Document title	**CLINICAL STUDY PROTOCOL**
Study official title	Randomized double-blind placebo-controlled study assessing efficacy and safety of luseogliflozin on the top of metformin in Caucasian patients with type 2 diabetes mellitus and inadequate glycemic control
Test drug code	Luseogliflozin (Lusefi®)
Indication	Type 2 diabetes mellitus
Development phase	Phase III
Protocol code	CL3-LUSEO-001
Sponsor:	*Joint Stock Company SERVIER (JSC SERVIER)*
Date of the document	31st July 2018
Version of the document	Final version

CONFIDENTIAL

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STUDY SUMMARY SHEET

Name of the sponsor: JSC Servier	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: **L**useogliflozin	**Page:**	

Title of study: Randomized double-blind placebo-controlled study assessing efficacy and safety of luseogliflozin on the top of metformin in Caucasian patients with type 2 diabetes mellitus and inadequate glycemic control

Protocol No.: CL3-LUSEO-001

Coordinator(s) *or* **Investigator** *or* **Steering Committee Chairman**

National coordinators and investigators: listed in a separate document

Study centre(s):
Total number of centres:36

Study period:	**Study development phase: III**
- Study duration for the participant: maximum 16 weeks - Study initiation date (planned date of first visit first participant): Q1 2019 - Study completion date: (planned date of last visit last participant): Q3 2019	

Objective(s):
The purpose of the study is to evaluate the efficacy and safety of 3 doses of luseogliflozin *versus* placebo on top of metformin in Caucasian patients with inadequately controlled type 2 diabetes mellitus (DM).
The primary objective is to demonstrate the efficacy of at least one dose (among 3 doses) of luseogliflozin *versus* placebo on top of metformin in reducing HbA1c between W12 and W0.
The secondary objectives are:

- to evaluate efficacy of 3 doses of luseogliflozin on fasting plasma glucose, postprandial plasma glucose, body weight, waist circumference
- to assess safety of 3 doses of luseogliflozin

The exploratory objectives are:

- to evaluate the proportion of patients with HbA1c<7% and <6.5% after 12 weeks of treatment
- to assess pharmacokinetic and pharmacodynamic parameters of luseogliflozin in a subset of patients

Methodology:
Study design: multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of 12-week treatment with 3 doses of luseogliflozin or placebo on top of metformin
The study will consist of 3 periods: selection period up to 2 weeks, double-blind treatment period with 4 parallel groups (doses 2.5 mg, 5 mg, 10 mg of luseogliflozin and placebo) on top of metformin for 12 weeks and the follow up period for 2 weeks after double blind treatment stop.

Number of participants:
Planned: 320 patients included into the study and randomised using Interactive Response System (IRS) with a randomization ratio 1:1:1:1 (80 patients in 2,5 mg Luseogliflozin group; 80 patients in 5mg Luseogliflozin group; 80 patients in 10 mg Luseogliflozin group; 80 patients in placebo group)

Diagnosis and main criteria for selection:
Out-patients (male and female) of Caucasian race aged 18-75 years inclusive with type 2 diabetes mellitus (diagnosed for not less than 3 months prior to selection), treated with metformin in stable dose equal or more than 1500 mg daily for at least 3 months and with inadequate glycemic control (HbA1c 7.5 %-10.0 % at

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central laboratory**).**
Body mass index less than 36 kg/m2,
Absence of any severe, uncontrolled conditions incompatible with study treatment or likely to interfere with the conduct of the study.

Test drug:
Name: Luseogliflozin
Dosage form: film-coated tablet
Dosages: 2,5 mg; 5 mg of luseogliflozin

Comparator:
Placebo
Dosage form: film-coated tablet

Dose regime:
Patients will have to take 3 tablets once daily orally before breakfast starting next day after inclusion visit and ending at Week 12 visit.
IMP intake will be as follows:

2.5 mg group: one tablet of Luseogliflozin 2.5 mg, one tablet of Placebo 2.5 mg and one tablet of Placebo 5 mg

5 mg group: two tablets of Luseogliflozin 2.5 mg and one tablet of Placebo 5 mg

10 mg group: two tablets of Luseogliflozin 2.5 mg and one tablet of Luseogliflozin 5 mg

Placebo group: two tablets of Placebo 2.5 mg and one tablet of Placebo 5 mg

Duration of treatment:
Selection period: no study treatment during 1-2 weeks
Double blind treatment period:12 weeks
Follow up period: no study treatment 2 weeks after double-blind treatment stop

Criteria for evaluation:
Efficacy measurements:

Primary evaluation variable:
-HbA1c (The change in HbA1c from baseline to Week 12)

Secondary evaluation variables:
- change in fasting plasma glucose,
- change in postprandial plasma glucose (2-hours after standardized meal)
- change in body weight
- change in waist circumference

Exploratory evaluation variables: proportion of patients at target (HbA1c<7% and HbA1c<6.5%)

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pharmacokinetic and pharmacodynamic parameters of luseogliflozin in a subset of patients.

Safety measurements:
Nature and frequency of emergent adverse events (AE), AE of Special Interest, serious AE / Events Requiring Immediate Notification (ERIN), AE related to the treatment with IMP (adverse drug reactions), AE leading to treatment withdrawal, laboratory parameters, vital signs (BP, HR) and 12-lead ECG.

Pharmacokinetic measurements:
About 18 patients per each dose group will be included into PK/PD subset. A total of 12 blood samples per patient will be collected at Week 4 for analysis of pharmacokinetic parameters of luseogliflozin. Sampling times: T0 (before administration); 0.25 (15 min); 0.5 (30 min); 1; 1.5; 2; 3; 4; 6; 8; 12 and 24 hours after IMP administration.
Pharmacodynamic measurements: 24-hours excreted urinary glucose (quantitative) will be measured at inclusion (Week 0) and at Week 4 visits. Urine samples of 24-hour urine will be collected in the patients, participating in the PK/PD measurement.

Statistical methods:
Analysis sets:

- **Randomized Set (RS):**
  All patients to whom a therapeutic unit was randomly assigned using IRS.
- **Per Protocol Set (PPS):**
  All the patients of the RS that do not have any significant protocol deviations. List of deviations will be reviewed for the determination of their significance prior to the database lock and randomization list unblinding.
- **Safety Set (SS):**
  All patients having taken at least one dose of study drug.
- **Pharmacokinetic set**: all patients for whom blood samples were collected with no deviations that might affect the pharmacokinetic interpretation
- **Pharmacokinetic/Pharmacodynamic set:** all included patients for whom blood samples and 24-hour urinary glucose measurements were collected with no deviations that might affect the PK and/or PD interpretations.

Efficacy analysis:

In order to take into account the multiplicity of comparisons induced by the assessment of three luseogliflozin doses versus placebo, a Bonferroni correction will be used.
Primary endpoint
In order to meet the primary objective of the study, the efficacy of at least one dose of luseogliflozin as compared to placebo after 12 weeks of treatment in glycemic control will be assessed from the change from baseline to W12 in HbA1c, in patients of the RS.
Analysis of covariance (ANCOVA) will be used as the main method of assessment of the primary endpoint, with baseline (W0) HbA1c value being a covariate.
Unrestricted least significant differences (LSD) method will be applied to the ANCOVA results with the calculation of least-square (LS) means with 95% CI for LS means for the difference between each dose level and placebo.

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Finally, to assess the dose-response of the investigation product with regards to the primary endpoint, contrasts will be built based on the ANCOVA results.
Before performing ANCOVA, a multiple imputation procedure will be used to impute:

- Missing data for the primary endpoint at 12 week (for patients with missing data at W8 and W12 and for patients with missing data at W12 only)
- Data collected after rescue therapy for non-controlled patients

This approach allow to evaluate, as primary analysis, the hypothetical « proper effect » of luseogliflozin without additional effect of rescue therapy.
Two additional analysis will be performed on the primary endpoint:

- Before performing ANCOVA, a multiple imputation procedure will be used to impute missing data for the primary endpoint at 12 weeks. Here data collected after rescue therapy will be taken into account in the analysis allowing to evaluate the effect of "the treatment policy" of luseogliflozin + rescue medication *versus* placebo + rescue medication.
- Last observation carried forward (LOCF) method will be used to impute post rescue evaluations and other missing data at 12 weeks for the primary endpoint (for a bridging objective with studies performed on Japanese population)

Study patients (disposition, baseline characteristics and follow-up) and safety analysis:
Descriptive statistics will be provided.

Sample size rationale:

The determination of the sample size was performed considering the primary endpoint, the HbA1c. It was estimated on the change from baseline at W12, for a difference objective between at least one dose of luseogliflozin and placebo, based on a two-sided t-test for independent samples and using the Bonferroni correction in order to maintain the experiment wise type I error at 5% (bilateral situation).

About 80 patients per treatment group (320 overall) allow to conclude that at least one dose of luseogliflozin is superior to placebo with a power of around 85% if a true difference is 0.6% for a standard deviation of 1.1%.

Pharmacokinetic analysis :
The pharmacokinetic parameters (such as AUC, C max, C min) will be calculated for the subset of patients, participating in the pharmacokinetic assessment using non-compartmental analysis. Corresponding individual and mean pharmacokinetics graphs will be plotted. Further analyses might be performed including population PK and PK/PD approaches.

Other measurements analysis: 24 hours urinary glucose excretion (UGE) at W0 and at W4 will be measured. Due to large inter individual variability of UGE "change of UGE" from W0 to W4 will be used to evaluate pharmacodynamics.

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Contractual signatories

I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice (GCP) and the applicable regulatory requirements**.**

NAME DATE SIGNATURE

COORDINATOR / INVESTIGATOR :

CENTER NUMBER	

DIRECTOR ON CLINICAL TRIALS EURASIAN ECONOMIC UNION (EAEU):

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AE	:	Adverse Event
AEOSI		Adverse Event of Special Interest
ALT	:	ALanine aminoTransferase
AST	:	ASpartate aminoTransferase
ATC		Anatomical Therapeutic Chemical classification system
AUC	:	Area Under the Curve
BMI	:	Body Mass Index
BP	:	Blood Pressure
CI	:	Confidence Interval
C_{max}	:	maximum Concentration
CRF	:	Case Report Form
CRO	:	Contract Research Organisation
DBP	:	Diastolic Blood Pressure
e.g.	:	Exempli gratia (for example)
EAEU	:	EuroAsian Economic Union
ECG	:	ElectroCardioGram
e-CRF	:	Electronic Case Report Form
eGFR	:	Estimated glomerular filtration rate
EoS		End of Study
ERIN	:	Event Requiring Immediate Notification
GCP	:	Good Clinical Practice
HbA1c	:	glycated Haemoglobin
HDL	:	High-Density Lipoprotein
HR	:	Heart Rate
i.e.	:	id est (that is)
ICH	:	International Conference on Harmonisation
IEC	:	Independent Ethics Committee
IMP	:	Investigational Medicinal Product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial (test drug / placebo / reference product)
IRB	:	Institutional Review Board
IRS	:	Interactive Response System
JSC Servier		Joint Stock Company Servier
Kg	:	kilogram
LDL	:	Low-Density Lipoprotein
MedDRA	:	Medical Dictionary for Regulatory Activities
NA	:	Not Applicable
NS	:	Not statistically Significant
NCA	:	Non-compartmental pharmacokinetic analysis
NYHA	:	New York Heart Association
PD	:	PharmacoDynamics
PK	:	PharmacoKinetics
SAE	:	Serious Adverse Event
SBP	:	Systolic Blood Pressure
SGLT2	:	Selective sodium glucose cotransporter 2 inhibitor
SMBG	:	Self-Monitoring of Blood Glucose

test drug	:	Drug substance in a given dosage form, tested in a clinical trial. It usually corresponds to luseogliflozin
t_{max}	:	time corresponding to C_{max}
ULN	:	Upper Limit of Norm
W	:	Week
WOCBP	:	Women of ChildBearing Potential

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non-sponsor parties, sponsor parties and CRO responsible for subcontracted activities of the study are described in a separate document entitled Administrative part of clinical study protocol.

The list of investigators is given in a document attached to the protocol.

2. BACKGROUND INFORMATION

According to the International Diabetes Federation, more than 382 million people in the world had diabetes in 2013, and this number is expected to reach 592 million by 2035 [1]. Treatment of patients with type 2 diabetes mellitus continues to present challenges, with considerable number of patients failing to achieve and maintain optimal glycaemic control. There is a growing body of literature that recognises the importance of adequate glycemic control in patients with type 2 diabetes due to the well-established association between sustained hyperglycemia and serious microvascular complications including retinopathy, neuropathy, and nephropathy [2]. According to the latest recommendations of the American Diabetes Association, glycemic control is fundamental to diabetes management. The glycated hemoglobin A1c (HbA1c) test is an indirect measure of average glycemia. The American Diabetes Association recommends A1c goal of less than 7,0% [3]. It has been shown in a range of clinical studies that at this HbA1c patients have significantly fewer long-term microvascular and macrovascular complications [4]. However, according to the data from the 1999-2000 National Health and Nutrition Examination Survey, only 37% of patients with type 2 diabetes mellitus achieve this goal [4]. Therefore, the search for novel antidiabetic therapeutic agents is urgent.

More recent attention has focused on the kidney as a potential therapeutic target, especially because renal glucose reabsorption is increased in type 2 diabetes mellitus. An on-going effort to identify new treatment strategies for diabetes has resulted in the development of luseogliflozin – a novel, selective sodium glucose cotransporter 2 inhibitor (SGLT2). Inhibition of SGLT2 facilitates urinary glucose excretion by preventing the reuptake of filtered glucose in the proximal tubules of the kidney, consequently lowering plasma glucose level [1]. Qiang et al. (2015) investigated the effects of luseogliflozin on for non-alcoholic steatohepatitis development using a rodent model with diabetes mellitus. It was demonstrated that luseogliflozin not only normalized high glucose blood levels, but also almost completely suppressed the development of steatohepatitis based on the histochemical findings, as well as measurements of hepatic lipid content and different serum markers of liver injury, fibrosis and inflammation [5]. A number of previous studies on rodents also demonstrated that SGLT2 inhibitors can ameliorate fatty liver with significant body weight loss, and the weight reducing effects of various SGLT2 inhibitors have also been documented in humans [5,6]. These extra effects may be exceptionally beneficial for diabetic patients as patients with type 2 diabetes are known to be suffering from obesity and all associated conditions fairly often [7].

Kojima et al. (2013) have studied the effect of long-term control of hyperglycemia with luseogliflozin, given alone or in combination with lisinopril on the progression of renal injury in the T2DN rat model of type 2 diabetic nephropathy. Reducing blood pressure with lisinopril prevented the fall in glomerular filtration rate and decreased proteinuria and the

degree of glomerular injury and tubular necrosis. What's more, combination therapy reduced the degree of glomerular injury, renal fibrosis, and tubular necrosis to a greater extent than administration of either drug alone. The authors have come to the conclusion that control of hyperglycemia with luseogliflozin slows the progression of diabetic nephropathy more than that seen with insulin, and combination therapy is more renoprotective than administration of either compound alone. Taken together, these findings may be used for improving therapeutic strategy for diabetic patients [8]. No major toxic effects of luseogliflozin were shown in preclinical studies.

Effectiveness of luseogliflozin was also demonstrated in a range of clinical studies. According to the results of the phase I study (Clinical Study Protocol Number: TS071-01-2), there were no serious or other significant adverse events in a total of 57 subjects (including 14 subjects in a placebo group).

In a total of 40 subjects (including 8 in placebo group), 9 adverse events occurred in 7 subjects (Clinical Study Protocol Number: TS071-02-2). There were no serious or other significant adverse events. All the adverse events were mild in severity and reversible.

Pharmacokinetics, pharmacodynamics and safety was assessed during single oral dosing of 5 mg of luseogliflozin to subjects with type 2 diabetes and renal dysfunction (Clinical Study Protocol Number: TS071-02-6). No cases of discontinuation of dosing due to serious adverse events or adverse events were observed among the total of 57 subjects. Twelve instances of adverse events were observed in 8 subjects, however, no severe adverse events were observed. Each of the subject groups showed an increase in the 24-hour urinary glucose excretion after treatment in comparison to the baseline prior to treatment.

Results from the previous 12-week exploratory and dose-finding (phases 2a and 2b, respectively) clinical trials have demonstrated that administration of luseogliflozin once a day results in considerable improvements in normalizing HbA1c levels as well as other glycemic parameters. Moreover, the drug was shown to be well tolerated, with a favorable safety profile [9,10]. Scheen (2015) have conducted a review and found out that according to the results to several placebo-controlled randomised clinical trials of 12–104 weeks duration administering SGLT2 inhibitors as monotherapy or in addition to other glucose-lowering therapies including insulin to patients with type 2 diabetes mellitus led to significant reductions in HbA1c and therefore a significant increase in the proportion of patients reaching HbA1c targets, and a considerable decreasing of fasting plasma glucose. However, the drug should be administered to elderly patients with safety cautions because of a higher risk of renal impairment, orthostatic hypotension and dehydration. Overall, SGLT2 inhibitors were proved to have good safety profile. The most frequently reported adverse events are female genital mycotic infections, while urinary tract infections are less commonly observed and generally benign [6].

Luseogliflozin was discovered and developed by Taisho Pharmaceutical. Since 2014 luseogliflozin is approved under the trade name Lusefi® in Japan for the treatment of type 2 diabetes mellitus in tablets 2.5 mg and 5 mg taken orally once a day.

JSC Servier has signed a licensing and supply agreement with Taisho Pharmaceutical Co., Ltd. Under this agreement, Taisho grants Servier the exclusive rights for manufacturing, development, distribution, commercialization and promotion of the finished pharmaceutical products containing luseogliflozin in Russia and Eurasian Economic Union (EAEU).

Due to potential racial/ethnic differences in drug disposition and response [11–13] it has been decided to conduct a clinical trial phase III where Caucasian patients with type 2 diabetes will

be included in order to assess luseogliflozin efficacy and safety for this population. Therefore, the patients aged 18-75 years with type 2 diabetes mellitus diagnosed for not less than 3 months prior to selection with inadequate control of diabetes mellitus as confirmed by HbA1c ≥ 7.5 % and ≤10% will be included into the study.

The study will be conducted in compliance with the protocol, GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND PURPOSE

The purpose of the study is to evaluate the efficacy and safety of 3 doses of luseogliflozin *versus* placebo on the top of metformin in Caucasian patients with inadequately controlled type 2 diabetes mellitus.

The primary objective of the study is to demonstrate the efficacy of at least one dose (among 3 doses) of luseogliflozin *versus* placebo on top of metformin in reducing HbA1c between W12 and W0.

The secondary objectives are

- to evaluate efficacy of 3 doses of luseogliflozin *versus* placebo after 12 weeks of treatment on fasting plasma glucose, postprandial plasma glucose, body weight, waist circumference
- to assess safety of 3 doses of luseogliflozin

The explaratory objectives are

- to evaluate the proportion of patients with HbA1c<7% and <6.5%) at week 12
- to assess pharmacokinetic and pharmacodynamic parameters of luseogliflozin in a subset of patients

4. STUDY DESIGN

Randomized, multicenter, double-blind, placebo-controlled, parallel-group dose-ranging study of 12-week treatment with 3 doses of luseogliflozin or placebo on top of metformin

4.1. Endpoint(s)

- Primary endpoint:

  Change in HbA1c

- Secondary endpoints:
  - Efficacy: change in plasma fasting glucose, change in postprandial plasma glucose level (2 hours after standardized meal), change in body weight, change in waist circumference
  - Safety: adverse events, in particular adverse events of Special interest (hypoglycaemia, polyuria, pollakiuria, events related to decreased fluid volume

(including dehydration and BP decrease), ketoacidosis, urinary tract infections, genital infections), BP, HR, as well as ECG and laboratory parameters (biochemistry, blood ketone, haematology, urine analysis).

- Exploratory:

  Proportion of patients at target (HbA1c < 7% & HbA1c < 6.5%), plasma concentrations of luseogliflozin in the PK/PD subset of patients; 24 hours excreted urinary glucose (quantitative) in the PK/PD subset of patients.

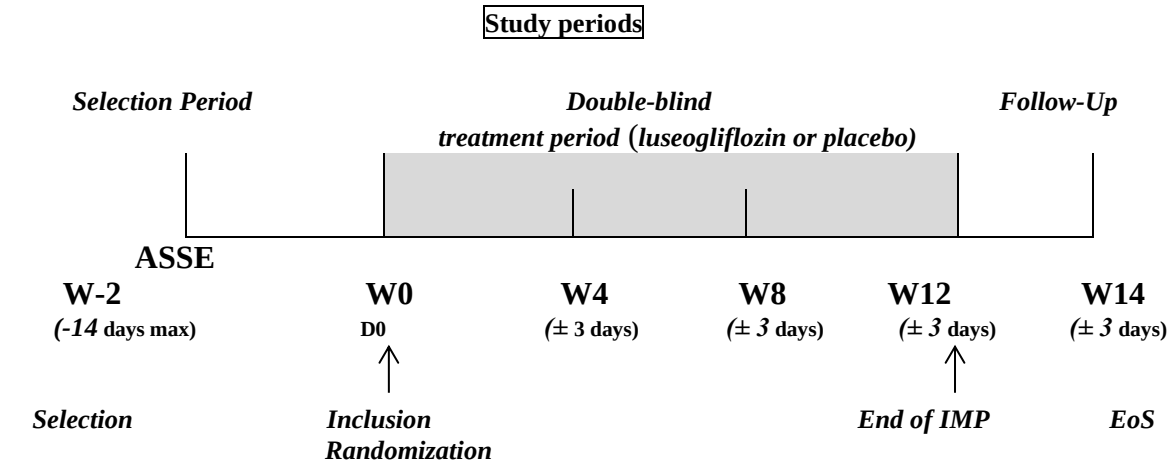
4.2. Experimental design

4.2.1. Study plan

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group dose-ranging study which will be conducted in study centers in Russian Federation.

The study will consist of 3 periods: selection period up to 2 weeks, double-blind treatment period for 12 weeks + Follow up period for 2 weeks after double-blind treatment stop. The study plan is shown in Figure 1.

Figure 1. Study plan



Ongoing treatment with metformin

No IMP	Luseogliflozin 2,5 mg group (n=80)	No IMP
No IMP	Luseogliflozin 5 mg group (n=80)	No IMP
No IMP	Luseogliflozin 10 mg group (n=80)	No IMP
No IMP	Placebo group (n=80)	No IMP

ASSE W0 W4 W8 W12 W14

Selection period will precede the inclusion into the study once the informed consent is signed and will last 7- 14 days before the randomization into the study to confirm the eligibility of the patients. Treatment with metformin in stable (during the previous 3 months) dose should be continued, the dosage frequency of metformin should be also unchanged. Diet and physical activity as routinely advised to the diabetic patients should be followed.

At inclusion visit the eligible patients will be randomized to receive either 2.5 mg, 5 mg, 10 mg Luseogliflozin or placebo in 1:1:1:1 manner. Randomization will be stratified on HbA1c (< 8.5% and ≥ 8.5 %) and center (stratum 'center performing PK sampling' and another one 'center not performing PK sampling').

The patients will start Luseogliflozin and/or placebo next day after inclusion visit in addition to the ongoing treatment with metformin.

After randomization the patients will undergo 4 study visits: Week 4 (W4), Week 8 (W8), Week 12 (W12) visits and the End of Study (EoS) follow up visit in 2 weeks after double-blind treatment stop (W14).

During the double-blind treatment the doses of luseogliflozin and metformin as well as dosage frequency of metformin should not be changed unless for safety reasons (e.g. hypoglycaemia); antidiabetic medications other than metformin are not allowed during the selection period and double-blind treatment period, except in case of rescue therapy (see section 6.3.1).

Antihypertensive drugs, diuretics and therapy for dyslipidemia should be stable 6 week prior to inclusion and should remain unchanged during the study attempting not to modify or discontinue the treatment. However, in case of medical necessity, the dose adjustment, change of the drug or discontinuation of the concomitant therapy could occur. The investigator should record all changes in details.

After the double-blind treatment stop, the management of diabetes mellitus will be left to the Investigator's and/or treating provider's judgment, according to the clinical guidelines and standards of care, however SGLT2 inhibitors are not allowed until the end of the study (W14) visit.

Total study duration for each patient will be up to 16 weeks, including up to 2 weeks of selection period, 12 weeks of double-blind treatment period and 2 weeks of follow up after double-blind treatment stop.

End of study is defined as the date of the last follow-up visit of the last participant.

4.2.2. Investigation schedule

Table 1 describes the measurement of efficacy and safety assessed during the study.

Table 1 Investigation schedule

Visits	ASSE W-2 Selection	W0 Inclusion	W4 ± 3 days	W8 ±3 days	W12 ± 3 days	W14 ± 3 days[1]
Informed consent	x					
Selection/inclusion criteria	x	x				
Medical history*	x	x				
Vital signs (BP, HR)	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x
Height	x					
Weight	x	x	x	x	x	x
Waist circumference	x	x	x	x	x	x
ECG	x				x	
Pregnancy test (urine test) for WOCBP	x	x				
Patient's number allocation via IRS	x					
Randomization via IRS		x				
IMP allocation via IRS		x	x	x		
IMP dispensing		x	x	x		
Compliance			x	x	x	
Patient diary dispensing	x	x	x	x	x	
Dispensing of self-monitoring of blood glucose device (glucometer)	x					
Patient's diary assessment		x	x	x	x	x
Assessment of glucometer measurements		x	x	x	x	x
HbAc1 (at central laboratory)	x	x		x	x	
Fasting plasma glucose	x	x	x	x	x	
Postprandial plasma glucose (2 hours after standardized meal)		x			x	
Adverse events	◄	─	─	─	─	►
Laboratory tests ** (haematology, biochemistry)	prescription	results			x	
Abridged laboratory tests ***			x	x		
Blood ketone (test strip)		x	x	x	x	x
Urine analysis	prescription	results	x	x	x	x

[1] At the EoS visit (W14) the measurement of BP, HR, weight, waist circumference, blood ketones and urine analysis will be performed, AE will be collected

Blood sampling for PK (subset)			x			
24-h urinary glucose(subset) at central lab)		x	x			

**Events occurring before the first intake of IMP and not associated with a procedure scheduled in the study protocol (exercise test, etc.), will be recorded in the medical history form in the e-CRF*

***Laboratory tests:*

Hematology: Hemoglobin, Hematocrit, Erythrocytes, Leukocytes, Neutrophils, Basophils, Eosinophils, Lymphocytes, Monocytes, Platelets

Biochemistry: total protein, creatinine, eGFR, total bilirubin, AST, ALT, serum sodium, potassium, chloride, uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides,

**** Abridged laboratory tests: Hematocrit; total bilirubin, ALT, AST, creatinine, eGFR, serum sodium, potassium, chloride*

Blood sampling for HbAc1 assessment should be sent to the central laboratory for all patients included into the study, the urine samples for 24-hour urinary glucose should be sent to the central laboratory for included patients of PK/PD subset.
The administration of IMP should start next day after inclusion visit.

The maximum total volume of blood collected per participant during the study will be about 70 ml for patients whose results will be used only for assessing efficacy and safety and about 140 ml for the PK/PD subset of patients.

4.3. Measures to minimise bias

The randomised design is one of the main aspects which helps to minimise bias. The important aspect of this study design is that the patients are randomly assigned to the study groups that help in avoiding bias in patient allocation-to-treatment that a physician might be subject to. Stratification of randomization on baseline HbA1c and centre will be used.

It also increases the probability that the differences between the groups can be attributed only to the study treatment. Therefore, in this particular study this design will help to evaluate effectiveness and safety of different dose regimes.

Bias is avoided not only by randomization but also by blinding. This study is double blind, which means that neither patient nor investigator knows to which treatment the patient has been assigned.

Randomization list will be generated by a dedicated unblinded biostatistician using the unique randomization seed number to ensure reproducibility of results. Randomization list will be shared with the unblinded parties only (as listed in the communication plan for the study). Randomization list will be shared with the blinded statistician only at the stage of final analysis after the database is fully locked.

Group allocation will be concealed from the site staff and all blinded staff as randomization codes will not have any direct relation to any group allocation (i.e. this can be figured out only if the randomization list is available). Thus, all information sources (source documents,

laboratory reports, PK reports, eCRF, etc.) will store only the patients number as study participant identifier.

Treatment randomization and allocation will be centralised by Interactive Response System (IRS). The structure responsible for designing and constructing the randomization lists in blind will be the CRO.

Test drug (luseogliflozin) and placebo will have the same appearance. As the tablet size of luseogliflozin 2.5 mg is smaller than tablet of luseogliflozin 5 mg, 1 tablet (luseogliflozin 2.5 mg or placebo depending on the group) has been added to each arm to maintain the blind.

The primary efficacy variable (HbA1c) will be measured by a central laboratory in order to centralize and harmonise the data.

As luseogliflozin, as other SGLT2 inhibitors, increases urinary glucose excretion, the measurements of urinary glucose in the PK/PD subset of patients are to be reported by the central laboratory to the sponsor and Investigators only after locking of study data.

Samples for pharmacokinetic analysis will be sent to the PK laboratory for analysis using a validated assay method. The PK laboratory will be provided with the treatment codes so that only samples from patients being treated with luseogliflozin will be assayed. The results of the luseogliflozin blood concentration will be transferred from PK laboratory after clinical database associated to the first statistical analysis (W0-W12 period) is locked and blind is broken.

4.4. Study products and blinding systems

4.4.1. Products administered

Table 2 provides a description of the IMP(s).

Table 2 Description of the IMPs

	Luseogliflozin 2.5 mg	***Luseogliflozin 5 mg***	**Placebo corresponding to Luseogliflozin 2.5 mg**	**Placebo corresponding to Luseogliflozin 5 mg**
Pharmaceutical form	*Film-coated tablet*	*Film-coated tablet*	*Film-coated tablet*	*Film-coated tablet*
Unit dosage	*2.5 mg*	*5.0 mg*	-	-
Appearance, colour	*Round White*	*Round White*	*Round White*	*Round White*
Diameter	*Approximately 7.1 mm*	*Approximately 8.6 mm*	*Approximately 7.1 mm*	*Approximately 8.6 mm*
Composition	*Luseogliflozin hydrate Lactose monohydrate*	*Luseogliflozin hydrate Lactose monohydrate*	*Lactose monohydrate*	*Lactose monohydrate*

Table 3 provides a description of the packaging of the IMP(s).

Table 3 Description of packaging

Number of units of the pharmaceutical form per primary packaging	21 tablets in blister (in paper card)
Number of primary packaging per secondary packaging	Box containing 5 blisters in aluminium pouch
Number of secondary packaging per participant and per treatment period	One box per each visit (visits W0, W4, W8)

The labelling of packages complies with the regulatory requirements of Russia.

4.4.2. IMP management

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to section 6.2), accountability and IMP collection are the responsibilities of the investigator and/or pharmacist of the medical institution.

Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements.

A certificated destruction will be performed according to standard modalities for that class of product. The practical procedures for destruction of used and unused IMP will be defined by the sponsor. An IMP collection and destruction form will be completed before the shipment of IMP to destruction.

The IMP should be stored in a secure area with restricted access. Specific storage conditions are mentioned on IMP labelling.

The investigator/pharmacist is responsible for the IMP temperature monitoring using "Therapeutic Unit temperature log sheet - centre" (recording Min-Max temperature every working day) or an equivalent document.

In case of temperature deviation, the investigator/pharmacist should immediately:
- block the IRS for the concerned IMPs and place them in quarantine with appropriate temperature conditions,
- alert the monitor or the local project manager if the monitor is absent, forward him all needed information and implement the instructions received.

Furthermore, the investigator/pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs in order to avoid recurrence

IMP management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time all the documents provided by the sponsor concerning IMP management (therapeutic unit tracking form or an equivalent document). Therapeutic unit tracking form, or an equivalent document, is the source document to fulfil.

The investigator and/or the pharmacist of the medical institution should only use the IMP provided for the participants involved in the study.

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor. The investigator will notify the monitor of all complaints set out by a participant (change of taste, appearance…).

In the event of anticipated return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the investigator and/or the pharmacist will identify the participants in possession of the IMP at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, or an equivalent document, and will contact them immediately.

4.4.3. Management of blinding systems

The decoding system used is a centralised decoding by IRS.

Every attempt will be made to maintain the treatment blinding throughout the study.

A blind for any study participant should only be broken by investigator or authorized person if it is absolutely necessary to ascertain the type of treatment given.

Whenever possible, the study sponsor should be notified prior to the unblinding of a subject's treatment assignment. The procedure for code breaking to be followed by Investigator is detailed in the IRS manual.

A code list will also be kept in a safe place by sponsor and will be accessible only to person authorized to unblind.

4.5. Discontinuation of the study

4.5.1. Premature discontinuation of the study or temporary halt

This study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause.

After having informed the coordinator, the sponsor or the investigator / coordinator or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the coordinator. The IRB/IECs and Competent Authorities will be informed according to local regulations.

If the study is prematurely discontinued, the on-going participants should be seen as soon as possible and the same assessments as described in Table 1 (W12 ± 3 days visit) should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant’s interests.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authorities.

4.5.2. Discontinuation of the study in the event of objective reached

Not applicable.

4.6. Source data

All information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents for which data should not be reported again in medical file (i.e. no need to duplicate information from source document to medical file) are participant diary, laboratory report, ECG report, print-outs of SMBG, PK requisition form. The main source data will be recorded to the eCRF. Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study. Each patient is identified by a unique patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel is able to identify the patient based on the patient identification code.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Selection criteria

5.1.1. Demographic characteristics

1. Age between 18 and 75 years both inclusive,
2. Caucasian race

5.1.2. Medical and therapeutic criteria

3. Out-patients with type 2 diabetes mellitus diagnosed for not less than 3 months prior to selection,
4. On-going monotherapy with Metformin ≥ 1500 mg daily in the stable dose for at least 3 months
5. Inadequate control of diabetes mellitus as confirmed by HbA1c ≥ 7.5% and ≤10% according to the previous laboratory result not more than 3 months ago
6. BMI less than 36 kg/m2

7. Antihypertensive drugs, beta-blockers, diuretics, drugs for treatment of dyslipidaemia, if administered, should be in a stable dose for at least 6 weeks prior to selection and to be continued during the study

5.1.3. Informed consent

8. Signed informed consent before any study investigations obtained as described in section 13.3 of the protocol. A specific written consent form is to be signed by the patients participating in PK/PD assessment.

5.2. Non-selection criteria

9. Patients who are in an insulin-dependent state (who regularly need to use an insulin preparation).
10. Patients with diabetes mellitus other than type 2 (type 1 diabetes mellitus, diabetes mellitus due to some specific mechanism condition other than type 1 or 2, gestational diabetes mellitus).
11. Unstable diabetes mellitus (documented severe hypoglycemia or hospitalization due to diabetes decompensation or due to hypoglycemia within 1 year prior to selection)
12. Current or previous treatment with 2 or more antidiabetic drugs, except if they were prescribed due to decompensation due to acute illness or surgery and not less than 3 months ago
13. Patient with any uncontrolled endocrine disease other than diabetes mellitus
14. Patients with any of the following renal conditions:
    - Known estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2
    - Stage 3 (overt nephropathy) or worse diabetic nephropathy
    - History of nephrectomy or renal transplantation
    - History of dialysis within 1 year prior to selection.
15. Patients with an acute or exacerbation of chronic urinary tract infection or of genital infection or patients who have frequent episodes of exacerbation of such infection in the Investigator's opinion or at least once in 2 months
16. Patients with an obvious urination disorder due to problems such as neurogenic bladder or prostatic hyperplasia
17. Use of systemic (excluding topical application, intranasal, ophtalmological, intraarticular or inhaled form) glucocorticoids for more than 10 consecutive days within 3 months prior to selection visit

18. Change in dosage of thyroid hormones within 6 weeks prior to selection
19. Treatment with anti-obesity drugs within 3 months prior to selection
20. Recent (i.e less than 6 months prior to selection) major cardiovascular events (myocardial infarction, cardiac surgery/revascularization, unstable angina, transitory ischemic accident or stroke)
21. Patients with severe hepatic disorder, pancreatic disorder, hematological disease, gastrointestinal disorder or patients with a history of surgery that may have had a significant effect on absorption.
22. Chronic heart failure NYHA class IV
23. Uncontrolled hypertension: sitting SBP>180 mm Hg and/or DBP>100 mm Hg at selection visit (exclusion should be based on the mean of 2 measurements)
24. Patients with a complication of severe diabetic microangiopathy (e.g., preproliferative or proliferative diabetic retinopathy, or diabetic neuropathy whose symptoms cannot be adequately controlled despite continued drug therapy)
25. History of diabetic ketoacidosis or hyperosmolar coma within 3 months prior to selection
26. Any acute disease or exacerbation of chronic diseases 1 month prior to selection
27. Lower extremity complications (such as skin ulcers, bacterial infection, osteomyelitis, and gangrene) at the selection
28. History of lower extremity amputation
29. Patients with malignant tumor with exception of basal cell carcinoma; patients who have been disease free for > 5 years may be included
30. Patients with mental disorder who are in an unstable state and in whom it may be difficult to obtain informed consent and conduct the study
31. Patients who received any other investigational drugs within 3 months before the selection visit
32. Patients who had received SGLT2 inhibitors in less than 1 year ago
33. History of allergic reaction, hypersensitivity or poor tolerance to any SGLT2 inhibitor
34. Alcohol or drug abuse and/or dependence
35. Pregnant women, lactating mothers, women suspected to be pregnant, women who desire to become pregnant during the study period, or women who test positive to a pregnancy test at selection

36. Women of childbearing potential and male participants with a partner of childbearing potential not willing to use highly-effective methods of contraception during the study
37. Unlikely to cooperate in the study,
38. Any other patients who are judged to be inappropriate for enrolment into this study by the investigator

Participation in non-interventional registries or epidemiological studies is allowed.

5.3. Contraception information

The investigator must inform the participant about the risks not to use an effective method of birth control during the course of the study.

Female patients should be either of non-child bearing potential (postmenopausal defined as at least 1 year without any mensis prior to selection visit in a women ≥50 years old or to be hysterectomized/surgically sterile) or, if of child-bearing potential, to use highly effective methods of contraception and have a negative pregnancy test at selection and inclusion visits.

The investigator should discuss with the participant the most appropriate method according to the recommendations below.

Female participants of childbearing potential must use an effective method of birth control, as described below, before the study start, during the study and lasting at least 1 month after the last dose of IMP.

For women of child-bearing potential highly effective methods of birth control refer to those which result in a low failure rate (i.e. less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, male partner sterilization (vasectomy). The barrier method of contraception *i.e.* condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository is considered as acceptable within the frame of this study.

Within the frame of this study, male participants and/or their partners of child-bearing potential must use an effective method of birth control as described above.

5.4. Inclusion criteria

The inclusion criteria:

39. HbA1c 7.5%–10.0% (inclusive) at central laboratory measured in selection period and assessed at inclusion visit. One re-test of this parameter is allowed during the selection period if the result is not reliable and re-test is considered appropriate at the Investigator's judgment

40. The lab results, taken in selection period, are available and free from any abnormalities likely to interfere with the study conduct or evaluation

Selection criteria must be still fulfilled at the time of the inclusion visit and no any non-selection/non-inclusion criteria might be present.

5.5. Non-inclusion criteria

The non-inclusion criteria on inclusion visit will be:

41. Antidiabetic treatment has not been stable since the time of selection visit
42. Fasting plasma glucose measured at selection visit or with self-monitoring of blood glucose (SMBG) above 240 mg/dl (13.3 mmol/l) during selection period and confirmed by another measurement (not on the same day)
43. Sitting SBP>180 mm Hg and/or DBP>100 mm Hg at inclusion visit (mean of the 2 measurements)
44. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2 (assessed by MDRD equation), measured in selection period and assessed at inclusion
45. Signs of urinary tract or renal infection based on urine analysis in the selection period
46. ALT or AST >3 ULN, measured in selection period and assessed at inclusion
47. Total bilirubin >2 ULN, measured in selection period and assessed at inclusion
48. Haemoglobin level equal or less that 100 g/l, measured in selection period and assessed at inclusion
49. Positive pregnancy test

5.6. Additional information recorded at the inclusion visit

A blood sample of HbA1C should be sent to the central laboratory for all included patients. A 24-hour urine should be collected starting the day preceding inclusion visit in patients from PK/PD subset; the urine sample should be sent to the central laboratory on the day of inclusion visit for patients included into PK/PD assessment.

5.7. Participant withdrawal

5.7.1. Withdrawal criteria

- HbA1c ≥ 11.0%
- Fasting plasma glucose ≥ 270 mg/dl (15.0 mmol/l) at two consecutive visits or if identified by SMBG and confirmed with lab testing before withdrawal or rescue therapy

- Major hypoglycaemia defined as symptoms requiring the assistance of another person due to disturbance of consciousness associated with hypoglycemia
- Sustained decrease of eGFR to 30 ml/min/1.73 m2 or ≥ 50% compared to the baseline

Furthermore, participation in the clinical study could be discontinued by the investigator or by the sponsor for any of the following reasons:

- **Adverse events** according to the judgement of the investigator (presents a risk to the participant or requires prescription of a treatment which is incompatible with the protocol or significant alteration of laboratory parameters). Continuation of a subject in the PK sampling who experiences emesis or diarrhea following drug administration will be evaluated on a case by case basis;
- **Major deviation to protocol** if it interferes with the study evaluations and/or if it jeopardises participant's safety
- The subject is uncooperative during the study
- **Non-medical reason**, e.g. consent withdrawal.

A complete final evaluation should be made at the time of the subject's withdrawal, and an attempt should be made to perform a follow-up evaluation. Information to be collected should be as at Week 12 visit as indicated in Table 1. The follow-up visit should be planned after 2 weeks from the IMP stop to perform investigations as for W14 visit.

5.7.2. Procedure

In the case of premature withdrawal from the study due to an adverse event (event requiring immediate notification or not), the investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (see section 8.9.2.2). This information is recorded in that part of the e-CRF which concerns adverse events. If the investigator cannot collect the information from a visit, he must collect it from the doctor ensuring the follow-up of the participant.
If the study is stopped / IMP is discontinued as a result of an event requiring immediate notification, the procedure described in section 8.9.2.4 is to be implemented.

The dispositions to be taken after the IMP discontinuation are described in section 6.5.

5.7.3. Lost to follow-up

When the investigator has no news of the participant, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones…etc.), to establish the reason for the discontinuation of IMP and to suggest the participant comes to an end-of-study visit. If all these attempts to contact the participant fail, the investigator can then declare the participant "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PARTICIPANTS

6.1. IMPs administered

Investigational medicinal product (IMP): Luseogliflozin and matching placebo in tablets for oral administration once daily (before breakfast)

Dose regime:

Patients will have to take 3 tablets of IMP per day (in addition to the ongoing treatment with metformin) as follows:

- 2.5 mg group: one tablet of Luseogliflozin 2.5 mg, one tablet of Placebo 2.5 mg and one tablet of Placebo 5 mg
- 5 mg group: two tablets of Luseogliflozin 2.5 mg and one tablet of Placebo 5 mg
- 10 mg group: two tablets of Luseogliflozin 2.5 mg and one tablet of Luseogliflozin 5 mg
- Placebo group: two tablets of Placebo 2.5 mg and one tablet of Placebo 5 mg

6.2. IMPs dispensing

Investigator will use IRS to perform the following:

- To create the patient's number (at ASSE)
- To randomize the patient and allocate the treatment at W0 visit
- To allocate the treatment at W4 and W8 visits

The IMP will be dispensed on the inclusion (randomization) visit and at the study visits at Week 4 and Week 8.

6.3. Previous and concomitant treatments

Information on previous treatment taken by the patient within 3 months prior to selection and stopped by the time of selection (previous treatment) as well as administered during the study (regarded as concomitant treatment) must be documented in the patient's medical records and on the appropriate eCRF pages. Any changes to the concomitant medications during the study need to be clearly recorded and the reason for the change should be documented.

Use of the following medications is prohibited during the study unless the patient requires rescue medication due to loss of glucose control as taking these drugs will affect the study endpoints:

- Insulin (within 3 months prior to selection and until the end of double-blind treatment (visit Week 12))
- Thiazolidinediones (within 3 months prior to selection and until the end of double-blind treatment (visit Week 12))

- Sulphonylureas, nateglinide, DPP4 inhibitors, alpha-glucosidase inhibitors, or GLP-1 analogues (within 3 months prior to selection and until the end of double-blind treatment (visit Week 12))
- SGLT2 inhibitors (within 1 year prior to selection and until Week 14)
- Anti-obesity drugs
- Oral or parenteral corticosteroids

Use of the following medications will be allowed during the study, provided that the subject has been on a stable dose for at least 6 weeks prior to selection:

- Beta-blockers
- Thyroid-hormones
- Antihypertensive drugs
- Diuretics
- Drugs for treatment of dyslipidaemia

The changes in concomitant treatment during the study will not systematically constitute a reason to withdraw a patient from the study, other that if the patient's safety is compromised or if it interferes with the study evaluation. The sponsor must be contacted before deciding to withdraw a patient in such context.

6.3.1. Rescue treatment for loss of glucose control

The patients with loss of glucose control according to the following criteria will be prescribed rescue treatment during the double blind period of the study and will be allowed to remain in the study:

- Week 1-4: glucose level at SMBG or at the visit 240-270 mg/dl (13.3-15.0 mmol/l) inclusive after overnight fast or >400 mg/dl (>22.2 mmol/l) in a randomly performed measurement
- Week 4-12: glucose level at SMBG or at the visit 220-270 mg/dl (12.2-15.0 mmol/l) inclusive after overnight fast or >400 mg/dl (>22.2 mmol/l) in a randomly performed measurement

Insulin therapy may be instituted as needed. Alternatively, at the discretion of the Investigator, other antidiabetic medication can be prescribed; SGLT 2 inhibitors are not allowed as rescue therapy.

A complete final evaluation should be made before initiation of rescue therapy, if possible. Information to be collected should be as at Week 12 visit as indicated in Table 1 5.7.2

The details of rescue medications should be recorded in the e-CRF.

In case of hypoglycaemia that may put the patient on risk (e.g. repeated symptomatic hypoglycaemia or major hypoglycaemia), appropriate dose adjustment of antidiabetic therapy such as dose reduction/discontinuation of ongoing rescue medication or existing background therapy should be imitated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing background therapy.

6.4. IMP compliance

The number of tablets dispensed and the number of tablets returned by the participant are to be counted by the investigator or a designated person from his/her team and recorded in the eCRF and therapeutic unit tracking form, or an equivalent document.

If the participant did not bring back all blisters dispensed at the previous visit, the investigator must estimate the number of IMP units taken by the participant since the previous visit, by questioning him/her.

IMP compliance will be assessed at visits W4, W8 and W12. It will be evaluated by the method described above.

6.5. Discontinuation of the IMP

After the discontinuation of the IMP, the participants' treatment is left to the physician's discretion. Further patient treatment after the discontinuation of the IMP will be conducted according to the Standards of specialized diabetes care approved in Russia [14].

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

Efficacy measurements performed during the study are indicated in Table 1.

Criteria for evaluation:

Primary evaluation variable:

- HbA1c (The change from baseline in HbA1c to Week 12)

Secondary evaluation variables:

- change in fasting plasma glucose
- change in postprandial plasma glucose (2-hours after meal)
- change body weight
- change in waist circumference

Exploratory: ratio of patients at target (HbA1c < 7% & HbA1c <6.5% at week 12), 24 hours excreted urinary glucose (quantitative), pharmacokinetic and pharmacodynamic parameters of luseogliflozin in the subjects in PK/PD subset.

7.2. Methods and measurement times

The study visits should be performed in the morning in fasting conditions before IMP intake on the day of the visit. IMP intake on the day of the Week 4 and W8 visits should be done from a new pack allocated using IRS at the visit.

HbAlc at central laboratory will be measured at selection, inclusion, W 8 and Week 12 visit. Fasting plasma glucose, body weight and waist circumference are to be measured at each study visit. Waist circumference will be measured at midway between the lowest ribs and the iliac crest in the standing position at the end of normal expiration, the tape should be in horizontal plane.

Before the start of the treatment (W0) and the end of the double-blind treatment (W12) blood will be collected 2 hours after the start of the standardized meal, and plasma glucose will be measured. A standardized meal (breakfast) containing energy about 600 kcal will provided. At W12 visit the IMP should be taken during the visit before standardized breakfast.

Regarding the PK assessment, in the subset of patients the sampling should be performed at Week 4 visit; 12 samples per patients are planned. Sampling times are as follows: T0 (before administration); 0.25 (15 min); 0.5 (30 min); 1; 1.5; 2; 3; 4; 6; 8; 12 and 24 hours after administration. In this subset of patients the 24-hour urinary glucose excretion will be measured at Week 0 and Week 4 visits as well. The diet, fluid intake and physical activity during the days of 24-hour urine collection at W0 and W4 should be similar as far as possible. The detailed instructions regarding the food, fluid, physical activity etc. related to 24-hour urine collection and the conditions for blood sampling will be described in the Investigator's Guide for PK/PD.

At visits, the proper timing of both drug intake and of blood sampling should be collected.

8. SAFETY MEASUREMENTS

All adverse events and other situations relevant to the safety of the participants must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.1. Specification of safety parameters

Safety measurements performed during the study are indicated in Table 1. This includes:

- Physical examination,
- Vital signs (HR, systolic and diastolic BP)
- 12-lead ECG
- Laboratory parameters (haematology, biochemistry, urine analysis, ketones),
- Adverse events recording (including AE of special interest).

8.2. Methods and measurement times

8.2.1. Physical examination

Physical examination will be carried out at each study visit and must be documented in the source documents. Any clinically significant abnormalities during the study should be recorded as an adverse event.

8.2.2. Vital signs

HR and BP will be measured at all visits after at least 5 min rest. BP should be assessed in the sitting position using 2 measurements taken at least 2 minute intervals, preferably with an automatic blood pressure device. Blood pressure should be measured at the same arm and using the same device, throughout the study as far as possible. Both measurements should be reported in the e-CRF and the mean value will be automatically calculated.
Uncontrolled hypertension is defined as a mean of 2 measurements for systolic blood pressure >180 mmHg and/or for mean diastolic blood pressure >100 mmHg. The criteria will be re-checked at inclusion; if the values are over these limits, the patient must not be included.

8.2.3. Standard electrocardiogram

A standard electrocardiogram (12-lead) will be performed at selection visit and Week 12. The ECG will be performed after 10 minutes at rest with patient in supine position. The interpretation of the ECG trace should be done by a qualified medical doctor associated with the centre.
The ECG traces should be kept in the patient's file for source documentation.

8.2.4. Blood glucose monitoring

Fasting blood glucose will be measured at selection, inclusion, Week 4, Week 8 and Week 12 in a local laboratory. In addition, during the study the patients will perform SMBG at home using a glucose meter and the test strips provided for the study:

- Selection period: One measurement every day in a fasting state before breakfast.
- After inclusion (during double-blind treatment period and until Week 14): One measurement every day in a fasting state before breakfast and 4 measurements during a day (including preprandial and postprandial state) once a week

SMBG can be performed more frequently, if necessary, according to investigator's judgement. The patient will record information in the study diary provided by the investigator at the visits. Patients experiencing symptoms of hypoglycaemia will also perform a blood glucose self-measurement at the time of the event.

The patients should be instructed to contact the investigator:

- If they record blood glucose levels equal or less than 3.9 mmol/L (70 mg/dL) at any time during the study. The investigator will determine whether the patient should return to the site for further assessment. In addition, the patient should be instructed on recognition of the symptoms of hypoglycaemia and requested to measure glucose by glucose meter when they experience these symptoms.
- If, between Inclusion and Week 4 the fasting glucose is equal or above 240 mg/d (13.3 mmol/l), and between Week 4 and Week 12 is equal or above 220 mg/gl (12.2

mmol/l) the investigator should make every effort to have the patient visit to the clinic for a fasting plasma glucose measurement as soon as possible but within 7 days as maximum.

Glucometer readings should be printed out at each study visit and kept in the patient's medical file.

The measurements of SMBG will not be recorded in the e-CRF, except in case of AE reporting.

8.2.5. Laboratory assessments

The blood and urine samples will be assayed by a local laboratory (except HbAc1 measurements and urinary glucose, which will be done at central laboratory). Blood ketones will be assessed using test strips during the visit.

The blood tests must be obtained under fasting conditions (i.e., after the patient has fasted for ≥ 10 hours). Fasting is defined as nothing ingested by mouth except water (and any essential medications). If a patient is not fasting, the Investigator will reschedule the blood sampling within the visit timeframe window previously defined. Laboratory certification (including expiration date) and normal reference ranges for all required parameters used during the study will be enclosed in file with the Sponsor prior to study initiation. Local laboratory normal ranges values will be collected, as well as any update in these values during the study and must be documented on the corresponding page of the e-CRF.

Outside of normal range values should be assessed by the Investigator. The Investigator will exercise medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The following parameters must be evaluated:

- Haematology: white cell count with differential formula (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red cell count, hemoglobin, hematocrit, and platelets count,
- Biochemistry: creatinine, eGFR (according to MDRD formula), total bilirubin, ALT, AST, total protein, sodium, potassium, chloride, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid,

  eGFR will be calculated in e-CRF using the MDRD formula (Modification of Diet in Renal Disease Study equation) (Levey, 2006): eGFR (mL/min/1.73 m2) = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female)
- Blood ketones using test strips
- Urine analysis: color, appearance, specific gravity, pH, protein, ketones, bilirubin, erythrocytes, leucocytes, nitrite, microscopic examination.

Haematology and biochemistry tests are to be performed at selection period and at W12 visit, blood ketones– at W0 and at every study visit including W14 visit, urine analysis – at selection period and at every study visit including W14. Abridged laboratory test (hematocrit; total bilirubin, ALT, AST, creatinine, eGFR, serum sodium, potassium, chloride) will be performed at W 4 and W8 visits.

8.3. Definition of Adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product (*GCP EAEU).*

During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol (*GCP EAEU).*

Considering that study participants are patients, who may have different disorders and diseases in medical history, and that laboratory, ECG and vital signs abnormalities will be included in the safety analysis in addition to AE, an AE should be registered by the Investigator in case of:

- any unfavourable and unintended sign (including an abnormal finding from an additional examination such as lab tests, ECG,…) which is deemed clinically relevant by the investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity), including the studied pathology,

and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in participant's diary).

Of note:

- Any **hospitalisation for PK sampling in the study, social reasons, educational purpose** (e.g. learning of diabetes management by the participant) or routine check-up should not be considered as an adverse event and should not be reported in the e-CRF.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, should be reported in the specific page **"Procedures not subsequent to an adverse event"** of the e-CRF:
  - therapeutic procedures related to a non-aggravated medical history (e.g. cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
  - prophylactic procedures (e.g. sterilisation, wisdom teeth removal),
  - comfort procedures (e.g. cosmetic surgery),
  - control procedures of a pre-existing condition without aggravation (e.g. colonoscopy to control the remission of colon cancer).

8.4. Definition of Serious adverse events

Any adverse event that at, any dose:

- results in death,
- is life-threatening(1),
- requires inpatient hospitalization or prolongation of existing hospitalization,

- is medically significant[(2)],
- results in persistent or significant disability/incapacity[(3)],
- is a congenital anomaly/birth defect[(4)].

[(1)] Life-threatening in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[(2)] Any event that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor.

[(3)] Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

[(4)] Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of Overdose

This refers to any intake of a quantity of IMP which is above the dose recommended to the patient in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol.

8.6. Definition of Adverse event of special interest

An adverse event of special interest (AEOSI) is one of scientific and medical interest or concern regarding the IMP for which recording rules, special documentation such as hospital records could be appropriate. It may be a serious or non-serious AE that may require further investigation in order to characterize and understand.

AEOSI include:
- hypoglycemia
- polyuria, pollakiuria
- events related to decreased fluid volume (including dehydration and BP decrease)
- ketoacidosis
- urinary tract infections
- genital infections

Hypoglycaemia or symptoms suggestive of hypoglycaemia

The following definitions relative to hypoglycaemia will be used in this study:
- Confirmed hypoglycaemia:

- Minor hypoglycaemia: event during which symptoms suggestive of hypoglycaemia are accompanied by a measured glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Major hypoglycaemia: event during which symptoms suggestive of hypoglycaemia require the assistance of another person due to disturbance in consciousness to actively administer carbohydrate, glucagon or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration
- Asymptomatic low blood glucose: event not accompanied by typical symptoms of hypoglycaemia but with a measured glucose ≤ 3.9 mmol/L (70 mg/dL)

- Symptoms that are suggestive of hypoglycaemia without a contemporaneous blood glucose measurement or with a glucose value > 3.9 mmol/L (70 mg/dL) but approaching that level.

Management of hypoglycaemia will be based on the Investigator's clinical judgement and may include adjustment of the patient's background antidiabetic medication.
Unless clinically indicated, patients reporting single episodes of hypoglycaemia or symptoms of hypoglycaemia should not be discontinued from any phase of treatment. If, following Inclusion visit, the patient has an SMBG value ≤ 3.9 mmol/L (70 mg/dL) with or without symptoms the patient should contact the Investigator.
When an event is reported to a site, the site staff should inquire regarding the symptoms experienced, SMBG obtained at time of event, and whether confounding factors (e.g., increased physical activity, intercurrent illness, new concomitant treatment, skipped meal, etc.) contributed to the event. In the presence of such confounding factors, the Investigator should advise the patient on how to avoid similar episodes in the future. In the absence of confounding factors, the dose of metformin may be decreased at the Investigator's discretion.

The confirmed or asymptomatic hypoglycaemia episodes, and symptoms suggestive of hypoglycaemia will be reported by the investigator in the e-CRF according to the general instructions for completion.

Major hypoglycaemia events should be reported as SAE.

Polyuria, pollakiuria
Events related to decreased fluid volume (including dehydration and BP decrease)

Polyuria or pollakiuria may occur due to the diuretic action of luseogliflozin.

Reduction of body fluid volume may occur.

Patients should be monitored sufficiently. Attention should be paid to the events related to decreased fluid volume.

When abnormalities including dehydration and decrease in blood pressure occur, appropriate measures should be taken, especially in patients who are likely to have hypovolemia (including elderly patients and patients with combined use of diuretics). Appropriate additional investigations will be performed as required. Management of the event, including fluid replacement and IMP interruption, will be based on the Investigator's clinical judgement.

The site staff should collect and document information on the timing of onset, concomitant drugs and other aspects of the event.

Ketoacidosis

Due to the mechanism of action of luseogliflozin, i.e., enhancement of urinary glucose excretion, fatty acid metabolism may be enhanced, which may lead to ketosis and ultimately ketoacidosis, even when plasma glucose is well controlled. Marked increase in blood glucose levels may be not observed.
Nausea/vomiting, decreased appetite, abdominal pain, severe thirst, malaise, dyspnea or disturbance of consciousness may be suggestive of ketoacidosis.

Appropriate ketone tests should be performed as required. Management of the event, including discontinuation of the IMP, will be based on the Investigator's clinical judgement.

The site staff should collect and document information on the timing of onset, signs and symptoms, concomitant drugs and other aspects of the event.

Urinary tract infection
Genital infection

In patients with impaired immune function, elderly patients, the incidence of urinary tract and genital infections can be increased.
Appropriate laboratory tests should be performed as required. Management of the event will be based on the Investigator's clinical judgement: appropriate treatment should be provided, and interruption of the IMP can be considered depending of the event nature and severity.

The site staff should collect and document information on the timing of onset, signs and symptoms, concomitant drugs and other aspects of the event.

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (i.e. without delay and within 24 hours at the latest) to the sponsor if it is:
- a serious adverse event,
- an adverse event of special interest,
- an overdose of the IMP even if asymptomatic,
- any intake of the IMP by a person around the participant,
- a pregnancy.

8.8. Classification of an adverse event (seriousness, severity, causality, expectedness)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the test drug. This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation the **expectedness** of the event (See Section 8.9.2.5).

The Seriousness should be evaluated according to international guidances (see definition Section 8.4 in accordance with ICH Topic E2A, Good Clinical Practice of the Eurasian Economic Union, adapted by the decision of the Council of Eurasian Economic Commission on 3 November 2016, N79, and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001.

The Intensity should be evaluated according to the following rule:
- mild: signs or symptoms, easily tolerated, relieved with symptomatic treatment,

- moderate: enough discomfort to cause interference with usual activity, only partially relieved with symptomatic treatment,

severe: incapacity in some regular activities, not easily relieved with symptomatic treatment.

The causal relationship

All unintended and noxious responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

The causal relationship will be assessed according to the international guidance of the CIOMS Working Group VI of 2005: Report of CIOMS Working Group VI "Management of Safety Information from Clinical Trials". A binary decision method for causality (related or not related) to the IMP or to the experimental procedures will be used when reporting the AE in the AE form. Only cases ticked "related to the IMP" by the investigator, or judged by the sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the mechanism of action of the test drug…), will be considered as suspected Adverse Drug Reaction. In general, the expression reasonable causal relationship means to convey that there is evidence or arguments to suggest a causal relationship.

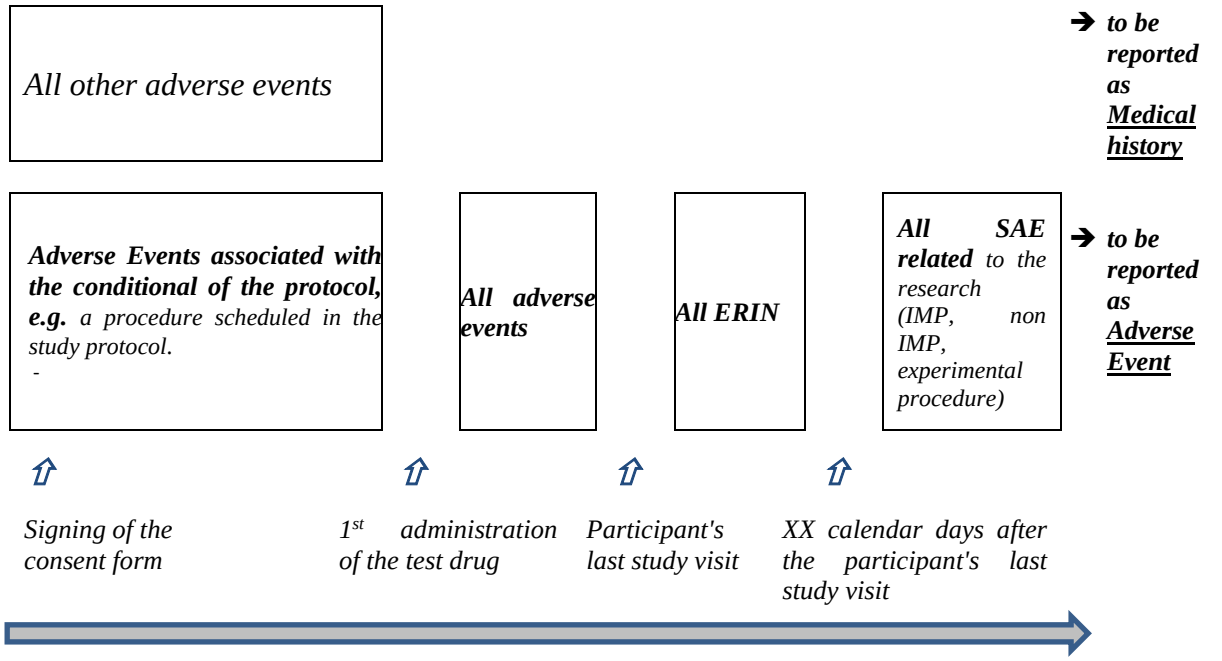
8.9. Reporting procedures

8.9.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see sections 8.3 to 8.7) must be reported to the sponsor on an adverse event form if it occurred:

- before the first intake of the test drug, **for event associated with any procedure/condition required by the study protocol**: e.g. procedure (laboratory test, etc.) .
- at any time after the first intake of the **IMP** up to the participant's last study visit for all events,
- after the participant's last study visit:
  - up to 30 calendar days after the participant's last study visit for all ERIN, regardless of the supposed role of the research (IMP or experimental procedure).
  - irrespective of the time of onset after the end of the study in case of serious adverse event related to the research (IMP or experimental procedure).

Of note, events occurring between the signature of the informed consent and the first administration of the IMP for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as **medical history** in the dedicated form of the e-CRF.



8.9.2. Responsibilities of the investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which he/she has learned of the event,
- **Assess** the event in terms of seriousness, intensity and causality,
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately-without any delay and within 24 hours at the latest),
- **Document** the event with additional useful information,
- Ensure the **follow-up** of the event,
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the test drug or that would be sufficient to consider changes in the test drug administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis (where possible, the results from pre-test drug assessments should be appended for comparison with the results obtained under test drug), or the autopsy report, if autopsy is performed.

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" form previously created for the event.

If the adverse event has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the outcome of the event will be noted on the « Adverse Event » form previously created for the event.

If the follow-up of the participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant.

8.9.2.3. Special situations (pregnancy, overdoses, intake of IMP by a person around the participant)

Pregnancy

If a female participant in the study becomes pregnant, the investigator must:
- stop immediately the IMP,
- report it on an « Adverse Event » form as well as on the specific paper pregnancy form (1st page) to be notified immediately-without any delay and within 24 hours at the latest (ERIN),
- contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form).

If the partner of a participant becomes pregnant during the course of the study, the pregnancy should not be reported in the e-CRF. The investigator should **immediately (**without any delay and within 24 hours at the latest) contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP
- In case of overdose, the investigator should report it on an "Adverse Event" form to be notified immediately- without any delay and within 24 hours at the latest (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - dose details (number of units, duration,…) and, if multiple overdose, details regarding other medicinal products or substance ,
  - context of occurrence, i.e. intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage),
  - related signs and symptoms ("No related adverse events" to be reported otherwise),
  - outcome.
- Insofar as possible, a blood sample should be collected for assay of the IMP taken.

Intake of IMP by a person around the participant
This event should not be reported in the e-CRF. The investigator should immediately contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.9.2.4. Recording Methods in the CRF/e-CRF

Adverse events must be documented on the « Adverse Event » form of the e-CRF.
The investigator should evaluate the events and record in the "Adverse Events" form of the e-CRF a diagnosis (when possible and appropriate) rather than each individual sign and symptom. When a diagnosis is reported, available corresponding signs, symptoms and other details are additionally described in the "Adverse Event" form.

Hypoglycaemia episodes must be additionally reported on a dedicated "Hypoglycaemia" form in the e-CRF.

In case of chronic disease:
- if the disease is known when the participant enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the « Adverse Event » form previously created for the event which will clearly describe the diagnosis.

8.9.2.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:
- **Immediately (**without any delay and within 24 hours at the latest) after being informed of this event, **fill in** the **participant's medical file** as well as the **« Adverse Event » form** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into FlexDatabases EDC&IWRS, an e-mail will be immediately and automatically sent to the sponsor.
- Provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

If an adverse event initially non-serious worsens and becomes serious (ERIN), this must be reported **immediately** on an "Adverse event" form of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:
- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page,
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,
- Immediately inform by telephone one of the following persons: the monitor of the centre or the Person Responsible for Pharmacovigilance Natalia KORNEEVA (tel. 8 495 937 07 00,

fax: 8 495 937 47 66, e-mail pvmail.rus@servier.com) and send them by e-mail or fax to the person(s) designated in the contact details provided in the investigator's study file, or outside working hours contact the SERVIER hotline in Russia 8 495 937 07 00, ext. 2.

- As soon as the e-CRF becomes available, the investigator should enter these data in the "Adverse Event" form of the e-CRF.

8.9.3. Responsibilities of the sponsor

In accordance with international guidelines, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data to the appropriate Authorities and to all the investigators involved, according to the requirements stated in ICH Good Clinical Practice guidelines and local regulations.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments related to selection/inclusion criteria.

An urinary pregnancy test will be performed for all women of child bearing potential at selection and inclusion. The results must be reported in the medical file, and must be negative to be eligible for participation in the study.

Height will be measured at selection period in order to calculate the body mass index.

9.2. Measurement of drug concentration

Measurement of plasma concentration of luseogliflozin will be performed in a subset of patients in each dose group of luseogliflozin. Eighteen patients per group are planned to be included at sites, participating in PK/PD assessment and who signed a specific informed consent form.
The patients from the PK/PD subset will be hospitalized for at least 24 hours (depending on the center organization) at the visit Week 4. The first blood sample for evaluation of the pharmacokinetic parameters will be collected in the morning before administration of IMP at

Week 4. Serial blood sampling up to 24 hours will follow IMP administration; totally, 12 samples per patient will be collected. Sampling times: T0 (before administration); 0.25; 0.5; 1; 1.5; 2; 3; 4; 6; 8; 12 and 24h after administration. Around 6 mL venous total blood for each sample will be collected into lithium-heparinised tubes.
The actual time of IMP intake and blood sampling will be recorded on the sample requisition form sent to the pharmacokinetic laboratory.
Pharmacokinetic analysis will be performed by the Exacte Labs (Russia).
Sampling, handling and shipment procedures will be detailed in the laboratory manual provided by the pharmacokinetic laboratory. This investigator manual will be sent to the investigator prior the start of the study and explained in detail during the initial monitoring visit. The investigator will be responsible for strict compliance to the instructions.
Plasma levels of luseogliflozin will be determined by a validated HPLC-MS/MS assay (high performance liquid chromatography, tandem mass spectrometry). The lower limit of quantification (LLOQ) of luseogliflozin will be no more than 0.1 ng/ml. The upper limit of quantification (ULQ, ULOQ) luseogliflozin will depend on the linearity of the LC-MS/MS method. Dilution integrity will be validated if necessary to cover the concentration range in the study samples. Evaluation of dilution integrity may be covered by partial validation.

Validation of HPLC-MS/MS method includes the following parameters:

- selectivity;
- linearity;
- lower limit of quantification (LLOQ);
- calibration range;
- inter-run/batch and intra-run/batch precision and accuracy;
- carry-over;
- recovery;
- matrix effect;
- stability.

Information regarding the validation and analysis procedures will be detailed in dedicated study plans. Detailed information on the analysis procedure and validation of results will be included in the final PK study report.

9.3. Pharmacokinetic assessment

Pharmacokinetic analysis will be performed by the Exacte Labs (Russia) under responsibility of the Division of Clinical Pharmacokinetics and Pharmacometrics in Servier.
The datasets needed for final analyses will be prepared by extraction under the responsibility of the clinical Business Intelligence Department using SAS® program and following the clinical PK project manager specifications.
NCA report will be subcontracted and the report will be writing by the responsible person of the Contract Research Organisation (CRO) using I.R.I.S. (Institut de Recherche Internationales Servier) format, under the responsibility of the PK actor.

The non-compartmental pharmacokinetic analysis (NCA) will be performed under the supervision of the Division of Clinical Pharmacokinetics using PhoenixWinNonlin® or Excel on the individual concentration-time data of luseogliflozin after the administration of study treatment, using the exact administration and sampling times for final analysis. Descriptive statistics, tables and figures will be generated using PhoenixWinNonlin® and Excel®.

Any suspicious concentration will be investigated and kept in the PK analysis if possible. All excluded concentrations will be justified in the report.

To calculate PK parameters, BLQ concentrations before the first concentration measured above the limit of quantification (e.g. before administration and in the ascending part of the plasma concentration-time curve) will be substituted by zero whereas other BLQ values will be left as BLQ and ignored in the NCA. When a single BLQ value occurred between two adjacent quantifiable values, it will be excluded from the analysis. However, when concentrations are BLQ for the whole profile of a participant, they will be substituted by zero and included in the analysis. A missing concentration will be stated MS (Missing) and ignored in the NCA.
The pharmacokinetic analysis will be performed on the pharmacokinetic set (PKS). The PKS corresponds to all included participants having completed treatment period without deviation affecting pharmacokinetic interpretation.

Summary statistics (n, mean, SD, min, median, max, Coefficient of Variation (CV)) will be calculated for these PK parameters as well as on concentrations-time profiles using PhoenixWinNonlin® and Excel®.

The pharmacokinetic parameters (Table 4) will be calculated from the measured plasma analyte concentrations using a noncompartmental method.

Table 4 Pharmacokinetic parameters

Pharmacokinetic parameter	**Definition**
$AUC_{0-\tau}$	The area under the concentration-time curve over the dosing interval or expected dosing interval.
C_{max}	The observed maximum plasma concentration
$C_{min, Dx}$	Concentration over the dosing interval after x days of administration just before D_{x+1} administration
T_{max}	The time to reach the maximum plasma concentration after dosing
$T_{1/2}$	Elimination half-life (if possible)

The pharmacokinetic analysis will be performed according to the plan below:

- determine the pharmacokinetic population based on primary data analysis,
- present concentrations measured at each sampling time point, for each subject
- plot concentration–time curves for each subject using linear and semi-log scales.
- make up “concentration-time” matrices for each study subject and respective matrices of blood sampling time deviations, and compare them to calculate actual sampling times;
- based on the actual blood sampling times and the “concentration-time” tables, calculate the pharmacokinetic parameters present in Table 4.

9.4. Pharmacodynamics

Considering the pharmacological effect of luseogliflozin, urinary glucose (quantitative) was selected to be measured in conjunction with the measurement of PK in the same subset of patients. The 24-hour pooled urine will be collected at Week 0 and Week 4 visits and the samples are to be sent to the central laboratory as detailed in the laboratory manual.

The results of urinary glucose are to be reported by the laboratory to the sponsor and Investigators only after locking of study data.

9.5. Dose proportionality, PopPK and PK/PD analysis

Dose proportionality will be assessed by plotting $AUC_{0-\tau}$/Dose versus Dose and Cmax/Dose versus Dose and additionally will be analysed by power model.

Population PK and PK/PD analyses may be performed using existing models previously developed for luseogliflozin. These analyses will be described in a separate Data Analysis Plan.

10. STATISTICS

10.1. Statistical analysis

This section briefly describes the planned statistical analysis. Details for the analysis will be provided in the separate statistical analysis plan (SAP) that should be finalized before the database lock.

Descriptive statistics:

- all quantitative data will be presented as number of valid observations, mean, 95%confidence interval (CI) for mean, standard deviation, median, min/max and 25th and 75th percentiles.

- all qualitative data will be presented as number of valid cases, number of cases for each response category, percentage of response category relative to the number of valid cases and exact Clopper-Pearson binomial confidence interval for proportion for each category.

Assessment of normality for the quantitative data will be performed using the Shapiro-Wilk test.

Disposition of study participants:

Disposition of study participants will be provided as follows:
- Number of screened patients (total)
- Screening failures (tabulated by reasons)
- Randomized patients by group
- Early terminated patients (tabulated by reasons)
- Study completers by group
- Allocation of patients to FAS and PPS populations

Baseline characteristics will be presented by group:

- Demographics (age, gender);
- Anthropometry (weight, height, BMI);
- Baseline laboratory data;
- Medical history and concomitant conditions;
- Prior and concomitant medications.

Efficacy analysis:

In order to meet the primary objective of the study, the efficacy of at least one dose of luseogliflozin as compared to placebo after 12 weeks of treatment in glycaemic control will be assessed from the change from baseline to W12 in HbA1c, in patients of the RS. Analysis of covariance (ANCOVA) will be used as the main method of assessment of the primary endpoint, with baseline (W0) HbA1c value being a covariate.

Unrestricted least significant differences (LSD) method will be applied to the ANCOVA results with the calculation of least-square (LS) means with 95% CI for LS means for the difference between each dose level and placebo.

Finally, to assess the dose-response of the investigation product with regards to the primary endpoint, contrasts will be build based on the ANCOVA results.

Before performing ANCOVA, a multiple imputation procedure will be used to impute :

- Missing data for the primary endpoint at 12 week (for patients with missing data at W8 and W12 and for patients with missing data at W12 only)
- Data collected after rescue therapy for non-controlled patients.

This approach allow to evaluate, as primary analysis, the hypothetical « proper effect » of luseogliflozin without additional effect of rescue therapy.

These analysis on primary endpoint will be done in the Randomised set (RS) and – additionally – in the per protocol set (PPS). Any differences between the results in RS and PPS will be investigated and explained, yet, RS will serve as the main analysis set at all times.

Two additional analysis will be performed on the primary endpoint on RS and PPS :

- Before performing ANCOVA, a multiple imputation procedure will be used to impute missing data for the primary endpoint at 12 weeks. Here data collected after rescue therapy will be taken into account in the analysis allowing to evaluate the effect of "treatment policy" of luseogliflozin + rescue medication VS placebo + rescue medication.
- Last observation carried forward (LOCF) method will be used to impute post rescue evaluations and other missing data at 12 weeks for the primary endpoint (for a bridging objective with studies performed on Japanese population)

The multiple imputation approach will be based on the regression method to impute values for each missing data at W008 and W012. Covariate use for the regression method will be auxiliary variables which might be predictive of both the chance of missing values and the underlying values themselves. Those additional auxiliary variables will be defined, before the blind is broken, in the SAP.

Secondary efficacy parameters – the following parameters will be assessed:

1) Quantitative parameters:

- Change in fasting plasma glucose,

- Change in postprandial plasma glucose,
- Change in body weight,
- Change in waist circumference

These parameters will be assessed and tested in the same spirit of the primary parameter and precision will be given in the SAP.

2) Qualitative parameters:

- The proportion of patients with HbA1c<7%
- The proportion of patients with HbA1c<6.5%

These parameters will be compared between the groups using the logistic model, including the fixed, categorical effect of treatment as well as the continuous, fixed covariates of baseline HbA1c.
Precision will be given in the SAP

Safety analysis will be performed by group for the following parameters:

- Frequency of emergent adverse events;
- Frequency of serious adverse events / ERIN;
- Frequency of adverse events related to the IMP (adverse drug reactions);
- Frequency of adverse events related to the conditions of the protocol;
- Frequency of any adverse events leading to treatment withdrawal;
- Frequency of all AE of Special Interest and frequency of each individual AEOSI;
- Laboratory parameters by visit;
- Frequency of laboratory parameter abnormalities by visit;
- Vital signs (HR, SBP, DBP) by visit;
- Frequency of vital signs (HR, SBP, DBP) abnormalities by visit;
- 12-lead ECG results by visit;
- Frequency of 12-lead ECG abnormalities by visit.

Frequency data will be compared between the groups using exact Fisher tests; numeric data will be compared between the groups using the t-test or Wilcoxon-Mann-Whitney test on ranks depending on the normality of the parameter distribution (which will be tested using Shapiro-Wilk test). Laboratory parameters, vital signs and 12-lead ECG data will be analysed using two-way ANOVA (or ANOVA on ranks, if the distribution is not meeting the normality criteria) to account for group and visit factors simultaneously.

Interim analysis

No interim analysis is planned for this study.

Study populations

- **Randomized Set (RS):**
  All patients to whom a therapeutic unit was randomly assigned using IRS.
- **Per Protocol Set (PPS):**
  All the patients of the RS that do not have any significant protocol deviations. List of deviations will be reviewed for the determination of their significance prior to the database lock and randomization list unblinding.
- **Safety Set (SS):**
  All patients having taken at least one dose of study drug.
- **Pharmacokinetic set**: all patients for whom blood samples were collected with no deviations that might affect the pharmacokinetic interpretation

- **Pharmacokinetic/Pharmacodynamic set:** all included patients for whom blood samples and 24-hour urinary glucose measurements were collected with no deviations that might affect the PK and/or PD interpretations.

Significance level:
The type I error of the statistical tests will be set at 5% (two-sided situation).

Multiplicity issues:

In order to take into account the multiplicity of comparisons associated with the primary objective of the study (demonstration of superiority of at least one luseogliflozin dose as compared to placebo on the primary efficacy endpoint); a Bonferroni correction will be used for the primary analysis.

For secondary endpoints, the same strategy as the one use for primary analysis will be used for handling multiplicity issues for doses comparison and no adjustment to control the type I error for multiple endpoints will be used.

Statistical software

Statistical analysis will be performed using Microsoft R Open software, version 3.4.3 or higher (distributed by Microsoft R Application Network under the public license) or any similar software that will be finally determined at the stage of statistical analysis plan finalization.

Data coding

Medical history, concomitant conditions and adverse events will be coded using the MedDRA dictionary (the most up-to-date version by the time of database lock).

Prior and concomitant treatment will be coded using the ATC coding system.

10.2. Determination of sample size

The determination of the sample size was performed considering the primary endpoint, the HbA1c.
It was estimated on the change from baseline at W12, for a difference objective between at least one dose of luseogliflozin and placebo, based on a two-sided Student's t-test for independent samples and using the Bonferroni correction in order to maintain the experiment wise type I error at 5% (bilateral situation).
About 80 patients per treatment group (320 overall) allow to conclude that at least one dose of luseogliflozin is superior to placebo with a power of around 85% if the true difference is 0.6% for a standard deviation of 1.1 %.

11. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the sponsor representatives, including the monitor, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the structure mentioned in Section 1.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

12.1.2. During the study

The investigator will allow the monitor to:

- review of the study site's processes and procedures,
- verify appropriate clinical investigator supervision of study site staff and third party vendors,
- inspect the site, the facilities and the material used for the study,
- meet all members of his/her team involved in the study,
- consult the documents relevant to the study,
- have access to the electronic case report forms (i.e. access to an analogic phone line or his/her computer),
- check that the electronic case report forms have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the electronic case report forms,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (i.e. audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:

- at the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (e.g. medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:

- all medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor,
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system,
- all original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form...).

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:

- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all of the documents relevant to the study.

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:

- give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all participants,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the list of investigators document, the insurance documents, the Investigator's Brochure of administered IMPs will be submitted to (an) IRB(s)/IEC(s) by the investigator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (see Appendix 1) with the GCP and with the applicable regulatory requirements

13.3. Participant information and informed consent

In any case, the participant (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is to collect written consent from each participant before his/her participation in the study. A specific written consent form is to be collected for patients participating in PK/PD assessment Prior to this, the investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs.

The participant will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

Two original information and consent forms must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The participant will be given one signed original information and consent form, the second original will be kept by the investigator.

A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required to eliminate an immediate risk to the study participants.

Each participant affected by the amendment and/or his/her legally acceptable representative or an independent witness must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

An electronic data capture system is going to be used for this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by the CRO in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the participant's Medical File.

Upon entry, data will be transmitted via the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, and all other documents provided by the sponsor (e.g. documents relating to the IMP management…).
The e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of Flex Databases EDC&IWRS including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.
Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data will be frozen during the study after their validation. However, the investigator has the possibility to modify a data if deemed via a request to the sponsor.

After the last visit of the participant, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her user name and password.

After the data base lock, the investigator will receive a CD-ROM containing participant data of his/her centre for the study file.

14.2. Data management

Data are collected via a CRF and stored in a secured database.

For data collected on the e-CRF, the CRO is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

The CRO is responsible for all data transfers. Data are transferred according to a transfer protocol issued by the CRO data manager.

The CRO is responsible for data coding including:
- medical / surgical history, adverse events and procedures using MedDRA,
- medications using ATC coding system.

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. 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 the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

When data validation is achieved, a blind review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and the IMP codes will be unblinded and made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 15 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator will be provided with a copy of each participant's data on a CD-ROM support. These data include all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

15. INSURANCE

Risks pertaining to the patients' participation in this study are covered by an insurance policy. In accordance with local laws on the conduct of clinical trials, the Sponsor will conclude an Insurance Contract for the Life and Health of Patients Participating in the Clinical Studies of a Medication.

Where an indemnification system and/or a mandatory policy are in place, JSC SERVIER will be insured under a local and specific policy in strict accordance with local applicable law.

All relevant insurance documentation are included in the file submitted to local authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

JSC SERVIER acting as the study sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

JSC SERVIER will ensure that upon study completion and finalization of the study report, the results of this study will be submitted for publication.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the sponsor in

accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The investigator, who submitted the project, shall take the sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under the responsibility of JSC SERVIER. The investigator commits himself not to publishing or communicating data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and JSC SERVIER has been provided.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the participant, the investigator will inform the participant’s general practitioner about his/her patient’s participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the coordinator and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate risk to the study participants.

When the submission is performed by the investigator, the latter must transmit a copy of IRB/IEC’s new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by the CRO in compliance with SERVIER standard operating procedure.

The sponsor's representative and the coordinator must mutually agree on the final version. One copy of the final report, must be dated and signed by the coordinator and the Director on Clinical Trials EAEU.

17.2. Concerning the sponsor

The sponsor undertakes to:
- supply the investigator with adequate and sufficient information concerning the IMP administered during the study to enable him/her to carry out the study,
- supply the investigator with investigator's brochure if the test drug is not marketed,
- obtain any authorisation to perform the study and/or import licence for the IMP administered that may be required by the local authorities before the beginning of the study,
- provide coordinator annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to Luseogliflozin and study CL3-LUSEO-001 are strictly confidential.
The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer, and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.
He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from JSC SERVIER, except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself/herself to informing JSC SERVIER prior to disclosure of information to these authorities.

A participant screening log and a full identification and enrolment list of each participant will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the investigator checks that a participant could potentially take part in the study (by assessment of participant medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist,…) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:
- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to provide any other document required by local regulation,
- to send, a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

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19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.