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Study assessing the glucose-lowering efficacy and safety of luseogliflozin on top of metformin in Caucasian patients with type 2 diabetes mellitus

Submission date
31/03/2021

Recruitment status
No longer recruiting

Registration date
14/04/2022

Overall study status
Completed

Last Edited
19/06/2023

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Type 2 diabetes mellitus (DM2) affects millions of people around the world. It is a chronic condition where cells are unable to respond to the insulin signal to use glucose for energy production. As a result, long-lasting high blood glucose levels occur and therefore one of the treatment goals for this condition is to lower the blood glucose level. For that purpose different glucose-lowering drugs (GLDs) have been proposed and used. Luseogliflozin is recommended for DM2 patients as a single medicine or in combination with other GLDs in particular with metformin when disease control is not achieved on other GLDs.
Currently, most of the data showing the effectiveness and safety of luseogliflozin in blood glucose reduction in DM2 patients originate from studies conducted in Japanese populations. Therefore, the main aim of this study is to assess the effectiveness and safety of taking three different doses of luseogliflozin (Luseo) versus placebo (PBO) given on top of metformin (MET) in reducing blood glucose in Caucasian patients with inadequately controlled DM2 on single treatment with metformin.

Who can participate?
Caucasian patients aged 18–75 years with stable DM2 treated with unchanged doses of metformin equal or more than 1500 mg per day for at least 3 months but not achieving blood glucose control

What does the study involve?
Participants are randomly allocated into one of four treatment groups to receive once daily on top of metformin either 2.5, 5 or 10 mg of luseogliflozin or a placebo (dummy drug). No additional glucose-lowering treatments are allowed (except rescue treatment in case of glucose control loss). In order to assess the effectiveness and safety after 12 weeks of treatment the following measurements are taken: changes in HbA1c levels, fasting blood glucose and blood glucose after eating. Changes in body weight and waist are also measured at week 12.

What are the possible benefits and risks of participating?
Participants may benefit from better DM2 management in terms of blood glucose reduction. There are risks of low blood glucose, cystitis (bladder inflammation), pollakiuria (frequent urination), and increased amounts of ketone bodies in the blood and protein in urine (proteinuria).

Where is the study run from?
JSC Servier (Russia)

When is the study starting and how long is it expected to run for?
March 2018 to August 2019

Who is funding the study?
JSC Servier (Russia)

Who is the main contact?
Dr Alexander Andreev
alexander.andreev@servier.com

Contact information

Type(s)
Public

Contact name
Dr Elena Isachenko

Contact details
Lesnaya,7, bld A
Moscow
Russian Federation
125196
+7 (0)4959370700
elena.isachenko@servier.com

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CL3-LUSEO-001

Study information

Scientific 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

Study objectives
To demonstrate the efficacy of at least one dose (among three doses) of luseogliflozin versus placebo on top of metformin in reducing HbA1c between week 12 and week 0 in Caucasian patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/09/2018, Ethics Council under the Ministry of Health of the Russian Federation (127994, Moscow, Rakhmanovsky. pereulok, 3, Russia; +7 (0)495 625 44 21; info@minzdrav.gov.ru), ref: 176

Study design
Multicenter randomized double-blind placebo-controlled parallel-group dose-ranging study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet. Available in Russian.

Health condition(s) or problem(s) studied
Type 2 diabetes mellitus

Interventions
Participants are randomized using Interactive Web Response System (IWRS) block randomization with stratification based on the baseline HbA1c level to four parallel groups with 1:1:1:1 distribution: 2.5 mg, 5 mg, 10 mg of luseogliflozin or placebo on top of metformin for 12 weeks. Patients take tablets once daily orally before breakfast starting the next day after the inclusion visit and ending at the Week 12 visit.

All participants are requested to make six visits in the three study periods:
1. Selection period up to 2 weeks on their standard metformin dose (selection visit and inclusion visit)
2. Double-blind treatment period for 12 weeks (three follow-up visits: at week 4, week 8 and

week 12 [end of the double-blind treatment])
3. Follow-up period for 2 weeks after the end of the double-blind treatment (end-of-study visit)

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Luseogliflozin, metformin

Primary outcome measure
Change of HbA1c measured using the validated method at the central laboratory between week 0 and week 12

Secondary outcome measures
1. Fasting plasma glucose level measured using the validated method at the central laboratory at each study visit (selection, inclusion, Week 4, Week 8, Week 12 and End-of-Study visits)
2. Post-prandial plasma glucose level measured using the validated method at the central laboratory 2 hours after the start of the standardized meal at baseline (week 0) and the end of the double-blind treatment (week 12). A standardized meal (breakfast) containing about 600 kcal was provided.
3. Body weight measured using the calibrated scale at each study visit (selection, inclusion, week 4, week 8, week 12 and end-of-study visit)
4. Waist circumference measured at midway between the lowest ribs and the iliac crest in the standing position at the end of normal expiration with the tape in the horizontal plane, at each study visit (selection, inclusion, week 4, week 8, week 12 and end-of-study visit)

Safety measurements performed throughout the study:
5. Physical examination documented in the source documents at each study visit (selection, inclusion, week 4, week 8, week 12 and end-of-study visit)
6. Vital signs (heart rate, systolic and diastolic blood pressure) at each study visit (selection, inclusion, week 4, week 8, week 12 and end-of-study visit) measured at the same arm after at least 5 min rest in the sitting position using two measurements taken with at least 2-minute intervals
7. A standard 12-lead ECG performed after 10 min at rest in a supine position and interpreted by a qualified physician at the selection visit and week 12
8. Laboratory parameters measured by a central laboratory using the validated methods:
8.1. Haematology and biochemistry at selection and week 12 visits
8.2. Abridged biochemistry at week 4 and week 8 visits
8.3. Urinalysis at all study visits
8.4. Ketones analyzed by the investigator using test strips at inclusion and all subsequent visits (including end-of-study visit)
9. Adverse events (including serious adverse events and adverse events of special interest) reported by the patients collected and reported by the investigator at each study visit (selection, inclusion, week 4, week 8, week 12 and end-of-study visit)

Overall study start date
22/03/2018

Completion date
19/08/2019

Eligibility

Key inclusion criteria
1. Age between 18 and 75 years both inclusive
2. Caucasian race
3. Outpatients with type 2 diabetes mellitus diagnosed for not less than 3 months prior to selection
4. Ongoing 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 planned to be continued during the study
8. Signed informed consent before any study investigations. A specific written consent form is to be signed by the patients participating in PK/PD assessment
9. HbA1c 7.5%–10.0% (inclusive) at central laboratory measured in selection period and assessed at inclusion visit
10. The lab results, taken in the selection period, are available and free from any abnormalities likely to interfere with the study conduct or evaluation

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
320

Total final enrolment
328

Key exclusion criteria
1. Patients who are in an insulin-dependent state (who regularly need to use an insulin preparation)
2. 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)
3. Unstable diabetes mellitus (documented severe hypoglycemia or hospitalization due to diabetes decompensation or due to hypoglycemia within 1 year prior to selection)
4. 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
5. Patient with any uncontrolled endocrine disease other than diabetes mellitus
6. Patients with any of the following renal conditions:
6.1. Known estimated glomerular filtration rate (eGFR) of <45 ml/min/1.73m²
6.2. Stage 3 (overt nephropathy) or worse diabetic nephropathy
6.3. History of nephrectomy or renal transplantation
6.4. History of dialysis within 1 year prior to selection.
7. 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.
8. Patients with an obvious urination disorder due to problems such as neurogenic bladder or prostatic hyperplasia
9. Use of systemic (excluding topical application, intranasal, ophthalmological, intraarticular or inhaled form) glucocorticoids for more than 10 consecutive days within 3 months prior to selection visit
10. Change in dosage of thyroid hormones within 6 weeks prior to selection
11. Treatment with anti-obesity drugs within 3 months prior to selection
12. 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)
13. Patients with a 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.
14. Chronic heart failure NYHA class IV
15. Uncontrolled hypertension: sitting SBP >180 mmHg and/or DBP >100 mmHg at selection visit (exclusion should be based on the mean of two measurements)
16. 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)
17. History of diabetic ketoacidosis or hyperosmolar coma within 3 months prior to selection
18. Any acute disease or exacerbation of chronic diseases 1 month prior to selection
19. Lower extremity complications (such as skin ulcers, bacterial infection, osteomyelitis, and gangrene) at the selection
20. History of lower extremity amputation
21. Patients with malignant tumor with exception of basal cell carcinoma; patients who have been disease free for > 5 years may be included
22. Patients with a mental disorder who are in an unstable state and in whom it may be difficult to obtain informed consent and conduct the study
23. Patients who received any other investigational drugs within 3 months before the selection visit
24. Patients who had received SGLT inhibitors less than 1 year ago
25. History of allergic reaction, hypersensitivity or poor tolerance to any SGLT inhibitor
26. Alcohol or drug abuse and/or dependence
27. 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
28. 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
29. Unlikely to cooperate in the study,
30. Any other patients who are judged to be inappropriate for enrolment into this study by the investigator

31. Antidiabetic treatment has not been stable since the time of selection visit
32. 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)
33. Sitting SBP >180 mmHg and/or DBP >100 mmHg at inclusion visit (mean of the two measurements)
34. Estimated glomerular filtration rate (eGFR) of <45 ml/min/1.73m² (assessed by MDRD equation), measured in selection period and assessed at inclusion
35. Signs of urinary tract or renal infection based on urine analysis in the selection period
36. ALT or AST >3 ULN, measured in selection period and assessed at inclusion
37. Total bilirubin >2 ULN, measured in selection period and assessed at inclusion
38. Haemoglobin level equal or less than 100 g/l, measured in selection period and assessed at inclusion
39. Positive pregnancy test

Date of first enrolment
13/02/2019

Date of final enrolment
08/05/2019

Locations

Countries of recruitment
Russian Federation

Study participating centre
St. Petersburg State Budgetary Health Care Institution " City Polyclinic No. 117»
Russian Federation
194358

Study participating centre
FGBOU of Additional Professional Education "Russian Medical Academy of Continuing Professional Education" of the Ministry of Health of the Russian Federation
Russian Federation
123995

Study participating centre
Limited Liability Company "Center "Diabetes»
Russian Federation
443067

Study participating centre

Non-governmental private healthcare Institution "Scientific Clinical Center of Open Joint Stock Company" Russian Railways»
Russian Federation
125315

Study participating centre
First St. Petersburg State Medical University named after I. P. Pavlov»
Russian Federation
197022

Study participating centre
Rostov State Medical University of the Ministry of Health of the Russian Federation
Russian Federation
344022

Study participating centre
Federal State Budgetary Institution "Almazov National Medical Research Center" of the Ministry of Health of the Russian Federation
Russian Federation
197341

Study participating centre
State Budgetary Institution of the Arkhangelsk region " The First State Clinical Hospital named after E. E. Volosevich»
Russian Federation
163000

Study participating centre
Limited Liability Company Clinic "Bessalar". Clinical Research Center
Russian Federation
123423

Study participating centre
GAU YAO " Clinical Hospital of Emergency medical Care named after N. V. Solovyov»
Russian Federation
150003

Study participating centre
Astarta Limited Liability Company»
Russian Federation
199226

Study participating centre
Autonomous Healthcare Institution of the Voronezh Region " Voronezh Regional Clinical Consultative and Diagnostic Center»
Russian Federation
394018

Study participating centre
Limited Liability Company "Mir Zdorovya" Medical Center»
Russian Federation
305014

Study participating centre
St. Petersburg State Budgetary Healthcare Institution " City Multidisciplinary Hospital No. 2»
Russian Federation
194354

Study participating centre
State Budgetary Healthcare Institution of the Nizhny Novgorod Region " Nizhny Novgorod Regional Clinical Hospital named after N. A. Semashko"
Russian Federation
603126

Study participating centre
State Autonomous Healthcare Institution of the Kemerovo Region " Kemerovo Regional Clinical Hospital named after S. V. Belyaev»
Russian Federation
650066

Study participating centre
Municipal budgetary health care institution City Clinical Hospital No. 6
Russian Federation
454047

Study participating centre
St. Petersburg State Budgetary Healthcare Institution " City Polyclinic No. 17»
Russian Federation
195176

Study participating centre
Limited Liability Company Multidisciplinary Medical Clinic "Anturium" (LLC MMK "Anturium")
Russian Federation
656043

Study participating centre
Regional State Budgetary Healthcare Institution "City Hospital No. 5, Barnaul"
Russian Federation
656045

Study participating centre
State Budgetary Institution of Healthcare of the City of Moscow "City Clinical Hospital No. 52 of the Department of Healthcare of the City of Moscow"
Russian Federation
123182

Study participating centre
State Budgetary Institution of Healthcare of the City of Moscow "Moscow Clinical Scientific and Practical Center of the Department of Healthcare of the City of Moscow"
Russian Federation
111123

Study participating centre
St. Petersburg State Budgetary Healthcare Institution "City Polyclinic No. 34"
Russian Federation
197198

Study participating centre
State Budgetary Institution of Healthcare "Clinical Medical and Sanitary Unit No. 1"
Russian Federation
614077

Study participating centre
Budgetary healthcare institution of the Udmurt Republic "City Clinical Hospital No. 9 of the Ministry of Health of the Udmurt Republic"
Russian Federation
426063

Study participating centre
Limited Liability Company "Medical Center" Healthy Family "
Russian Federation
630061

Study participating centre
FSBI "Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences"
Russian Federation
630090

Study participating centre
Federal State Budgetary Educational Institution of Higher Education “Perm State Medical University named after Academician E.A. Wagner "of the Ministry of Health of the Russian Federation
Russian Federation
614990

Study participating centre
Federal State Budgetary Institution "National Medical Research Center of Endocrinology" of the Ministry of Health of the Russian Federation
Russian Federation
117036

Study participating centre
Kirov Regional State Budgetary Healthcare Institution "Kirov Clinical Hospital No. 7 named. IN AND. Yurlova "
Russian Federation
610014

Study participating centre

State Budgetary Healthcare Institution of the Nizhny Novgorod Region "City Clinical Hospital No. 13 of the Avtozavodsky District of Nizhny Novgorod"
Russian Federation
603018

Study participating centre
Federal State Budgetary Educational Institution of Higher Education "Tyumen State Medical University" of the Ministry of Health of the Russian Federation
Russian Federation
625023

Study participating centre
FGB military educational institution of higher education "Military Medical Academy named after S.M. Kirov "of the Ministry of Defense of the Russian Federation
Russian Federation
194044

Study participating centre
State Budgetary Healthcare Institution of the Novosibirsk Region "State Novosibirsk Regional Clinical Hospital"
Russian Federation
630087

Sponsor information

Organisation
JSC Servier (Russia)

Sponsor details
Lesnaya, 7, bld A
Moscow
Russian Federation
125196
+7 (0)4959370700
alexander.andreev@servier.com

Sponsor type
Industry

Website
https://servier.ru/

Funder(s)

Funder type
Industry

Funder Name
JSC Servier (Russia)

Results and Publications

Publication and dissemination plan
Planned publication in an international peer-reviewed journal. All data generated or analyzed during this study will be included in the subsequent results publication.

Intention to publish date
30/06/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available and the study database is stored at the sponsor company level.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		31/07/2018	14/04/2022	No	No
Results article		01/06/2023	19/06/2023	Yes	No