complete the patient's diary. BGMs will be calibrated if needed and the date and time will be set correctly. Patients will be recommended to make at least 4 measurements of glucose per day by the provided BGM regardless of the type of diabetes: 3 before meals (one of which is before breakfast) and one measurement before bedtime. More measurements may be performed in accordance with clinical practice. The recommended measurements as listed above should be performed during the following time periods:
    a. within 2 weeks after screening,
    b. the last 2 weeks before the visit of the 3rd month, and
    c. the last 2 weeks before the visit of the 6th month.

    The rest of the time, the patient may measure the level of glucose in the blood in accordance with accepted clinical practice.

    During the same 2 weeks periods the patient is asked to complete the diary with basal and bolus insulin doses on a daily basis. Also, the patient has to complete the diary with all episodes of hypoglycemia.

14. The next meeting with the physician-investigator is scheduled in 90-100 days (visit № 3), as well as the interim visits, which include phone contacts in 45 +/-10 days (visit № 2) and in 135 +/-10 days (visit № 4).
15. A preliminary scheduled blood test for glycated hemoglobin takes place in 90 +/-10 days as well as in 180 +/- 10 days after the screening visit, to be carried out in the laboratory of the center participating in a given clinical trial at the investigator's place of work. The test must be done not sooner than a week before the study completion visit or on the day of the completion visit.
16. The Investigator informs the patient they have to visit the investigator before the next scheduled personal visit in case they do not have sufficient strips. Also, the patient can visit the investigator personally instead of the phone visit if the patient realizes they do not have enough strips to cover the period until the next scheduled personal visit. In this case, the patients have to bring the diary and his BGM for the visit and the Investigator will download the data from BGM and return it back to the patient. The diary will be kept by the investigator and the patient will receive the new diary. The patient also will receive the required number of strips in amount enough to the next scheduled personal visit.

1-week visit (optional, phone).

In 1 week +/- 2 days after the visit № 1, the investigator must be sure that the patient has viewed the recommended video lessons. To this end, the Sponsor provides the investigator with the report on the patient's use of the education resource. If the patient has not viewed recommended video lessons, then the investigator reminds him about the necessity of viewing the recommended video lessons. The information about video lesson viewing is marked in the patient's eCRF.

Visits № 2 and № 4- follow-up visits (over-the-phone visits, or personal visit).

1. The interim contacts with the patient are maintained over the phone in 45 +/-10 days and 135 +/-10 days from the first visit, with the view to evaluate the patient's adherence to the study design, review diary completion and to provide recommendations on the correction of the injection technique, as well as to evaluate the progress of his/her distance learning.
2. Information on the patient's glycemic control (glucose level), total daily insulin dose (the day prior to the phone visits) and hypoglycemic events since the last visit is requested and the information is entered in the eCRF.
3. To remind the patient to bring the BGM back on the next personal visit and to remind the patient on the appointment for having the HbA1c test, as was scheduled on the first and third visit
4. Data regarding possible AEs is collected in a special form of the patient's eCRF.
5. In case of the occurrence of adverse events (AE) in the course of the study after the screening visit, the investigator will record these in a special form (eCRF). In case of serious adverse events (SAE), the corresponding eCRF must be filled in and the event reported to the Sponsor and to the corresponding Ethics Committee within 2 working days after the investigator has become aware of the event.
6. The investigator has to remind the patient to measure their glucose levels upon the protocol requirements and complete the diary with insulin doses 2 weeks before the next personal visit. The same reminder will be also done 2 weeks before or even earlier the next personal visit.
7. The Investigator informs the patient they have to visit the investigator before the next scheduled personal visit in case they do not have sufficient strips. Also, the patient can visit the investigator personally instead of the phone visit if the patient realizes they do not have enough strips to cover the period until the next scheduled personal visit. In this case, the patients have to bring the diary and his BGM for the visit and the Investigator will download the data from BGM and return it back to the patient. The diary will be kept by the investigator and the patient will receive the new diary. The patient also will receive the required number of strips in amount enough to the next scheduled personal visit.

Visit № 3 – follow-up visit (personal).

1. The physician-investigator enters the latest results of the glycated hemoglobin (HbA1c) measurements and insulin TDD (basal and boluses of the day prior to the visit) in the patient's eCRF.
2. The data, saved in the patients' BGMs should be downloaded by the investigator. The

downloaded data will be transmitted to the Sponsor for analysis. The data will be transferred for analysis and storage to Becton, Dickinson and Company in the United States of America.

3. The existing level of glycemic control and cases of hypoglycemia since the last visit are assessed.
4. The physician conducts an examination of the injection sites and the injection technique, the size and localization of lipohypertrophy (if present).
5. The physician will collect and review correct completion of the diary and will provide the patient with a new diary.
6. Data regarding possible AEs is collected in a special form of the patient's eCRF. If necessary, a subsequent medical follow-up is arranged for the patient.
7. Patients will receive a new batch of 32G (0.23mm/32G x 4 mm) needles, BGM strips, and lancets for the next 3 months of the study.
8. Confirm the telephone follow up at Day 135 +/-10 days (visit № 4).
9. Confirm appointment to measure HbA1c for visit № 5 (6 months follow up).
10. The Investigator informs the patient they have to visit the investigator before the next scheduled personal visit in case they do not have sufficient strips. Also, the patient can visit the investigator personally instead of the phone visit if the patient realizes they do not have enough strips to cover the period until the next scheduled personal visit. In this case, the patients have to bring the diary and his BGM for the visit and the Investigator will download the data from BGM and return it back to the patient. The diary will be kept by the investigator and the patient will receive the new diary. The patient also will receive the required number of strips in amount enough to the next scheduled personal visit.

Visit № 5 – study completion visit (personal).

1. The final patient examination is conducted by the physician-investigator, and, during this visit, the patient will be asked several questions, of which the answers are documented in the eCRF.
2. The physician-investigator enters the latest results of the glycated hemoglobin (HbA1c) measurements and insulin TDD (basal and boluses, of the day prior to the visit) in the patient's eCRF.
3. The data, saved in the patients' BGMs should be downloaded by the investigator. The downloaded data will be transmitted to the Sponsor for analysis. The data will be transferred for analysis and storage to Becton, Dickinson and Company in the United States of America.
4. The BGM must be returned to the site and transferred to the Sponsor.
5. The existing level of glycemic control and cases of hypoglycemia are assessed.
6. The physician conducts an examination of the injection sites and the injection technique, the size and localization of lipohypertrophy (if present).
7. The physician will review and collect the subject diaries.
8. Patients are requested to complete the EQ-5D questionnaire,
9. Data regarding possible AEs is collected in a special form of the patient's eCRF. If necessary, a subsequent medical follow-up is arranged for the patient.
10. The patient's exit from the study form is filled in.

Table 2 Calendar of events

Period	Screening	Follow-up		Study completion
Visit	**1**	**2 and 4**	**3**	**5**
Time / **Actions**	**5 working days**	**In 45 and 135 +/- 10 days after visit № 1**	**In 90 +/-10 days after visit № 1**	**In 180 +/-10 days after visit № 1**
Informed consent	X			
Co-morbidities and medical history, demographic data	X			
Pregnancy urine test for female patients in childbearing age	X			
Inclusion/exclusion criteria	X			
Setting the dates for subsequent visits	X		X	
Setting the dates for blood HbA1c tests	X		X	
Patient questionnaire	X	X	X	X
Quality of Life questionnaire (EQ-5D)	X			X
Patient examination for lipohypertrophy	X		X	X
Glycated hemoglobin (HbA1c)	X		X	X
Collect information on occurrences of hypoglycemia	X	X	X	X
Patient education classes, video lessons scheduling, provision of needles	X			
Control of video lessons' viewing	X	X	X	X
Exit from the study				X
Collection of adverse event information		X	X	X

7.6.Patient training of correct injection technique

At the beginning of the trial, the physician interviews the patient in order to evaluate the existing injection technique. The gaps and downsides found are sorted out for each patient in terms of the correct injection technique practice, as set forth in the Russian Procedural Guidelines on injection techniques and infusions used in the treatment of diabetes mellitus [1] and in the international guidelines FITTER [5]. The physician-investigator recommends that patients view the video lessons which best suit their specific needs. Video lessons highlight the following topics:

1. How to deliver an injection with an insulin pen
2. Insulin delivery to the right place/injection sites
3. Using the right length of needles
4. Injection site swelling or induration
5. Injection site care

6. Insulin is absorbed differently by your body
7. Injections, possible problems and their solutions, idiopathic hypoglycemia and blood glucose spikes.
8. How to store insulin and safely dispose of injection devices At study entry, patients receive a 3-month supply of BD Micro-Fine Plus 4 mm 32G injection pen needles, depending on the type of their injection therapy, in order to secure their single use, as well as access to on-line education. Moreover, patients receive an extra package of BD Micro-Fine Plus 4 mm 32G injection pen needles (100 items per package) to cover losses or other contingencies (Table 3).

At visit No. 3 patients will receive another 3-month supply of BD Micro-Fine Plus 4 mm 32G injection pen needles.

Table 3.

Total number of injections per day	Number of packages (3-month supply), given that each needle is used only once	Number of packages to cover losses or other contingencies	Total number of packages per patient
1	1	1	2
2	2	1	3
3	3	1	4
4	4	1	5
5	5	1	6
6	6	1	7

Depending on patient's condition, insulin TDD and other factors, the physician can recommend that the patient reduces insulin TDD after visit № 1.

The physician must recommend to the patient not to change the insulin preparations (for intermediate- and long-acting insulins) and/or the insulin subgroup (for short- and ultra short-acting insulins) throughout the period of the patient's participation in the study.

7.7.Patient safety

The trial will be carried out in accordance with Russian law, the regulatory requirements for quality clinical studies, and the WMA Declaration of Helsinki in so far as relevant to research ethics. Patients will be entitled to forego participation or pull out of the study for any reason and at any stage, which will not affect the quality or availability of their health care.

Participation in the study does not put patients at any significant risk, but encourages them to adopt the correct injection technique, including the avoidance of insulin injection in lipohypertrophic areas. Patients who stop injecting insulin in lipohypertrophic areas and start to inject into healthy tissue often note the necessity to reduce insulin TDD (sometimes up to 20%) in order to avoid hypoglycemia. This information is made available to the investigators, who instruct patients accordingly.

Strict confidentiality is guaranteed for all patients. Patients are not paid for their participation in the study; however, during the study, the Sponsor provides the participants free

of charge with a sufficient supply of BD Micro-Fine Plus 4 mm 32G needles for pen injectors. Also, the Sponsor provides the participants free of charge blood glucose meters, with sufficient amount of strips and lancets. Blood glucose meters must be returned to the sites by the patients on the 6 months follow up (completion) visit.

8. Monitoring plan

Clinical monitoring of this clinical trial will be carried out by the Sponsor, the «Becton Dickinson and Company», Russia. Study monitoring will be conducted by a clinical monitor with an appropriate background and experience. The duties of the clinical monitor include the maintenance of regular contacts with every research center by phone and/or during personal visits to the research center to make sure that:

- The study is carried out in accordance with the requirements of GOST R ISO 14155-2014 [6];
- Study design is adhered to;
- Complete, timely and accurate data are provided;
- Problems with discordant or incomplete data are being solved;
- Cases of complications and unforeseen undesirable effects are brought to the attention of the Sponsor and the research center ethics committee;
- Technical abilities of the research center keep complying with the study requirements.

The clinical monitor will start the conduct of the study in the research center during the site initiation visit or in the course of the study activation visit, and continue the monitoring visits to the research center at the required frequency. The first monitoring visit can usually be made immediately after the start of a patient's enrollment. At this visit and all other monitoring visits, the clinical monitor will compare data entered in the eCRF with that from the medical documents (primary documents) in the center. The primary documents include the medical card, the filled in laboratory analysis form, physician's notes, the patient's medical history, recorded data from automated instruments or any other documents prepared and supported by the investigator/medical staff or support services which contain records of patient monitoring and other data pertaining to the trial. For the purpose of confirming the correctness of the obtained informed consent, adherence to the protocol requirements, the adequacy of reporting adverse events (AE) and subsequent AE follow-up, and information about procedures, the primary documents must be available to the clinical monitor and kept at the research center. Data from the analysis of the eCRF and the primary documents will be discussed with the investigator during the monitoring visits. The dates of the monitoring visits will be entered in the registration book (Appendix A) kept at the research center. The Sponsor assumes that during the monitoring visits the principal investigator and investigator must be available for contacts, the primary documents must be available for viewing, and the required site conditions provided for the assessment of documents pertaining to the trial.

The research centers must get in touch with all patients, making every endeavor to make sure that they turn up for consequent follow up visits. The research centers must have log books with records of patient contact dates and the results of such contacts. After 3 unsuccessful attempts of contact (e.g., by phone or e-mail) to arrange a patient's visit, the patient will be considered as lost to subsequent follow-up.

8.1. Electronic data capture and storage.

Data management will be carried out by Becton, Dickinson and Company in the United States of America. Data will be collected electronically, and electronically entered records present on the website will be entered directly into the controlled database. Data safety is secured by password protection, restricted access, control books and regular data backup. Upon completion of the data investigation and verification, the data will be checked for accuracy and completeness, after which the database will be blocked to prevent any additional modification. A copy of the blocked database will be passed on to the BD Corporate Statistics Department (USA) for statistical analysis.

Electronic data collection in the eCRF is based on the use of Oracle software, and is developed, supported and allocated by Becton, Dickinson and Company in the United States of America..

8.2.Patient identification

In order to rule out a prejudiced attitude and preconception, each patient will be assigned a participant identification code which is filled in the individual registration card (IRC) and study participant information sheet. The code consists of six digits, which designate the following:

☐☐☐ - ☐☐☐, the first three digits are the number of the research center, e.g. 001, 002, 003 etc., which will be assigned in the course of a trial depending on the time of the study entry of each center, and the other three digits indicate the consecutive number of the study participant in a given center.

9. Investigator's range of responsibilities

All research centers will have to sign an agreement with the Sponsor. All principal investigators and investigators will undergo training in study protocol, data entry in the electronic database and the use of disposable BD Micro-Fine Plus: 32G (0.23 x 4 mm) needles for the pen injector.

10. Statistical analysis

It is of the utmost importance that patients invited to participate in the study comprise a representative sample of Russian patients receiving insulin injections. For this reason, the chosen eligibility criteria are as comprehensive as possible.

10.1. Projected sample size

Based on data observed in internal studies with similar designs, assuming an HbA1c decrease of 0.4% between baseline and 6 months and a standard deviation of paired differences of 1.2%, a sample size of 73 subjects would be needed to demonstrate statistical significance using a one sample t-test with a power of 80% and alpha equal to 0.05.

10.2. Statistical analysis plan

For descriptive statistics and conclusive statistics, R 3.4.4 or more recent version and Rstudio will be used. The HbA1c and insulin total daily dose will be analyzed using linear models with mixed effects (with transformation or without it, whenever necessary) where

lipohypertrophy will be a fixed effect. Analyses will be done overall and per lipohypertrophy sub-group (with or without LH) whenever the sub-group effect is significant.. Generalized linear models with mixed effects will include logistic models for binomial responses or Poisson models for count responses.
Fixed effect models can be used when models with mixed effects cannot be employed. The effect of different covariates will be studied (including, but not limited to these), such as site, age, BMI, gender and diabetes type, as well as their interaction. The threshold to keep covariates in a model will be $p < 0.05$.

Non-parametric tests will be used if basic assumptions do not hold for the models.

McNemar's test will be used, when necessary, for contingency tables.

Statistical methods will be detailed in a Statistical Analysis Plan. Additional analyses may be performed and will be defined in the Statistical Analysis Plan.

11. Data management

All documents containing personal information of the study participants must be stored at the trial conduct site.

The data collected during the course of the study will be entered in the eCRF. The study participants will be identified by the study participant code which is generated by the eCRF. Patient confidentiality will be maintained throughout the study, including the publication of the study results. The principal investigator or sub-investigator will review and sign each form (eCRF, AE), the system will record the date when it was signed. The investigator's signature is the confirmation that clinical and laboratory data entered in the form are complete, accurate and veracious.

The data obtained and entered in the eCRF are the property of Becton, Dickinson and Company.

The study data, copies of the study materials and the medical documents will be provided to the Ethics Committee of the research center, the authorized bodies for internal audit should it be conducted, and on the audit demand. All data obtained in the course of the study will be stored confidentially for at least 3 years after the end of this trial.

12. Appendices to the clinical trial protocol

In case of the introduction of amendments or additions to the protocol, an amended protocol of the clinical trial will be created, which will be assigned a new version number. A list of introduced amendments and additions indicating their containing pages will be attached to the amended protocol. The protocol will be used in the study only after its approval by the Ethics Committee of the research center.

13. Adverse events, unfavorable effects of the device and its disadvantages

In this study, the Sponsor does not anticipate the occurrence of adverse events, except for those listed in paragraph 5 of this protocol.
All adverse events (defined below) are recorded, and serious adverse events (defined below) are reported to the principal investigator, the Ethics Committee and the Sponsor.

Adverse event (AE) is any unfavorable and involuntary event (including non-typical data of laboratory investigation), symptom or disease diagnosed in a subject and associated with his/her participation in the study. Such events imply the ones which were not seen at the baseline and/or deteriorated as compared with the baseline level. An undesirable event does not necessarily have to be causally related to the patient's participation in the study.

Serious adverse event (SAE) is an unfavorable event occurring in the course of study which leads to any of the following outcomes:

a) a lethal outcome;
b) a serious deterioration of the health of the subject, which, in turn, leads to either:
    1) disease or a life-threatening injury, or
    2) injury, or
    3) hospitalization or its extension, or
    4) medical or surgical intervention for the prevention of the life-threatening disease or injury;
c) a fetal injury, fetal death or abnormalities or defects of fetal development.

All AE (related and unrelated to injections) which meet the criteria for SAE must be immediately reported to the Sponsor and LEC, followed by filling in forms provided by the Sponsor to give a full description of the course of the event, the treatment conducted, and the final outcome. The first SAE reporting to the Sponsor must be carried out not later than two (2) working days after the Principal investigator has become aware of the event.

Unanticipated serious adverse device effect (**USADE)**s any serious undesirable and unanticipated effect on the state of health state or safety of the patient, or any life-threatening problem or death caused by or related to the injection needle if this event, problem or death has not been mentioned in the study design or in the application to conduct a research study (including additional plan or application) with an indication of its nature, severity or frequency of occurrence, or any other unforeseen serious problem related to the device and pertaining to the rights, safety or wellbeing of the patients.

Any USADE will be immediately reported to the Sponsor and LEC. That said, this report must be received by the Sponsor and LEC not later than two (2) working days from the moment when the Principal investigator has become aware of it.

In case of an occurrence of a SAE or USADE, the patient must contact the Principal investigator or investigator, whose contact phone numbers are given in the patient information leaflet.

13.1. Adverse Event (AE) Management

At each study contact, subjects will be questioned in an open-ended manner regarding any new or worsening undesirable signs or symptoms they may have experienced since the previous contact. Elicited signs and symptoms must be comprehensively documented on the appropriate source documentation.

Each sign, symptom, disease or illness reported must be evaluated by the Investigator or designee to determine if it meets the definition of an Adverse Event.

The clinical course of the event will be followed according to accepted standards of medical practice until the event resolves, stabilizes, or in the opinion of the Investigator, is no longer considered clinically significant. The Investigator must supply the Sponsor with information concerning the follow up and/or resolution of the AE.

Some reported or observed signs and symptoms are inherent to subcutaneous injection and are likely to occur transiently for nearly all subjects in this study. Such signs or symptoms will **not** be considered AEs as long as they are mild (transient, easily tolerated, no interference with daily activities) and the Principal Investigator agrees. The following will not be **not** be considered AEs:

- Mild, self-limited pain, swelling at the injection site
- Mild bruising at the injection site
- Mild self-limited bleeding at the injection site

However, these signs and symptoms ***must be considered AEs and*** documented on the Adverse Event eCRF should any of them occur in such a way that the extent or nature of the experience exceeds that normally associated with the procedure, as judged by the Subject to be excessive pain, bruising or bleeding.

Some signs and symptoms are inherent to the conditions under study (i.e. diabetes) and are likely to occur transiently for nearly all subjects in this study. Episodes of hyperglycemia and hypoglycemia occurring after subject enrollment and exposure to study product and/or study procedures, should be reported based on the following criteria:

- All blood glucose values <2.8 mmol/L (hypoglycemia) or >22.2 mmol/L (hyperglycemia) that require 3rd party (defined as, assistance of another person to administer carbohydrates or glucagon) or medical assistance for recovery will be recorded as an AE and assessed for seriousness.
- Any self-identified hypoglycemia or hyperglycemia without a BG reading or with any BG reading that requires 3rd party or medical assistance for recovery will be recorded as an AE and assessed for seriousness.
- All blood glucose values >22.2 mmol/L (and no symptoms of ketosis) will not be considered an AE.
    - Signs of ketosis are elevated BG along with nausea but individual has the ability to drink fluids and nausea is resolved with additional insulin and oral fluids, this may be considered an AE per the discretion of the PI or designee.

All blood glucose values <2.8 mmol/L, or self-identified as hypoglycemia that resolves with standard carbohydrate administration will not be recorded as an AE unless otherwise determined by the Principal Investigator. However, these signs and symptoms ***must be considered AEs and*** documented on the Adverse Event eCRF should any of them occur in such a way that the extent or nature of the experience exceeds that normally associated with the procedure, as judged by the PI, or the event meets the criteria for a Serious Adverse Event (SAE).

13.2. Assessment of Adverse Events (AEs)

All AEs must be assessed for Seriousness, Severity, and Relationship. All AEs, regardless of classification, must be comprehensively documented in the eCRF and on the SAE form, if applicable, and reported to BD. This includes AEs related to marketed study products. The following information about the event is to be reported on the AE eCRF:

- Seriousness, classified as: Non-Serious or Serious
- Severity, classified as:
  - Mild: Transient symptoms, easily tolerated, no interference with daily activities
  - Moderate: Marked symptoms, moderate interference with daily activities, tolerable
  - Severe: Considerable interference with daily activities, intolerable
- Relationship, to the study product or study procedures:
  - Not Related: Evidence suggests absolutely no possible causal relationship between the event and the investigational study device (or procedures).
  - Unlikely Related: Evidence suggests that other possible causes or contributing etiological factors may have caused the event other than the investigational study device (or procedures).
  - Possibly Related: Evidence suggests a causal relationship between the event and the investigational study device (or procedures) cannot be ruled out
  - Definitely Related: Evidence suggests a reasonable causal relationship between the event and the device (or procedures) is likely

In addition, the following should be recorded for each AE:

- Action(s) taken to remedy the AE, including change in study treatment or participation, or medical/surgical treatments
- Duration of the AE from onset through resolution, as applicable
- Cause (including suspected product/procedure and/or other cause)
- Outcome of the event, including resolution and sequelae, as applicable

13.3. Incidents

A Clinical Study Incident is defined as any problem or issue involving the study device(s), reference methods, associated procedures or equipment, or represents a product-related injury (or potential for injury) to study subjects or personnel as a result of execution of this protocol. Clinical Study Incidents may adversely (or potentially adversely) affect human safety, the integrity of the evaluation data, or the operation of devices or systems, and warrant prompt attention.

Incidents involving injury to study subjects will also be reported as Adverse Events (as explained above). Examples of Clinical Study Incidents that are not Adverse Events might be mislabeling or adulteration of the study device, device malfunctions, errors in the device instructions, damage to devices caused by shipping or handling or improper

storage, or injury to study personnel due to execution of the protocol. If appropriate, an Incident may also be documented and reported as a protocol deviation.

The Monitor should be contacted immediately when site becomes aware of or suspects any defective or malfunctioning product. This includes:

- BD Micro-Fine Plus 4mm 32G pen needles that are involved in Study Incidents,
- BD Micro-Fine Plus 4mm 32G pen needles that are found to be expired, damaged or defective,
- BD Micro-Fine Plus 4mm 32G pen needles that are possibly the cause of an adverse effect, regardless of whether the product was believed to be damaged, defective or malfunctioning.

The Study Monitor should be contacted with any questions regarding return of study products.

14. Sensitive populations

According to GOST R ISO 14155-2014, a sensitive subject is an individual whose preparedness to participate in the clinical trial can be unduly affected by anticipation, reasonable or not, participation-related benefits or negative reaction of administration in case of his/her refusal to partake. In this study, only *non-sensitive populations* will be enrolled, and all procedures will be carried out under Compulsory Medical Insurance and subsidized pharmaceutical provision. Based on the definition of a sensitive subject, research center staff and Sponsor employees cannot be enrolled in the trial as study subjects.

15. CT suspension or premature termination

The Sponsor can suspend or terminate the trial in case of substantial and documented reasons, including cases of occurrence of serious AE. The Sponsor can also stop participation in the trial of the research center or the investigator should any breach of, and deviation from the protocol on the part of the investigator be found. Disqualification of the investigator can be done if the following violations by the investigator have been revealed:
-repeated and deliberate violation of the protocol,
- repeated and deliberate communication of incorrect, incomplete and inaccurate information to the Sponsor (in eCRF, reports, etc.).

The principal investigator or Ethics Committee of the research center can suspend or terminate the participation of the center which they are responsible for. In order to suspend or terminate the study, the party initiating the suspension must notify, in writing, all parties about the decision taken (including the Sponsor, the investigator and the Ethics Committee of the research center) and provide substantiation of such a decision. When necessary, the investigator must notify patients, in writing, about study suspension or termination. Trial resumption may be possible only after approval by the Ethics Committee of the research center.

16. Publication principles

We intend to publish the study results obtained at the premises of all the participating

research centers. The publication media will be chosen by the Principal investigator jointly with the Sponsor.

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4. Ji L, Li Q, Wei G. Lipohypertrophy - prevalence, risk factors and clinical characteristics of insulin-requiring patients in China. Submitted, J. Diabetes.
5. Frid, Anders H. et al. New Insulin Delivery Recommendations. Mayo Clinic Proceedings , Volume 91 , Issue 9 , 1231 – 1255. http://www.mayoclinicproceedings.org/article/S0025-6196(16)30321-4/fulltext
6. “GOST R ISO 14155-2014 Clinical investigations. Good Clinical Practice” (in Russian).

Appendix A: Accompanying regulatory documents

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
ACCOUNTING FORM FOR RECORDING NEEDLE SUPPLY **For disposable BD Micro-Fine Plus: 32G (0.23 x 4 mm) needles for injection pen**		**PAGE _____ OF _____**

Dates of needle receipt, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of return of unused needles, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____

Investigator's signature _____ Date _____

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
ACCOUNTING FORM FOR RECORDING GLUCOMETERS, STRIPS and LANCETS SUPPLY		**PAGE _____ OF _____**

Dates of glucometers receipt, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of strips receipt, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of lancets receipt, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of return of unused glucometers, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of return of unused strips, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of return of unused lancets, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____
Dates of return of USED glucometers, number of packages, № and batch	☐☐ ☐☐ ☐☐☐☐ day month year	Packages _____Batch № _____

Investigator's signature _____ Date _____

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
NEEDLE USE LOG BOOK **For disposable BD Micro-Fine Plus: 32G (0.23 x 4 mm) needles for injection pen**		**PAGE _____ OF _____**

Patient code	Number of packages of 100 items each

Investigator's signature

Date

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
STRIPS USE LOG BOOK		**PAGE _____ OF _____**
Patient code		**Number of packages of 100 items each**

Investigator's signature

Date

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
LANCETS USE LOG BOOK		**PAGE _____ OF _____**
Patient code		**Number of packages of 100 items each**

Investigator's signature

Date

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
CT PATIENT ACCOUNTING LOG BOOK		**Page _____of _____**

Patient's initials	Patient code	Date of signing the informed consent (dd. mm. yy)

_____ _____

Investigator's signature Date

«The role of proper insulin injection technique in the treatment of diabetes mellitus»		
Principal investigator:	**Name of research center:**	**Research center number:**
RECORDS OF MONITOR SITE VISITS		**Page _____of _____**

Date of visit dd/mm/yy	Signature	Purpose of visit	Initials of center staff member

Investigator's signature

Date

Appendix B: EQ-5D (English and Russian version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

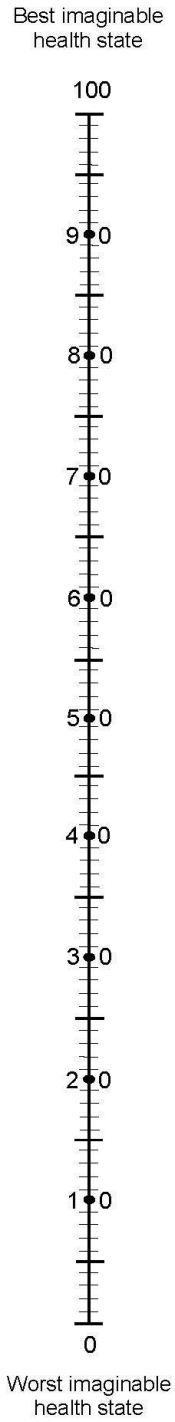
I am extremely anxious or depressed ❑

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Отметьте галочкой один квадратик в каждом из разделов, приведенных ниже. Укажите такие ответы, которые наилучшим образом отражают состояние Вашего здоровья на сегодняшний день.

Подвижность

Я не испытываю никаких трудностей при ходьбе ❑

Я испытываю некоторые трудности при ходьбе ❑

Я прикован (-а) к постели ❑

Уход за собой

Я не испытываю никаких трудностей при уходе за собой ❑

Я испытываю некоторые трудности с мытьем или одеванием ❑

Я не в состоянии сам (-а) мыться или одеваться ❑

Привычная повседневная деятельность *(например: работа, учеба, работа по дому, участие в делах семьи, досуг)*

Моя привычная повседневная деятельность дается мне без труда ❑

Моя привычная повседневная деятельность для меня несколько затруднительна ❑

Я не в состоянии заниматься своей привычной повседневной деятельностью ❑

Боль / Дискомфорт

Я не испытываю боли или дискомфорта ❑

Я испытываю умеренную боль или дискомфорт ❑

Я испытываю сильную боль или дискомфорт ❑

Тревога / Депрессия

Я не испытываю тревоги или депрессии ❑

Я испытываю умеренную тревогу или депрессию ❑

Я испытываю сильную тревогу или депрессию ❑

Для того, чтобы помочь опрашиваемым высказать свое мнение о том, насколько плохо или хорошо их состояние здоровья, мы изобразили шкалу, похожую на термометр, на которой наилучшее состояние здоровья, которое Вы можете себе представить, обозначено цифрой 100, а наихудшее состояние, которое Вы можете себе представить, обозначено цифрой 0.

Мы бы хотели, чтобы на этой шкале Вы указали, насколько хорошим или плохим по Вашему мнению является состояние Вашего здоровья на сегодняшний день. Для этого Вы должны провести линию от квадрата внизу до той точки на шкале, которая соответствует состоянию Вашего здоровья на сегодняшний день.

Состояние Вашего здоровья на сегодняшний день