

CLINICAL TRIAL PROTOCOL

COMPOUND: Sotagliflozin (SAR439954)

A randomized, double-blind, parallel-group, 2-treatment multiple dose study to assess the intestinal, metabolic and cardiovascular effects of an 8 weeks treatment with sotagliflozin QD as compared with empagliflozin QD in T2DM patients with mild to moderate hypertension

STUDY NUMBER: PDY15010

| | | | |
|-----------------|--------------|---------------------------------------------------------|---------------------------------------------|
| Version Number: | 1 | EudraCT IND Number(s) WHO universal trial number: | 2017-002309-36 102191 U1111-1186-2962 |
| Date: | 22-Sept-2017 | Total number of pages: | 118 |

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

NAMES AND ADDRESSES OF INVESTIGATOR

| | |
|----------|---------------------------------------------------------------------------------|
| Name: | Dr. Maximilian Posch, MD |
| Address: | Charité Research Organisation GmbH Charitéplatz 1 10117 Berlin Germany |
| Tel: | +49 30 450 539 200 |
| Fax: | +49 30 450 539 900 |
| E-mail: | maximilian.posch@charite.de |

STUDY MEDICAL MANAGER (MONITORING TEAM'S REPRESENTATIVE)

| | |
|----------|----------------------------------------------------------------------------------------------------------------------------|
| Name: | Dr. Raphael Dahmen, MD |
| Address: | Sanofi-Aventis Deutschland GmbH Research & Development Industriepark Hoechst D-65926 Frankfurt am Main Germany |
| Tel: | +49 69 305 22045 |
| Mobile: | +49 173 689 6079 |
| Fax: | +49 69 305 17230 |
| E-mail: | raphael.dahmen@sanofi.com |

GLOBAL STUDY MANAGER

| | |
|----------|-------------------------------------------------------------------------------------------------------------|
| Name: | Dr. Elke Denke |
| Address: | Sanofi-Aventis Deutschland GmbH Industriepark Hoechst, Building H831 65926 Frankfurt am Main, Germany |
| Tel: | +49 69 305 27840 |
| Fax: | +49 69 305 17230 |
| E-mail: | elke.denke@sanofi.com |

SPONSOR'S MEDICAL OFFICER

| | |
|----------|----------------------------------------------------------------------------------------------------------------------------|
| Name: | Dr. Raphael Dahmen, MD |
| Address: | Sanofi-Aventis Deutschland GmbH Research & Development Industriepark Hoechst D-65926 Frankfurt am Main Germany |
| Tel: | +49 69 305 22045 |
| Mobile: | +49 173 689 6079 |
| Fax: | +49 69 305 17230 |
| E-mail: | raphael.dahmen@sanofi.com |

SPONSOR

| | |
|----------|----------------------------------------------------------------|
| Company: | Sanofi Recherche & Développement |
| Address: | 1, Avenue Pierre Brossolette 91385 Chilly Mazarin France |
| Tel: | +33 1 60 49 77 77 |
| Fax: | +33 1 60 49 67 67 |

CLINICAL TRIAL SUMMARY

COMPOUND: SAR439954

STUDY No : PDY15010

| | |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TITLE | A randomized, double-blind, parallel-group, 2-treatment multiple dose study to assess the intestinal, metabolic and cardiovascular effects of an 8 weeks treatment with sotagliflozin QD as compared to empagliflozin QD in T2DM patients with mild to moderate hypertension. |
| INVESTIGATOR/TRIAL LOCATION | Dr Maximilian Posch Charite Research Organization Berlin, Germany |
| STUDY OBJECTIVE(S) | <p>Main objective:</p> <p>To compare the metabolic and gastrointestinal PD effects of an 8 weeks treatment with 400 mg sotagliflozin QD to an 8 weeks treatment to 25 mg empagliflozin QD in mild or moderate hypertensive T2DM patients on a stable treatment regimen with metformin and an ACE inhibitor or ARB (angiotensin receptor blocker) under standardized diet conditions.</p> <p>Other objectives:</p> <p>To compare the renal and cardiovascular PD effects of an 8 weeks treatment with 400 mg sotagliflozin QD to an 8 weeks treatment to 25 mg empagliflozin QD in mild or moderate hypertensive T2DM patients on a stable treatment regimen with metformin and an ACE inhibitor or ARB.</p> <p>To evaluate the safety and tolerability of an 8 weeks QD treatment with 400 mg sotagliflozin or 25 mg empagliflozin in mild to moderate hypertensive T2DM patients on a stable treatment with metformin and an ACE inhibitor or ARB</p> <p>To evaluate the PK profile of sotagliflozin in steady state conditions.</p> |
| STUDY DESIGN | <ul style="list-style-type: none">• This is a Phase-IIa, single-center, randomized, double-blind, double-dummy, active-control, parallel-group multiple dosing study.• After an initial in-house period to evaluate pharmacodynamic baseline parameters under standardized conditions, patients will be randomized 1:1 to an 8 weeks multiple dosing treatment of 400 mg sotagliflozin QD or empagliflozin 25 mg QD.• Patients will return for a second in-house period to the unit in the last 5 days of treatment for re-analyses of all PD assessments on treatment under the same standardized conditions. |

| STUDY POPULATION | |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Main selection criteria: | <p>Adult T2DM patients with mild or moderate hypertension, aged 18 to 75 years</p> <ul style="list-style-type: none"> • Grade 1 or 2 hypertension: SBP (systolic blood pressure) 140-179 mmHg, DBP(diastolic blood pressure) 90-109 mmHg. • On stable treatment with ACE inhibitor or ARB for at least 4 weeks prior to screening and until randomization (ie. no change in drug, no dose adjustment). • T2DM with HbA1c 6.5-10%. • diabetic comedication: Metformin, to be stable for at least 3 months prior to screening and until randomization. • Body mass index (BMI) between 18 and 35 kg/m², inclusive. • Renal function: CKD (chronic kidney disease) Stages I - II: eGFR \geq 60 mL/min/1.73m². <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • On thiazides, spironolactone or loop diuretics. • On insulins, DPP-IV inhibitors, GLP-1 agonists, sulfonylureas (SUs), SGLT2 inhibitors, glitazones or meglitinides (glinides). • History of myocardial infarction in the last 12 months prior to screening. • History or presence of pulmonary hypertension. • Heart failure New York Heart Association Class III-IV. • Presence at screening or recurrent occurrence of cholelithiasis within 12 months prior to first dosing. |
| Total expected number of patients: | <p>A total of up to 40 patients are planned to be enrolled into this study, ie, 20 per treatment arm.</p> |
| Expected number of sites: | <p>1</p> |
| STUDY TREATMENT(s) | <p>Treatment A (Test):</p> <p>Sotagliflozin:</p> <p>Sotagliflozin 400 mg administered as two (2) 200-mg tablets QD prior to the first meal of the day for 56 days.</p> <p>with</p> <p>Empagliflozin placebo:</p> <p>One empagliflozin placebo capsule will be administered QD prior to the first meal of the day for 56 days.</p> <p>The 2 tablets of 200 mg Sotagliflozin and the empagliflozin placebo capsule have to be taken orally together with 240 mL of water once a day prior to the first meal of the day.</p> |

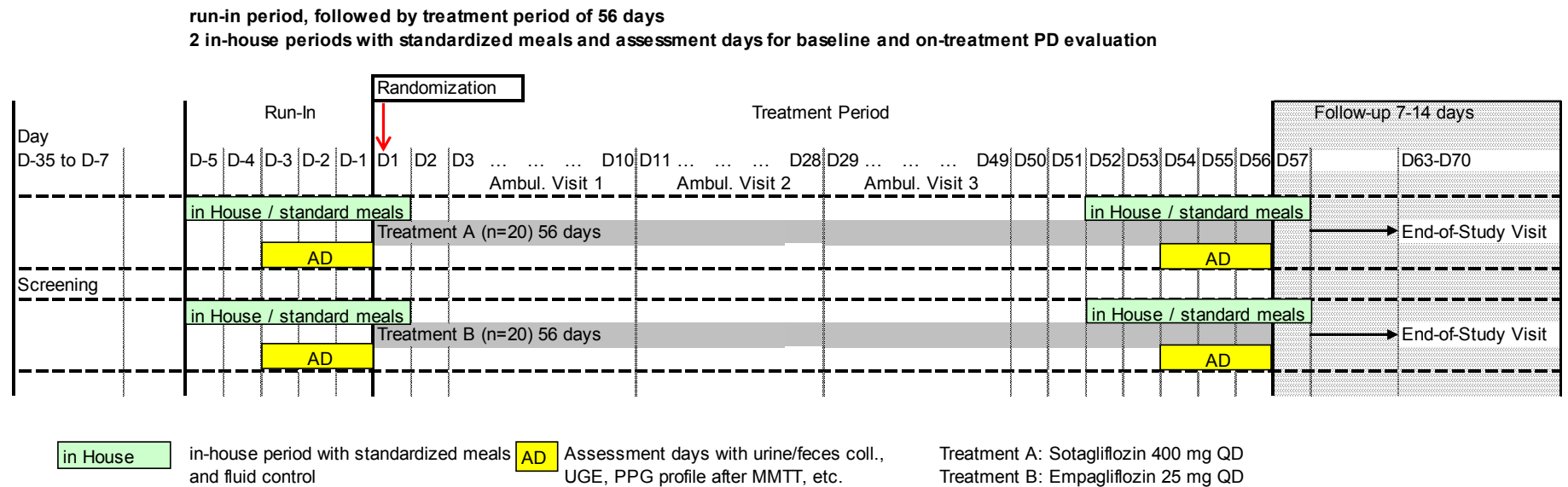
| | |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <p><u>Treatment B (Reference):</u></p> <p>Empagliflozin: Empagliflozin administered as one 25 mg capsule QD prior to the first meal of the day for 56 days.</p> <p>with</p> <p>Sotagliflozin placebo: Two Sotagliflozin placebo tablets will be given QD prior to the first meal of the day for 56 days.</p> <p>The 2 tablets of Sotagliflozin placebo and the 25 mg empagliflozin capsule have to be taken orally together with 240 mL of water once a day prior to the first meal of the day.</p> |
| MAIN ENDPOINT(S) AND FURTHER ENDPOINT(S) | <p>Main endpoints are :</p> <p>Change from baseline in fecal sodium, potassium, chloride, glucose and SCFAs (butyrate, propionate, acetate), also average volume and weight/day (incl. water contents), pH/bicarbonate, Firmicutes (Bacteroidetes ratio).</p> <p>Change from baseline in 24h urinary glucose, electrolytes (sodium, potassium, calcium, magnesium, phosphate), pH, creatinine, uric acid, urea; albumin, proteins, ketones (β-hydroxybutyrate, total ketone bodies) and volume excretion.</p> <p>14 hour plasma profiles of glucose/insulin/intact pro-insulin/C-peptide/glucagon/GLP1 (active and total), PYY and pancreatic polypeptide (PP) over 14 hours after standardized meals (MMTT) at breakfast, lunchtime and dinner, performed at baseline and on the last day of treatment.</p> <p>Further endpoints :</p> <p>Change from baseline in fasting metabolic parameters: acetate, propionate, β-hydroxybutyrate, total ketones, et al.</p> <p>Average 24h mean, systolic and diastolic blood pressure as measured per ABPM (ambulatory blood pressure monitoring) during the in-house periods (change from baseline).</p> <p>Change from baseline in cardiovascular parameters: PRA, AT1/2, aldosterone, NT-proBNP, CT-pro vasopressin, et al.</p> <p>Carotid-radial and carotid- femoral pulse wave velocity and radial augmentations index (change from baseline).</p> <p>Estimation of plasma volume (by indocyanine-green method).</p> <p>CGM (continuous glucose monitoring): average diurnal glucose; change from baseline; further CGM parameters.</p> <p>Echocardiography: left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, velocity time index (VTI) over left ventricular outflow tract (LVOT), tissue Doppler imaging (TDI) with (E/e') ratio and (E/A) ratio and the diastolic filling patterns</p> <p>Safety endpoints as reported by AEs, physical examination, body weight, vital signs, body temperature, ECG and standard laboratory parameters for hematology, biochemistry, coagulation and urinalysis</p> <p>PK of sotagliflozin will be assessed in steady state calculating C_{max}, C_{trough}, AUC_{tau}, t_{max} and other PK parameters as described in the Section 9.3.5 (Table 10).</p> |

| | |
|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>ASSESSMENT SCHEDULE</p> | <p>For the 5-days baseline PD assessment period the patients are admitted to the unit on Day -5. They receive standardized meals 3 times a day plus a standardized snack at bedtime during these days. The ABPM is set up for the time of the in-house stay. On specific days, the CV (cardiovascular) baseline assessment will be performed, ie, pulse wave velocity (Day-2) and echocardiography (Day -3) as described in the flowchart. On Day -1 the further pharmacodynamic baseline assessments are performed starting at 08 am. with fractioned 24h urine collection, blood sampling for post-prandial glucose and insulin/glucagon profiles. Feces collection is performed over 48 hours (Days -2 and -1). In the morning of Day 1 the collection period ends and the first dose of IMP is given prior to breakfast. Thereafter the patients are released from the unit.</p> <p>They continue dosing once daily for 56 days (Days 1 through 56), with at least 3 out-patients visits, one between Days 3-10, one between Days 11-28, one between Days 29 and 49, at least 7 days apart.</p> <p>On Day 52 the on-treatment PD in-house assessment period starts with admission to the unit and the same schedule of standardized meals as at baseline. On specific days , echocardiography (Day 54) and pulse wave velocity (Day 55) are assessed again, please refer to the flowchart. On Day 56 the on-treatment PD assessments will be performed with identical schedule as at baseline on Day -1. In the morning of Day 57, the collection period ends and the patients can be discharged after breakfast.</p> |
| <p>STATISTICAL CONSIDERATIONS</p> | <p>Pharmacodynamics</p> <p>The continuous PD endpoints (change from Baseline to Week 8) will be analyzed by the ANCOVA model with treatment groups (Sotagliflozin, Empagliflozin) as fixed effects, and baseline values as a covariate.</p> <p>Adjusted mean change from Baseline to Week 8 for each treatment group will be provided from the model, as well as the between-group difference (comparing sotagliflozin vs empagliflozin) and the 95% CI for the difference.</p> <p>Descriptive statistics and graphs will be provided by treatment.</p> <p>Safety</p> <p>The safety analysis will be based on the review of the individual data and descriptive statistics.</p> <p>The safety analysis will focus on the treatment emergent AEs (TEAE) period, defined as the time interval from the first IMP administration up to 7 days after the last administration of IMP (excluded). Adverse events (AE) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of patients experiencing TEAEs will be summarized by treatment.</p> <p>Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results, vital signs and ECG will be flagged and summarized by treatment using frequency tables.</p> |

| | |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Pharmacokinetics The PK parameters will be presented descriptively. |
| DURATION OF STUDY PERIOD (per patient) | <p>The run-in and treatment periods last altogether 62 days including the day of discharge from the unit at the end of the treatment period. The screening should be performed within 30 days prior to the first admission to the unit, but not later than 2 days prior to first admission to the unit (D-35 to D-7).</p> <p>A follow-up visit has to be performed 7 to 14 days after last dosing (D 63-70)</p> <p>Duration of each part of the study for one patient:</p> <ul style="list-style-type: none"> • Screening: 2-30 days. • Run-in period: 5 days. • Treatment period: 56 days. • Follow-up: 7 to 14 days. • Total study duration: 70-105 days. |

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

| Phase | Screening | Run-In | | | Treatment Period | | | | | End-of-treatment period | End of study |
|------------------------------------------|-------------|--------|------------|-----|------------------|----------------|-----|------------|-----|-------------------------|--------------|
| Day | D-35 to D-7 | D-5 | D-4 to D-2 | D-1 | D1 | D2 - 51 | D52 | D53 to D55 | D56 | D57 | D63 to D70 |
| Informed consent | X | | | | | | | | | | |
| Institutionalization | | X | X | X | | | X | X | X | | |
| Discharge | | | | | X | | | | | X | |
| Visit at clinical site | X | | | | | x ^a | | | | | X |
| Inclusion/exclusion criteria | X | X | | | x ^d | | | | | | |
| Medical/surgical history | X | | | | | | | | | | |
| Prior/concomitant medications | < | - | - | - | - | - | - | - | - | - | > |
| Inclusion | | | | | x ^d | | | | | | |
| Randomization | | | | | x ^d | | | | | | |
| Study treatment administration | | | | | | | | | | | |
| IMP administration QD ^g | | | | | X | X | X | X | X | | |
| IMP accountability | | | | | | x ^a | X | X | X | | |
| Standardized meals in house ^b | | X | X | X | x ^h | | X | X | X | x ^h | |
| Diary dispensation | | X | | | X | x ^a | X | | | | |
| Diary recordings | | X | X | X | X | X | X | X | X | | |
| Diary collection | | | | | X | x ^a | X | | | X | |
| Safety | | | | | | | | | | | |
| Physical examination | X | X | | | | | X | | | | X |
| Height | X | | | | | | | | | | |
| Body weight | X | | | X | | | | | X | | |
| Archival blood sample | | | | | x ^d | | | | | | |
| Serology tests | X | | | | | | | | | | |
| Urine drug screen, alcohol test | X | X | | | | | X | | | | |
| Vital signs, ECG | X | X | | | | | X | | | | X |

| Phase | Screening | Run-In | | | Treatment Period | | | | | End-of-treatment period | End of study |
|----------------------------------------------------------------------------------|-------------|--------|-------------------|----------------|-------------------|----------------|-----|----------------|-------------------|-------------------------|--------------|
| Day | D-35 to D-7 | D-5 | D-4 to D-2 | D-1 | D1 | D2 - 51 | D52 | D53 to D55 | D56 | D57 | D63 to D70 |
| Auricular body temperature | X | X | | X | | | X | | X | | X |
| Hematology, biochemistry, coagulation ^k | X | X | | X ^q | | X ⁱ | X | | X ^q | | X |
| urinalysis | X | X | | | | X ⁱ | X | | X | | X |
| β-HCG blood test (if applicable) | X | X | | | | | X | | | X | |
| Plasma FSH (if applicable) | X | | | | | | | | | | |
| Adverse event collection | < | - | - | - | - | - | - | - | - | - | > |
| Pharmacokinetics | | | | | | | | | | | |
| Sotagliflozin + sotagliflozin-3-o glucuronide pharmacokinetic plasma samples | | | | | | | | | X | X ^o | |
| DNA | | | | | | | | | | | |
| DME DNA sample | | | | | X ^d | | | | | | |
| Pharmacogenetic DNA sample (optional) | | | | | X ^d | | | | | | |
| Pharmacodynamics | | | | | | | | | | | |
| ABPM | | X | X | X | X ^p | | X | X | X | X ^p | |
| Seated BP measurements ^j | | | X ^e | X ⁿ | X ^{d, n} | X ^a | | X ^e | X ^{d, n} | X ⁿ | |
| MMTT with postprandial blood sampling profile | | | | X | | | | | X | | |
| Fasting blood sample for PD parameters, incl. hematology, metabolic and CV panel | | | | X ^d | | | | | X ^d | | |
| Pulse wave velocity | | | X ^l | | | | | X ^l | | | |
| Echocardiography ^f | X | | X ^{f, e} | | | | | X ^f | | | |
| Urine collection (fractioned 24h urine collection) | | | | X | X | | | | X | X | |
| Feces collection ^c | | | X ^c | X | | | | X ^c | X | | |
| Plasma volume (Indocyanine green) | | | X ^e | | | | | X ^e | | | |

| Phase | Screening | Run-In | | | Treatment Period | | | | | End-of-treatment period | End of study |
|---------------------------|-------------|--------|------------|-----|------------------|----------------|-----|------------|-----|-------------------------|--------------|
| Day | D-35 to D-7 | D-5 | D-4 to D-2 | D-1 | D1 | D2 - 51 | D52 | D53 to D55 | D56 | D57 | D63 to D70 |
| CGM | | X | X | X | | | X | X | X | | |
| Fasting SMPG | | | X | | X | X ^m | X | X | | X | |
| SMPG profile ^j | | | | X | | X ^m | | | X | | |

- a* Three ambulatory visits on site during the out-patients dosing period; one between Days 3 and 10, one between Days 11 and 28, and one between Days 29 and 49, at least 7 days apart; IMPaccountability to be performed and diaries to be collected and checked at these visits; new diaries to be dispensed.
- b* Standardized meals in house with breakfast directly after dosing by 08:10 a.m., lunch at 1:00 p.m., dinner at 6:00 p.m., and a snack at 10:00 p.m.
- c* Feces collection over 48 hours on Days -2 and -1, then on Day 55 and 56
- d* Predose
- e* On Days -3 and 54 only
- f* Full set of measurements on Days -3 and 54 only; at screening only qualitative assessments
- g* QD dosing prior to first meal of the day; during in-house days between 07:00 a.m. and 09:00 a.m. directly prior to breakfast (in the study protocol the dosing time will be presented at 08:00 as an example)
- h* Only breakfast given in-house on D1 and D57
- i* Only at first ambulatory on-site visit
- j* At least 5-point profile (prior to breakfast, dinner and lunch, as well as 2 hours after start of lunch and at bedtime)
- k* In fasting condition for at least 10 hours
- l* On Days -2 and 55 only
- m* During the out-patients treatment period, a 5-point profile has to be performed at least once per week and fasting SMPG to be performed at least twice per week. All results have to be entered into the diary. If a profile is measured on the day of an ambulatory visit, the patients have to measure the SMPG at the unit only as far as the time points fall within the visit time on site. Other measurements can be done at home.
- n* Once in the morning in fasting condition, prior to breakfast
- o* Prior to breakfast
- p* Only until 08:00 a.m. (can be discontinued prior to breakfast)
- q* Only hematology

1.3 PERIOD FLOW CHART (IN-HOUSE PERIODS)

[illegible]

| Day | D-5 | D-4 | D-3 | D-2 | D-1 | | | | | | | | | | | | | | | D1 |
|----------------------------------------------------------------------------------|-----|----------------|----------------|----------------|----------------|---------|---------|---------|------|-------|-------|-------------------|---------|------|------|-------------------|------|------|-------------------|-------------------|
| Time (hour/minute) ^a | | | | | 0H | 0H10 | 0H25 | 0H40 | 1H | 2H | 3H | 5H | 5H30 | 6H | 7H | 10H | 11H | 12H | 14H | 24H |
| Indicative clock time | | | | | 8 am | 8:10 am | 8:25 am | 8:40 am | 9 am | 10 am | 11 am | 1 pm | 1:30 pm | 2 pm | 3 pm | 6 pm | 7 pm | 8 pm | 10 pm | 8 am |
| Pharmacodynamics | | | | | | | | | | | | | | | | | | | | |
| ABPM | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → |
| Seated BP measurements | | | X ^e | | X | | | | | | | | | | | | | | | X ^{g, i} |
| MMTT: postprandial blood samplings | | | | | PD00 | | PD01 | PD02 | PD03 | PD04 | PD05 | PD06 ^c | PD07 | PD08 | PD09 | PD10 ^c | PD11 | PD12 | PD13 ^c | |
| Fasting blood sample for PD parameters, incl. hematology, metabolic and CV panel | | | | | X | | | | | | | | | | | | | | | |
| CGM | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | |
| Fasting SMPG | | X ⁱ | X ⁱ | X ⁱ | | | | | | | | | | | | | | | | X ⁱ |
| SMPG profile | | | | | X ^f | | | | | | | X ^f | | | X | X ^f | | | X | |
| Pulse wave velocity | | | | X | | | | | | | | | | | | | | | | |
| Echocardiography | | | X | | | | | | | | | | | | | | | | | |
| Urine collection | | | | | ← | U01 | → | → | → | → | → | → ← | U02 | → | → | → ← | U03 | → | → ← | U04 → |
| Feces collection | | | | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → |
| Plasma volume (Indocyanine green) | | | X | | | | | | | | | | | | | | | | | |

^a Time (hour/minute) is expressed in reference to the last administration of sotagliflozin (T0H)

^b Refer to Safety section for detailed safety investigations

Note: when several items take place at the same time, the following order should be respected: pharmacodynamics, ECG, vital signs, blood sampling, drug administration, meal

In order to respect exact timing of pharmacokinetic samples, the other measures will be done ahead of the scheduled time.

DME = drug metabolizing enzymes; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

^c To be taken directly prior to start of meal consumption

^d High calorie meal test with high fraction of carbohydrates

^e 5 times per day: prior to breakfast, lunch and dinner, as well as 2 hours after start of lunch and at bedtime

^f Prior to meal

^g Predose

^h In fasting condition for at least 10 hours

ⁱ Only once per day in fasting condition, prior breakfast

j Standardized meals in house with breakfast directly after dosing by 08:10 a.m., lunch at 1:00 p.m., dinner at 6:00 p.m., and a snack at 10:00 p.m.

k Only hematology

| Day | D52 | D53 | D54 | D55 | D56 | | | | | | | | | | | | | | | | D57 |
|-----------------------------------------------------------|----------------|----------------|----------------|----------------|------------------|---------|---------|---------|------|-------|-------|-------------------|---------|------|------|-------------------|------|------|-------------------|------------------|-----|
| Time (hour/minute) ^a | | | | | 0H | 0H10 | 0H25 | 0H40 | 1H | 2H | 3H | 5H | 5H30 | 6H | 7H | 10H | 11H | 12H | 14H | 24H | |
| Indicative clock time | | | | | 8 am | 8:10 am | 8:25 am | 8:40 am | 9 am | 10 am | 11 am | 1 pm | 1:30 pm | 2 pm | 3 pm | 6 pm | 7 pm | 8 pm | 10 pm | 8 am | |
| Institutionalization | X | X | X | X | X | | | | | | | | | | | | | | | | |
| Discharge | | | | | | | | | | | | | | | | | | | | X | |
| Concomitant medications | < | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | > | |
| Study treatment administration | | | | | | | | | | | | | | | | | | | | | |
| IMP administration | X ^f | X ^f | X ^f | X ^f | X | | | | | | | | | | | | | | | | |
| Standardized meals | X | X | X | X | | X | | | | | | X ^d | | | | X | | | X | X | |
| Safety^b | | | | | | | | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | | | | | | | | |
| Body weight | | | | | X ^g | | | | | | | | | | | | | | | | |
| Vital signs, ECG | X ^g | | | | | | | | | | | | | | | | | | | | |
| Body temperature | X ^g | | | | X ^g | | | | | | | | | | | | | | | | |
| Hematology, biochemistry, coagulation | X | | | | X ⁱ | | | | | | | | | | | | | | | | |
| urinalysis | X | | | | X | | | | | | | | | | | | | | | | |
| Adverse event collection | < | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | > | |
| Pharmacokinetics | | | | | | | | | | | | | | | | | | | | | |
| Sotagliflozin/Sotagliflozi-3-O-glucuronide plasma samples | | | | | P00 ^g | | | | P01 | P02 | P03 | P04 | | | P05 | P06 | | | | P07 ^f | |
| Pharmacodynamics | | | | | | | | | | | | | | | | | | | | | |
| ABPM | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | |
| Seated BP measurements | | | X ^e | | X | | | | | | | | | | | | | | | X ^{f,h} | |
| MMTT: postprandial blood | | | | | PD14 | | PD15 | PD16 | PD17 | PD18 | PD19 | PD20 ^c | PD21 | PD22 | PD23 | PD24 ^c | PD25 | PD26 | PD27 ^c | | |

| Day | D52 | D53 | D54 | D55 | D56 | | | | | | | | | | | | | | | D57 |
|----------------------------------------------------------------------------------|----------------|----------------|----------------|----------------|----------------|---------|---------|---------|------|-------|-------|----------------|---------|------|------|----------------|------|------|-------|----------------|
| Time (hour/minute) ^a | | | | | 0H | 0H10 | 0H25 | 0H40 | 1H | 2H | 3H | 5H | 5H30 | 6H | 7H | 10H | 11H | 12H | 14H | 24H |
| Indicative clock time | | | | | 8 am | 8:10 am | 8:25 am | 8:40 am | 9 am | 10 am | 11 am | 1 pm | 1:30 pm | 2 pm | 3 pm | 6 pm | 7 pm | 8 pm | 10 pm | 8 am |
| samplings | | | | | | | | | | | | | | | | | | | | |
| Fasting blood sample for PD parameters, incl. hematology, metabolic and CV panel | | | | | X ^g | | | | | | | | | | | | | | | |
| CGM | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → |
| Fasting SMPG | X ^h | X ^h | X ^h | X ^h | | | | | | | | | | | | | | | | X ^h |
| SMPG profile | | | | | X ^f | | | | | | | X ^f | | | X | X ^f | | | X | |
| Pulse wave velocity | | | | X | | | | | | | | | | | | | | | | |
| Echocardiography | | | X | | | | | | | | | | | | | | | | | |
| Urine collection | | | | | ← | U05 | → | → | → | → | → | → ← | U06 | → | → | → ← | U07 | → | → ← | U08→ |
| Feces collection | | | | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → |
| Plasma volume (Indocyanine green) | | | X | | | | | | | | | | | | | | | | | |

^a Time (hour/minute) is expressed in reference to the last administration of sotagliflozin (T0H)

^b Refer to Safety section for detailed safety investigations

Note: when several items take place at the same time, the following order should be respected: pharmacodynamics, ECG, vital signs, blood sampling, drug administration, meal

In order to respect exact timing of pharmacokinetic samples, the other measures will be done ahead of the scheduled time.

DME = drug metabolizing enzymes; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

^c To be taken directly prior to start of meal consumption

^d High calorie meal test with high fraction of carbohydrates

^e 5 times per day: prior to breakfast, lunch and dinner, as well as 2 hours after start of lunch and at bedtime

^f Prior to meal

^g Predose

^h Only once per day, prior to breakfast

ⁱ Only hematology, predose

2 TABLE OF CONTENTS

| | |
|-------------------------------------------------------------------|-----------|
| CLINICAL TRIAL PROTOCOL..... | 1 |
| 1 FLOW CHARTS..... | 8 |
| 1.1 GRAPHICAL STUDY DESIGN | 8 |
| 1.2 STUDY FLOW CHART | 9 |
| 1.3 PERIOD FLOW CHART (IN-HOUSE PERIODS) | 12 |
| 2 TABLE OF CONTENTS | 17 |
| 2.1 LIST OF TABLES | 23 |
| 3 LIST OF ABBREVIATIONS | 24 |
| 4 INTRODUCTION AND RATIONALE..... | 25 |
| 4.1 INTRODUCTION..... | 25 |
| 4.2 RATIONALE | 26 |
| 4.2.1 Study rationale | 26 |
| 4.2.2 Design rationale and risk assessment | 26 |
| 4.2.3 Specific parameters rationale | 29 |
| 4.3 BENEFIT/RISK OF SOTAGLIFLOZIN | 30 |
| 5 STUDY OBJECTIVES | 32 |
| 5.1 MAIN OBJECTIVE | 32 |
| 5.2 OTHER OBJECTIVES | 32 |
| 6 STUDY DESIGN | 33 |
| 6.1 DESCRIPTION OF THE STUDY | 33 |
| 6.2 DURATION OF STUDY PARTICIPATION | 33 |
| 6.2.1 Duration of study participation for each patient | 33 |
| 6.2.2 Determination of end of clinical trial (all patients) | 34 |
| 6.3 INTERIM ANALYSIS..... | 34 |
| 7 SELECTION OF PATIENTS..... | 35 |
| 7.1 NUMBER OF PATIENTS PLANNED | 35 |

| | | |
|----------|--------------------------------------------------------------|-----------|
| 7.2 | INCLUSION CRITERIA..... | 35 |
| 7.3 | EXCLUSION CRITERIA | 36 |
| 8 | STUDY TREATMENTS | 40 |
| 8.1 | INVESTIGATIONAL MEDICINAL PRODUCT(S) | 40 |
| 8.2 | NONINVESTIGATIONAL MEDICINAL PRODUCTS | 41 |
| 8.3 | OTHER PRODUCTS | 41 |
| 8.4 | DESCRIPTION OF BLINDING METHODS | 41 |
| 8.4.1 | Methods of blinding | 41 |
| 8.5 | METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP | 42 |
| 8.6 | PACKAGING AND LABELING | 42 |
| 8.7 | STORAGE CONDITIONS AND SHELF LIFE | 43 |
| 8.8 | RANDOMIZATION CODE BREAKING DURING THE STUDY | 43 |
| 8.9 | RESPONSIBILITIES | 44 |
| 8.10 | CONCOMITANT MEDICATION..... | 44 |
| 8.11 | TREATMENT ACCOUNTABILITY AND COMPLIANCE | 45 |
| 8.12 | RETURN AND/OR DESTRUCTION OF TREATMENTS | 45 |
| 9 | ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT | 46 |
| 9.1 | PHARMACODYNAMIC PARAMETERS..... | 46 |
| 9.1.1 | Main endpoints..... | 46 |
| 9.1.2 | Further endpoints | 46 |
| 9.1.3 | Assessment methods..... | 48 |
| 9.1.3.1 | 24H Urine collection | 48 |
| 9.1.3.2 | 48H Feces Collection | 48 |
| 9.1.3.3 | High-calorie Meal Challenge Tolerance Test..... | 48 |
| 9.1.3.4 | ABPM | 49 |
| 9.1.3.5 | Pulse Wave Velocity | 50 |
| 9.1.3.6 | Echocardiography | 50 |
| 9.1.3.7 | Seated SBP/DBP diurnal profile | 50 |
| 9.1.3.8 | Plasma Volume Measurement..... | 51 |
| 9.1.3.9 | Fasting pharmacodynamic blood samplings..... | 51 |
| 9.1.3.10 | Continuous Glucose Monitoring | 52 |
| 9.1.4 | Assessment schedule | 53 |
| 9.2 | SAFETY | 53 |

| | | |
|-----------|-----------------------------------------------------------------------|-----------|
| 9.2.1 | Baseline demographic characteristics: | 53 |
| 9.2.2 | Safety assessment at screening, at baseline and during the study..... | 54 |
| 9.3 | PHARMACOKINETICS..... | 56 |
| 9.3.1 | Sampling times..... | 56 |
| 9.3.2 | Number of pharmacokinetic samples..... | 56 |
| 9.3.3 | Sample handling procedure | 56 |
| 9.3.4 | Bioanalytical methods | 57 |
| 9.3.5 | Pharmacokinetic parameters | 57 |
| 9.4 | DNA SAMPLES..... | 58 |
| 9.4.1 | Mandatory drug metabolizing enzymes DNA samples | 58 |
| 9.4.2 | Optional pharmacogenetic DNA sample..... | 58 |
| 9.5 | SAMPLED BLOOD VOLUME | 59 |
| 9.6 | FUTURE USE OF SAMPLES | 60 |
| 9.7 | MEASURES TO PROTECT BLINDING OF THE TRIAL | 60 |
| 10 | PATIENT SAFETY..... | 61 |
| 10.1 | ADVERSE EVENT MONITORING | 61 |
| 10.2 | DEFINITIONS OF ADVERSE EVENTS..... | 61 |
| 10.2.1 | Adverse event | 61 |
| 10.2.2 | Serious adverse event | 62 |
| 10.2.3 | Adverse event of special interest..... | 62 |
| 10.3 | OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING | 62 |
| 10.3.1 | General guidelines for reporting adverse events | 62 |
| 10.3.2 | Guidelines for reporting serious adverse events | 63 |
| 10.3.3 | Guidelines for reporting adverse events of special interest..... | 64 |
| 10.3.4 | Events of Special Interest (EOSIs) | 65 |
| 10.3.5 | Guidelines for management of specific laboratory abnormalities | 66 |
| 10.4 | SAFETY INSTRUCTIONS FOR EOSI OF HYPOGLYCEMIA..... | 66 |
| 10.4.1 | Hypoglycemia..... | 66 |
| 10.4.1.1 | Severe hypoglycemia..... | 66 |
| 10.4.1.2 | Documented symptomatic hypoglycemia | 67 |
| 10.4.1.3 | Asymptomatic hypoglycemia | 67 |
| 10.4.1.4 | Probable symptomatic hypoglycemia | 67 |
| 10.4.1.5 | Relative hypoglycemia | 67 |
| 10.5 | OBLIGATIONS OF THE SPONSOR | 68 |

| | | |
|-----------|--------------------------------------------------------------------------|-----------|
| 11 | HANDLING OF PATIENT WITHDRAWAL | 69 |
| 11.1 | LIST OF TREATMENT WITHDRAWAL CRITERIA..... | 69 |
| 11.2 | REASONS FOR TREATMENT WITHDRAWAL | 69 |
| 11.3 | REPLACEMENT OF PATIENTS | 69 |
| 11.4 | TREATMENT WITHDRAWAL FOLLOW-UP PROCEDURE..... | 69 |
| 12 | STUDY PROCEDURES | 71 |
| 12.1 | VISIT SCHEDULE..... | 71 |
| 12.1.1 | Screening procedures..... | 71 |
| 12.1.2 | Inclusion procedures | 71 |
| 12.1.3 | Description by type of visit | 72 |
| 12.1.4 | Study restriction(s) | 73 |
| 12.2 | DEFINITION OF SOURCE DATA..... | 73 |
| 13 | STATISTICAL CONSIDERATIONS | 75 |
| 13.1 | DETERMINATION OF SAMPLE SIZE..... | 75 |
| 13.2 | PATIENT DESCRIPTION | 75 |
| 13.2.1 | Disposition of patients | 75 |
| 13.2.2 | Protocol deviations..... | 76 |
| 13.3 | ANALYSIS POPULATION | 76 |
| 13.3.1 | Safety population | 76 |
| 13.3.2 | Pharmacokinetic population..... | 76 |
| 13.3.3 | Pharmacodynamic population..... | 76 |
| 13.3.4 | Pharmacokinetic/Pharmacodynamic population..... | 76 |
| 13.4 | DEMOGRAPHIC AND BASELINE CHARACTERISTICS | 77 |
| 13.4.1 | Patient demographic characteristics, medical history and diagnoses | 77 |
| 13.4.2 | Baseline pharmacodynamic parameters..... | 77 |
| 13.4.3 | Baseline safety parameters | 77 |
| 13.5 | EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE..... | 77 |
| 13.6 | PRIOR/CONCOMITANT MEDICATION/THERAPY | 78 |
| 13.7 | ANALYSIS OF PHARMACODYNAMIC VARIABLES..... | 78 |
| 13.7.1 | Description of pharmacodynamic variable(s)..... | 78 |
| 13.7.2 | Main analysis | 78 |

| | | |
|-----------|--------------------------------------------------------------------------------------------------|-----------|
| 13.7.3 | Further analysis/analysis of further variables | 79 |
| 13.8 | ANALYSIS OF SAFETY DATA..... | 79 |
| 13.8.1 | Adverse events | 79 |
| 13.8.1.1 | Definitions | 79 |
| 13.8.1.2 | Treatment-emergent adverse events..... | 80 |
| 13.8.1.3 | Deaths, serious, and other significant adverse events | 80 |
| 13.8.1.4 | Adverse events leading to treatment discontinuation | 80 |
| 13.8.1.5 | Adverse events of special interest | 80 |
| 13.8.2 | Clinical laboratory evaluations | 80 |
| 13.8.3 | Vital signs | 81 |
| 13.8.4 | Electrocardiogram | 82 |
| 13.8.5 | Other related safety parameters | 83 |
| 13.9 | ANALYSIS OF PHARMACOKINETIC DATA..... | 83 |
| 13.9.1 | Pharmacokinetic parameters | 83 |
| 13.9.2 | Statistical analysis..... | 83 |
| 13.10 | PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS..... | 83 |
| 13.11 | INTERIM ANALYSIS..... | 83 |
| 14 | ETHICAL AND REGULATORY CONSIDERATIONS..... | 84 |
| 14.1 | ETHICAL AND REGULATORY STANDARDS | 84 |
| 14.2 | INFORMED CONSENT | 84 |
| 14.3 | HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)..... | 85 |
| 15 | STUDY MONITORING..... | 86 |
| 15.1 | RESPONSIBILITIES OF THE INVESTIGATOR(S)..... | 86 |
| 15.2 | RESPONSIBILITIES OF THE SPONSOR..... | 86 |
| 15.3 | SOURCE DOCUMENT REQUIREMENTS..... | 87 |
| 15.4 | USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST | 87 |
| 15.5 | USE OF COMPUTERIZED SYSTEMS..... | 87 |
| 16 | ADDITIONAL REQUIREMENTS..... | 88 |
| 16.1 | CURRICULUM VITAE..... | 88 |
| 16.2 | RECORD RETENTION IN STUDY SITE(S)..... | 88 |

| | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------|
| 16.3 | CONFIDENTIALITY | 88 |
| 16.4 | PROPERTY RIGHTS..... | 89 |
| 16.5 | DATA PROTECTION..... | 89 |
| 16.6 | INSURANCE COMPENSATION..... | 89 |
| 16.7 | SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES | 89 |
| 16.8 | PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE | 90 |
| 16.8.1 | By the Sponsor..... | 90 |
| 16.8.2 | By the Investigator | 90 |
| 16.9 | CLINICAL TRIAL RESULTS | 91 |
| 16.10 | PUBLICATIONS AND COMMUNICATIONS | 91 |
| 17 | CLINICAL TRIAL PROTOCOL AMENDMENTS | 92 |
| 18 | BIBLIOGRAPHIC REFERENCES..... | 93 |
| 19 | APPENDICES..... | 97 |
| APPENDIX A. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION | | 98 |
| APPENDIX B. RECOMMENDATIONS ON BASIC GENITOURINARY HYGIENE, MAINTAINING HYDRATION AND RECOGNIZING DIABETIC KETOACIDOSIS | | 105 |
| APPENDIX C. DECISION CHARTS | | 108 |
| APPENDIX D. BLOOD PRESSURE AND PULSE RATE MONITORING | | 113 |
| APPENDIX E. PROCEDURE FOR COLLECTION, HANDLING, STORAGE AND SHIPMENT OF SOTAGLIFLOZIN (AND ITS METABOLITE) SPECIMENS PLASMA CONCENTRATIONS MEASUREMENTS..... | | 115 |

2.1 LIST OF TABLES

| | |
|-------------------------------------------------------------------------------------------|----|
| Table 1 - Summary of blood sampling for the post-meal profiles on Day -1 and Day 56 | 49 |
| Table 2 - Number of blood sampling for post-prandial profiles test | 49 |
| Table 3 - Summary of blood sampling for the cardiovascular panel | 51 |
| Table 4 - Number of blood samples for the fasting cardiovascular panel | 51 |
| Table 5 - Summary of blood sampling for the fasting metabolic panel | 52 |
| Table 6 - Number of blood samples for the fasting metabolic panel | 52 |
| Table 7 - Number of plasma samples | 56 |
| Table 8 - Summary of handling procedures | 57 |
| Table 9 - Summary of bioanalytical method | 57 |
| Table 10 - List of pharmacokinetic parameters and definitions | 57 |
| Table 11 - Sampled blood volume | 59 |
| Table 12 - Highly Effective Contraceptive Methods | 99 |

3 LIST OF ABBREVIATIONS

Pharmacokinetic parameter definitions are provided in [Section 9.3.5](#).

| | |
|-------|-------------------------------------------|
| AE: | adverse event, adverse event |
| AESI: | adverse events of special interest |
| ALT: | alanine aminotransferase |
| ARB: | angiotensin receptor blocker |
| BP: | blood pressure |
| CGM: | continuous glucose monitoring |
| CKD: | chronic kidney disease |
| CV: | cardiovascular |
| DBP: | diastolic blood pressure |
| DILI: | drug-induced liver injury |
| DKA: | diabetic ketoacidosis |
| DME: | drug metabolizing enzymes |
| EOSI: | events of special interest |
| FPG: | fasting plasma glucose |
| FSH: | follicle stimulating hormone |
| GCP: | good clinical practice |
| IB: | Investigator's Brochure |
| ICH: | International Conference on Harmonization |
| MACE: | major adverse cardiac event |
| MI: | myocardial infarction |
| P-gp: | P-glycoprotein |
| PK: | pharmacokinetic |
| SAE: | serious adverse event |
| SBP: | systolic blood pressure |
| SCFA: | short chain fatty acid |
| SGLT: | sodium dependent glucose transporter |
| SMPG: | self measured plasma glucose |
| SU: | suflonylurea |
| T1DM: | type 1 diabetes mellitus |
| T2DM: | type 2 diabetes mellitus |
| TEAE: | treatment-emergent adverse event |
| ULN: | upper limit of normal |
| UTI: | urinary tract infection |
| VTE: | venous thrombotic event |

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Sotagliflozin (SAR439954) is an orally administered small molecule dual inhibitor for sodium-glucose cotransporter type 1 (SGLT1) and type 2 (SGLT2), formulated as 200-mg coated tablets and currently in Phase-III clinical development for T1DM and T2DM. The compound, a member of the pharmaceutical class of SGLT-inhibitors known as gliflozins, lowers blood glucose by effects in both SGLT-1 and SGLT-2. The effect on SGLT-1 decreases and delays SGLT1-mediated glucose absorption in the gastrointestinal tract (1). It also enhances glucose excretion in the urine by reducing renal glucose re-absorption via inhibition of SGLT2 in the kidney.

Sotagliflozin is being evaluated as a potential treatment for patients with Type 1 diabetes mellitus (T1DM), a disorder in which the patient's body produces too little or no insulin, and Type 2 diabetes mellitus (T2DM), a metabolic disorder characterized by insulin insensitivity and hyperglycemia. Both T1DM and T2DM are frequently comorbid with hypertension and cardiovascular disease, and T2DM is often comorbid with obesity. Despite a number of available treatment options, there are still great unmet medical needs for both T1DM and T2DM and additional safe and efficacious therapies are very much needed. Unlike selective SGLT2 modulators currently in development, sotagliflozin increases glycemic and metabolic control through dual inhibition, representing a unique mechanism of action and a potential new treatment option (2). Studies with sotagliflozin have shown that this agent produces significant glucosuria in preclinical animal models, healthy human subjects (3), and patients with T2DM. Single- and multiple-dose administration of sotagliflozin to healthy human subjects has resulted in dose-dependent increases in glycosuria. Multiple-dose (28-day and 12 weeks) administration to diabetic patients produced improvements in several metabolic parameters, including urinary glucose excretion, fasting plasma glucose (FPG), glycosylated hemoglobin A1C, Glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY) (4, 5). These data suggest that sotagliflozin may be of therapeutic benefit to patients with T2DM. Because sotagliflozin lowers blood glucose by insulin-independent mechanisms, it is expected to reduce the need for exogenous insulin especially in the postprandial period (6). This is expected to simplify insulin-dosing in T1DM and insulin-requiring T2DM. Lower insulin requirements in these patients may translate to lower rates of hypoglycemia. A reduction in hypoglycemia while maintaining or improving glycemic control would significantly improve clinical care.

Extensive clinical studies conducted for selective SGLT2 inhibitors have established this class as effective agents for the treatment of T2DM (1, 2, 3) and have led to approvals by the Japanese Pharmaceutical and Medical Device Agency, the US Food and Drug Administration (FDA), and the European Medicines Agency.

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2, designed to reduce glucose absorption in the GI tract via SGLT1 inhibition and renal glucose reabsorption via SGLT2 inhibition. Unlike selective SGLT2 modulators currently in development, sotagliflozin provides dual inhibition, representing a potentially unique mechanism of action.

More detailed information is provided in the Investigator's Brochure.

4.2 RATIONALE

4.2.1 Study rationale

It has been shown in previous studies that sotagliflozin can reach similar efficacy in terms of HbA1c lowering as selective SGLT2 inhibitors, while the urinary glucose excretion remains below the levels seen with the latter class (7). It is hypothesized that this suggests that there is additional glucodynamic effects of sotagliflozin by means of SGLT1 inhibition, probably primarily in the small bowels from the intraluminal side (1).

In a single dose triple tracer study on oral glucose absorption in healthy subjects it has been shown that the rate of oral glucose appearance is delayed under sotagliflozin at breakfast and lunch, while this effect is only visible at breakfast under canagliflozin, the latter of which has in-vitro a much weaker inhibition potency on SGLT1 than sotagliflozin. It is considered that the delayed and – maybe – overall reduced intestinal glucose absorption has some indirect effects that are beneficial for metabolic and cardiovascular parameters. This refers in particular to the conversion of glucose into short chain fatty acids (SCFAs) by the gut microbiome, which has been described previously for other drugs such as acarbose in particular for butyrate (8, 9). Although the mode of action is different from sotagliflozin, part of these downstream intestinal effects may be similar. This includes increases in the postprandial GLP-1 and PYY excursions (10), as well as blood pressure reduction (11, 12, 13).

It has already been described for SGLT2 inhibitors that their mode of action can reduce blood pressure and improve cardiovascular functions (14, 15, 16). For sotagliflozin, it has been shown in a Phase-IIb study that there is a significant lowering of systolic blood pressure observed in T2DM with baseline levels above 130 mmHg, while those with baseline levels below this threshold remain nearly unchanged. However, it is not known yet as to what extent the indirect effects of intestinal SGLT1 inhibition may contribute to the blood pressure effects and if the dual mode of action is superior in its CV effects over a mere SGLT2 inhibition.

The intestinal effects of sotagliflozin also have not been elucidated yet, with exception of the post-prandial profiles of the intestinal incretins. In particular the impact on intestinal sodium and volume depletion and the gut microbiome have not been investigated in humans yet.

Empagliflozin has been reported to reduce blood pressure in T2DM patients and has been approved to treat adult patients with type 2 diabetes mellitus and established cardiovascular disease (17).

This study is now designed to assess the intestinal, metabolic and cardiovascular effects of sotagliflozin in a head-to-head comparison to empagliflozin, a pure SGLT2 inhibitor, in T2DM patients with increased baseline blood pressure and to elucidate the knowledge gaps for its dual mode of action.

4.2.2 Design rationale and risk assessment

As for sotagliflozin the higher dose of 400 mg QD is the primary dose used in the Phase III program in T2DM patients and as the blood pressure lowering effect seems to further increase from 200 mg to 400 mg QD (study 202), this higher dose regimen will also be used in PDY15010.

For the head-to-head comparison to a selective SGLT2 inhibitor, empagliflozin has been selected, which will also be given in the highest dose regimen it is approved for. This is 25 mg per day.

Previous studies have shown that most of the renal effects under sotagliflozin treatment have reached a new steady state after 2 weeks of once daily treatment (4). However, some cardiovascular parameters such as those for PWV and cardiac function and indirect effects possibly to be expected by changes in the gut microbiome are considered to rather need a minimum of 8 weeks of treatment (15). As the hypothesized changes in the gut microbiome may not be fully or only very slowly reversible, a cross-over design is not considered suitable for this study and, therefore, a parallel group design has been selected.

The study population is T2DM patients with a baseline SBP of 140 mmHg or above. This threshold has been shown suitable to discriminate those patients being sensitive for a blood pressure lowering effect. As – for ethical reasons – a severe hypertension revealed at screening would require for the patient to have a further approved antihypertensive drug prior to study inclusion added, this study plans to enroll only patients with mild - moderate hypertension (below 180 mmHg SBP).

The antihyperglycemic treatment of the T2DM in this study could impact several endpoints of this study. Therefore, limitations are needed to keep possible variability as small as possible. Metformin is known to impact GLP-1 secretion (18). Since it is hardly possible to recruit a relevant number of patients with diagnosed T2DM who are not prescribed this first-line medication, co-medication with a stable dose of metformin is a requirement for all patients. All other diabetes medications, such as GLP-1 agonists, DPP-IV inhibitors, insulins, glitazones or SUs are prohibited in this study.

The renal SGLT2 inhibition has an impact on the tubuloglomerular feedback mechanism. The increase in tubular sodium concentration at the macula densa results in a reduction of the glomerular perfusion due to constriction of the afferent arteriole, effective renal plasma flow and in an increase in renal vascular resistance. Thus, in diabetic patients the GFR is reduced by SGLT2 inhibition (19). Furthermore, angiotensin II and aldosterone levels are increased significantly under SGLT2 inhibition in diabetic patients with glomerular hyperfiltration (20).

A diabetic patient with this condition can benefit from a treatment with an ACE inhibitor or an angiotensin receptor blocker. To avoid increased variability in cardiovascular parameters due to possible co-medication with these classes of hypertensive agents, all patients have to be on a stable regimen of an ACE inhibitor or an ARB for inclusion into this study, as previously applied in a similar study (21).

The feces constitution can have a high day-to-day variability within a patient dependent on nutrition, environment and physical activity. To maximize here the standardization as far as possible, the patients will stay in-house for 5 days in the unit with standardized meals and no physical activity for two periods: one at baseline, and one at the end of the treatment period, both with an exactly matching meal schedule. The metabolic and feces assessments will be performed in the end of the two in-house periods.

From a safety perspective, sotagliflozin was well-tolerated across studies. In healthy patients, sotagliflozin was well-tolerated following single doses up to 2000 mg, and in multiple doses up to 800 mg over 10 days. Furthermore, in a thorough QT study, single doses of sotagliflozin (800 mg and 2000 mg) were well-tolerated and did not prolong the QT interval. Additionally, evaluation of metabolites in urine and plasma of healthy subjects resulted in no safety concerns following single doses of 400 mg sotagliflozin. In patients with T2D, single doses of 400 mg in combination with sitagliptin, and multiple doses up to 400 mg in combination with metformin over 12 weeks were also well-tolerated.

Approximately 840 subjects (698 assigned to sotagliflozin and 229 assigned to placebo) have participated in completed clinical studies of sotagliflozin. No significant safety concerns have been identified in the sotagliflozin drug program, and sotagliflozin has been well-tolerated in all studies to date. Serious adverse events (SAEs) and discontinuations due to adverse events (AEs) have been infrequent and have been balanced between treatment and comparator groups. Reports of treatment-emergent adverse events (TEAEs) across all sotagliflozin studies for which data are available were generally balanced between treatment and comparator groups. The most frequently reported TEAEs ($\geq 2.0\%$) were headache, nausea, diarrhea, constipation, dizziness, and upper respiratory tract infection, all of which were reported at a frequency greater than placebo. However, the majority were described as mild to moderate, and most resolved spontaneously and without discontinuation of the study drug.

In completed and ongoing clinical trials, no additional safety issues beside those already described in the current Investigator's Brochure (IB) have been observed. In general, no significant imbalances of SAEs/AEs between sotagliflozin and comparators were observed in completed studies. Cumulatively, across the completed studies, 8 SAEs were reported in 6 patients (4 patients with T2D and 2 with T1D), all of which were assessed as unrelated to study drug; those reported in 4 patients with T2D who received sotagliflozin included pulmonary embolism, deep vein thrombosis, bile duct stone, cholangitis and lower limb fracture, while a patient receiving placebo had a myocardial infarction (MI).

Two SAEs of diabetic ketoacidosis (DKA) were reported in 2 patients with T1D in the ongoing (blinded) Phase 2 T1D study (LX4211.1-203-T1DM) using insulin pumps; in each case basal insulin was within 7% of Baseline, and both SAEs were assessed as due to failure of insulin delivery via insulin pump. Both cases were associated with high blood glucose readings >300 mg/dL, a finding expected in DKA and notable in that this value did not appear to be masked by sotagliflozin treatment.

A drug interaction study with digoxin, a sensitive P-glycoprotein (P-gp) substrate, indicated that sotagliflozin acts as a weak P-gp inhibitor. Thus, sotagliflozin increases systemic exposure of digoxin and could also increase the exposure of other P-gp substrates. Patients taking sotagliflozin with concomitant digoxin should have digoxin concentrations monitored and doses reduced as needed. In addition, other P-gp substrates may be affected and the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments.

Safety, tolerability, pharmacokinetic (PK) and pharmacodynamic effects of sotagliflozin are supported by Phase 1 and Phase 2 studies and animal toxicology data in rats up to 26 weeks and dogs up to 39 weeks as well as 2-year carcinogenicity data in rats.

More information on the safety of sotagliflozin and on the clinical program can be found in the IB.

Empagliflozin is a selective SGLT2 inhibitor that has been approved for the treatment of T2DM in 2014. It is indicated for the treatment of adults with insufficiently controlled Type 2 diabetes mellitus as an adjunct to diet and exercise

- As monotherapy when metformin is considered inappropriate due to intolerance.
- In addition to other medicinal products for the treatment of diabetes (22).

In patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced heart failure hospitalization and cardiovascular death, with a consistent benefit in patients with and without baseline heart failure (23).

The dose of 25 mg empagliflozin is the higher of the approved dose levels for once daily administration and is considered to be appropriate to be compared to a once daily dose of 400 mg sotagliflozin.

4.2.3 Specific parameters rationale

A feces analysis will be performed at baseline and at end of treatment to elucidate the intestinal downstream effects of sotagliflozin by SGLT1 inhibition. From published data of other drugs with delayed and/or reduced intestinal carbohydrate absorption it is known that SCFAs could be increased in feces (24). Changes in feces pH and the gut microbiome would also be related to this mechanism. As absolute amounts of the gut microbiome are subject to large between-patient variability, a ratio of the firmicutes over bacteroidetes classes of bacteria is used to quantify the impact of a possibly increased carbohydrate metabolism in the lower small and the large bowels under SGLT1 inhibition (25, 26). Parameters looking at direct effects of intestinal SGLT1 inhibition will be the fecal sodium amount and the overall weight and fluid contents in feces.

The change from baseline in systolic blood pressure will be measured by means of under in-house conditions to reduce the variability, as punctual BP measurements are subject to be influenced by activities prior to the measurements. To evaluate the possible mechanisms of blood pressure reduction, a panel of cardiovascular serum/plasma parameters will be taken at baseline and at end of treatment during the in-house periods. This CV panel comprises plasma renin activity (PRA), angiotensin 1 and 2 (AT1/2), aldosterone, MR-proANP, NT proBNP, CT-pro Vasopressin (Copeptin) (27). The effects on plasma volume reduction are measured by means of the indocyanine green method as described before (28, 29, 30).

It is also hypothesized that SGLT inhibition may reduce arterial stiffness. This characteristic is going to be quantified by means of a pulse wave velocity measurement at baseline and at the end of treatment. Common parameters of this method are carotid-radial and the carotid-femoral pulse wave velocity and the radial augmentations index (15, 31). Furthermore, possible effects on the cardiac motility and contractility will be assessed in an echocardiography, also to be performed during the in-house stays at baseline and at end of treatment. The parameters planned to be assessed by this method are velocity time index (VTI) over left ventricular outflow tract (LVOT), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), tissue Doppler imaging (TDI) and the diastolic filling patterns (32).

The metabolic effects of the two treatments, sotagliflozin and empagliflozin, are assessed by a panel of serum/plasma parameters, which are also taken at baseline and at end of treatment. The selection refers to the known and hypothesized effects of SGLT1 and 2 inhibition described in the above. These include FPG, fasting insulin + intact proinsulin, C-peptide, fasting glucagon, fasting GLP-1 (total and active), PYY, Triglycerides, FFAs, SCFAs (acetate, propionate) and ketones (beta-hydroxybutyrate, total ketone bodies). On the last day of each in-house period (baseline and last day of treatment), blood samples will be taken over 24 hours to assess the post-prandial profiles of glucose, insulin, C-peptide, glucagon, total and active GLP-1 and PYY under sotagliflozin as compared to empagliflozin. A mixed meal tolerance test with high carbohydrate contents will be performed at lunchtime on these days.

4.3 BENEFIT/RISK OF SOTAGLIFLOZIN

Sotagliflozin is currently being investigated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The development program will also provide efficacy and safety data for sotagliflozin in combination with other antidiabetes medications. In addition, the program will evaluate clinical outcomes in patients with high CV risk and in patients with renal impairment. The use of sotagliflozin in the treatment of T1D is also being studied in a separate development program.

Sotagliflozin may benefit a wide variety of diabetic patients based on multiple potential beneficial effects of dual SGLT1/SGLT2 inhibition, and its insulin-independent mechanism of action. Improvements in HbA1c, FPG, and postprandial glucose were observed with sotagliflozin in multiple studies. As anticipated from the mechanism of action, treatment with sotagliflozin resulted in increased urinary glucose excretion (from inhibition of SGLT2) as well as increased levels of the intestinal peptides GLP-1 and PYY (from inhibition of SGLT1). In addition, the improvements in BW and blood pressure (BP) observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

Phase 2 data indicated that sotagliflozin may reduce SBP by 10 to 15 mmHg in patients with SBP \geq 130 mmHg at Baseline, while having no significant effect in patients with SBP <130 mmHg, and did not induce hypotension in normotensive patients. Since this could be of benefit to patients with T2D, this finding is being followed up as an objective in this trial.

SGLT2 inhibitors class have been associated with small decreases of glomerular filtration rate and increased rate of genital infections, which are usually mild and well tolerated in clinical trials. Overall, sotagliflozin has been well-tolerated in all studies to date, with the majority of events assessed as mild to moderate; most of which resolved spontaneously. Serious AEs and discontinuations due to AEs have been limited and balanced between treatment and comparator groups.

Events of special interest (EOSI) are evaluated based on either their potential link to the drug's mechanism of action, events that occur in other SGLT-inhibitor drugs, or regulatory interest/guidance for diabetes products, but found not to be in imbalance in clinical trials. In addition to the identified and potential risks (genital mycotic infections [male and female], metabolic acidosis, DKA, urinary tract infections [UTIs], volume depletion, severe hypoglycemia)

for the sotagliflozin program, other EOSI have been defined. These EOSI are: major adverse cardiac events (MACEs) and other CV events, venous thrombotic events (VTEs), drug-induced liver injuries (DILIs)/alanine aminotransferase increase >3 times the upper limit of normal (ULN), diarrhea, pancreatitis, bone fractures, renal events, malignancies of special interest (including but not limited to: breast, bladder, renal cell, Leydig cell, pancreatic, prostate and thyroid cancer), and AEs leading to amputation.

However, reports of these events have been infrequent and have responded to standard treatment. The improvement in glycemic control, the reductions in weight and BP, and the tolerability and safety profile of sotagliflozin to date demonstrate a favorable benefit-risk assessment for sotagliflozin.

5 STUDY OBJECTIVES

5.1 MAIN OBJECTIVE

To compare the metabolic and gastrointestinal PD effects of an 8 weeks treatment with 400 mg sotagliflozin QD to an 8 weeks treatment with 25 mg empagliflozin QD in mild or moderate hypertensive T2DM patients on a stable treatment regimen with metformin and an ACE inhibitor or ARB under standardized diet conditions.

5.2 OTHER OBJECTIVES

To compare the renal and cardiovascular PD effects of an 8 weeks treatment with 400 mg sotagliflozin QD to an 8 weeks treatment with 25 mg empagliflozin QD in mild or moderate hypertensive T2DM patients on a stable treatment regimen with metformin and an ACE inhibitor or ARB.

To evaluate the safety and tolerability of an 8 weeks QD treatment with 400 mg sotagliflozin or 25 mg empagliflozin in mild to moderate hypertensive T2DM patients on a stable treatment with metformin and an ACE inhibitor or ARB.

To evaluate the PK profile of sotagliflozin in steady state conditions.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a Phase-IIa, single-center, randomized, double-blind, double-dummy, active-control, parallel-group multiple dosing study.

After an initial in-house period to evaluate pharmacodynamic baseline parameters under standardized conditions, patients will be randomized 1:1 to an 8 weeks multiple dosing treatment of 400 mg sotagliflozin QD or empagliflozin 25 mg QD.

Patients will return for a second in-house period to the unit in the last 5 days of treatment for re-analyses of all PD assessments on treatment under the same standardized conditions.

For the 5-days baseline PD assessment period the patients are admitted to the unit on Day-5. They receive standardized meals 3 times a day plus a standardized snack at bedtime during these days. The ABPM is set up for the time of the in-house stay. On specific days, the CV baseline assessment will be performed, ie, pulse wave velocity (Day-2) and echocardiography (Day-3) as described in the flowchart. On Day -1 the further pharmacodynamic baseline assessments are performed starting at 08 a.m. with fractioned 24h urine collection, blood sampling for post-prandial glucose and insulin/glucagon profiles. Feces collection is performed over 48 hours (Days -2 and -1). In the morning of Day 1 the collection period ends and the first dose of IMP is given prior to breakfast. Thereafter the patients are released from the unit.

They continue dosing once daily for 56 days (Days 1 through 56), with at least 3 out-patients visits, one between Days 3-10, one between Days 11-28, one between Days 29 and 49, at least 7 days apart.

On Day 52 the on-treatment PD in-house assessment period starts with admission to the unit and the same schedule of standardized meals as at baseline. On specific days, echocardiography (Day54) and pulse wave velocity (Day55) are assessed again. On Day 56 the on-treatment PD assessments will be performed with identical schedule as at baseline on Day -1. In the morning of Day 57, the collection period ends and the patients can be discharged after breakfast.

The timing of all assessment methods including blood, urine and faces samples will be performed as per study flow charts – please refer to flow charts and Graphical study design in [Section 1](#).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The run-in and treatment periods last altogether 62 days including the day of discharge from the unit at the end of the treatment period. The screening should be performed within 30 days prior to the first admission to the unit, but not later than 2 days prior to first admission to the unit (D-35 to D-7). A follow-up visit has to be performed 7 to 14 days after last dosing (D63-70).

Duration of each part of the study for one patient:

- Screening: 2-30 days.
- Run-in period: 5 days.
- Treatment period: 56 days.
- Follow-up: 7 to 14 days.
- Total study duration: 70-105 days.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as the day the last patient completed his/her last visit planned in the protocol.

6.3 INTERIM ANALYSIS

One or more interim analyses may be performed in case of unexpected safety concerns and/or for internal decision making. In this case a Study Medical Manager (and potentially a Statistician and a Statistical Programmer) will work independently to the study team on this interim analysis to ensure the blinding is preserved notably toward the Investigator. A dissemination plan of the results should be established upfront before the unblinding. The outcome of this interim analysis may lead to early termination of the trial, continuation without any changes, or continuation with changes.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS PLANNED

A total of up to 40 T2DM patients with mild or moderate hypertension are to be enrolled into the study.

7.2 INCLUSION CRITERIA

Demography

- I 01. Male or female patients with T2DM (diagnosed at least 1 year before screening visit), between 18 and 75 years of age, inclusive, with:
- Hypertension grades 1 or 2 as defined by the ESH/ESC (33) at screening, ie, SBP 140-179 mmHg and DBP 90-109 mmHg (after 10 minutes resting in supine position, measurement in triplicate with each measurement to be within this range at screening). If the BP range is not met at screening, one repeat measurement at another occasion is allowed prior to inclusion into the study.
 - HbA1c at screening between 6.5% and 10%.
- I 02. On a stable treatment with metformin, ie, no change in dose regimen or in dose levels in the last 3 months prior to screening and until randomization.
- I 03. On a stable treatment with an ACE inhibitor or an angiotensin receptor blocker, ie, no change in dose regimen or in dose levels in the last 4 weeks prior to screening and until randomization.
- I 04. Body weight between 50.0 and 120.0 kg, inclusive, if male, and between 40.0 and 105.0 kg, inclusive, if female, body mass index between 18.0 and 35.0 kg/m², inclusive.

Health status

- I 05. Normal heart rate at screening after 10 minutes resting in supine position:
- 50 bpm <heart rate (HR) <100 bpm.
- I 06. Standard 12-lead electrocardiogram (ECG) parameters after 10 minutes resting in supine position without any clinically significant abnormalities as judged by the Investigator based on age, gender and medical history of the individual patient.

- I 07. Female patient must use a double contraception method including a highly effective method of birth control, except if she has undergone sterilization at least 3 months earlier or is postmenopausal.
The accepted double contraception methods include the use of intrauterine device or hormonal contraception in addition to one of the following contraceptive options: (1) condom; (2) diaphragm or cervical/vault cap; (3) spermicide. Menopause is defined as being amenorrheic for at least 2 years with plasma FSH in the laboratory's range for postmenopausal phase ([Appendix A](#)).
- I 08. Male patient, whose partners are of childbearing potential (including lactating women), must accept to use, during sexual intercourse, a double contraception method according to the following algorithm: (condom) plus (intra-uterine device or hormonal contraceptive) from the inclusion into the study up to 3 months after the last dosing ([Appendix A](#)).
- I 09. Male patient, whose partners are pregnant, must use, during sexual intercourse, a condom from the inclusion up to 3 months after the last dosing.
- I 10. Male patient has agreed not to donate sperm from the inclusion up to 3 months after the last dosing.

Regulations

- I 11. Having given written informed consent prior to undertaking any study-related procedure.
- I 12. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.
- I 13. Not under any administrative or legal supervision.

Specific to the study

- I 14. Estimated GFR (as calculated with MDRD formula) at screening must be 60 mL/min/1.73m² or higher.

7.3 EXCLUSION CRITERIA

Medical history and clinical status

- E 01. Patients with severe anemia, severe cardiovascular, gastrointestinal, respiratory, neurological, osteomuscular, psychiatric, or active malignant tumor or other major systemic disease or patients with infectious disease, signs of acute illness, or short life expectancy making implementation of the protocol or interpretation of the study results difficult (as evaluated by detailed medical history and complete physical and laboratory examination).
- E 02. Patients with renal impairment Stage III or higher.
- E 03. Heart failure NYHA III/IV.

- E 04. Any clinically significant abnormality in echocardiography performed at screening as judged by the Investigator based on age, gender and medical history of the individual patient.
- E 05. History of myocardial infarction within the last 12 months prior to screening.
- E 06. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol (eg, long-term systemic glucocorticoids) and refusing or unable to take alternative treatment.
- E 07. Type 1 diabetes mellitus.
- E 08. Secondary hypertension of any etiology (eg, renovascular disease, pheochromocytoma, Cushing's syndrome).
- E 09. Clinically significant pulmonary hypertension, in particular WHO Classes IV (Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)) and V (miscellaneous) (34).
- E 10. Diabetic retinopathy.
- E 11. History of diabetic ketoacidosis or non-ketotic hyperosmolar coma within 12 weeks prior to the screening visit.
- E 12. History of severe hypoglycemia resulting in hospitalization or unconsciousness/seizures within 6 months prior to the screening visit.
- E 13. History of prior gastric or intestinal surgical procedure including gastric banding within 3 years before the screening visit. Any gastrointestinal surgery with removal of part of the bowels or the stomach.
- E 14. Presence at screening or recurrent occurrence of cholelithiasis within 12 months prior to first dosing.
- E 15. Cholecystectomy within 12 months prior to first dosing.
- E 16. History of unexplained pancreatitis, chronic pancreatitis, stomach/gastric surgery, inflammatory bowel disease.
- E 17. Patients with hepatic impairment of Child-Pugh Class B or C.
- E 18. AST and/or ALT: >3 times the upper limit of the normal laboratory range.
- E 19. Total bilirubin: >1.5 times the upper limit of the normal laboratory range (except in case of Gilbert's syndrome).
- E 20. Amylase and/or lipase $>3 \times \text{ULN}$.
- E 21. Hemoglobin $<10.0 \text{ g/dL}$ and/or neutrophils $<1,500/\text{mm}^3$ and/or platelets $<100,000/\text{mm}^3$.
- E 22. Hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products within 3 months prior to the time of screening.

- E 23. Patient is unwilling to perform SMPG, and complete the patient's diary as required per protocol.
- E 24. Contraindication to empagliflozin as per local labelling.
- E 25. The participant works a night (third) shift (defined as 11 PM [2300] to 7 AM [0700]).
- E 26. Weight change of more than 5 kg during the 3 months preceding the screening visit.
- E 27. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month).
- E 28. Blood donation or any blood loss more than 300 mL within 2 months before inclusion.
- E 29. Presence or history of drug hypersensitivity, or presence of rheumatic or autoimmune disease.
- E 30. History or presence of drug or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis).
- E 31. If female, pregnancy (defined as positive β -HCG blood test), breast-feeding.

Interfering substance

- E 32. Any hypertensive treatment with other drugs than ACE inhibitors, angiotensin receptor blockers in the last 4 weeks prior to screening, eg, thiazides, spironolactone, loop diuretics.
- E 33. Treatment with a glitazone, DPP-IV inhibitor, a sulfonyl urea, a meglitinide (glinides), GLP-1 agonists and/or an SGLT2 inhibitor within the last 3 months prior to screening.
- E 34. Previous Insulin use >1 month (at any time, aside from treatment of gestational diabetes).
- E 35. On any medication that is metabolized by P-glycoprotein (P-gp), eg, digoxin.
- E 36. Patient who has taken other investigational drugs or prohibited therapy for this study within 3 months or 5 half-lives from screening or randomization, whichever is longer.
- E 37. Use of systemic glucocorticoids (excluding topical or ophthalmic, application or inhaled forms) for more than 10 consecutive days within 90 days prior to the screening visit.

General conditions

- E 38. Any patient who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.
- E 39. Patients considered by the Investigator or any sub Investigator as inappropriate for this study for any medical, psychological, social, or geographical reason (eg patients unable to fully understand the nature, scope, and possible consequences of the study; patients unable to fully understand patient's study documents; impossibility to meet specific protocol requirements, such as scheduled visits; being unable or unwilling to do self-pricking and blood glucose monitoring using the sponsor-provided blood glucose meter at home; likelihood of requiring treatment with drugs not permitted by the clinical study protocol, night shift workers, etc).

- E 40. Any patient in the exclusion period of a previous study according to applicable regulations.
- E 41. Any patient who cannot be contacted in case of emergency.
- E 42. Any patient who is the Investigator or any subinvestigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study.

Biological status

- E 43. Positive result on any of the following tests: hepatitis B surface (HBs Ag) antigen, anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency Virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab).
- E 44. Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
- E 45. Positive alcohol test.

Specific to the study

- E 46. Urinary tract infection or genitourinary mycotic infections in the last 4 weeks prior to start of dosing.
- E 47. Any antibiotic treatment in the last 6 months prior to dosing.
- E 48. Any diarrhea at inclusion or a gastrointestinal infection in the last 4 weeks prior to start of dosing.
- E 49. Presence or history of any chronic disease of the bowels or indigestions.
- E 50. Patients who are vegan, a vegetarian or have any other dietary restriction.
- E 51. Presence of any contraindication to receive IV indocyanine green (hypersensitivity of indocyanine green/sodium iodide, iodine allergy, clinically manifest hyperthyreosis, autonomous thyroid adenoma or focal and diffuse thyroid autonomy).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Treatment A (Test):

Sotagliflozin: 200 mg tablet

Sotagliflozin 400 mg administered as two (2) 200-mg tablets QD prior to the first meal of the day for 56 days (D1 to D56).

with

Empagliflozin placebo: capsule

One empagliflozin placebo capsule will be administered QD prior to the first meal of the day for 56 days (D1 to D56).

The 2 tablets of 200 mg sotagliflozin and the empagliflozin placebo capsule have to be taken orally together with 240 mL of water once a day prior to the first meal of the day (during in-house days at 8:00 a.m. directly prior to breakfast).

Treatment B (Reference):

Empagliflozin: 25 mg capsule

Empagliflozin administered as one 25 mg capsule QD prior to the first meal of the day for 56 days (D1 to D56).

with

Sotagliflozin placebo: tablet

Two sotagliflozin placebo tablets will be given QD prior to the first meal of the day for 56 days (D1 to D56).

The 2 tablets of sotagliflozin placebo and the 25 mg empagliflozin capsule have to be taken orally together with 240 mL of water once a day prior to the first meal of the day (during in-house days at 8:00 a.m. directly prior to breakfast).

All investigational medicinal products (IMPs) are supplied by the sponsor

For conditions, details are provided into [Section 12.1.4](#).

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

Indocyanine-green (intravenous bolus/ 0.25 mg/kg over 5 seconds), please refer to [Section 9.1.3.8](#).

Indocyanine-green will be provided by study site.

8.3 OTHER PRODUCTS

Not applicable.

8.4 DESCRIPTION OF BLINDING METHODS

8.4.1 Methods of blinding

Patients will receive either test treatment (T, Treatment A) or reference treatment (R, Treatment B) in a randomized, double-blind, double-dummy, active-control, and parallel-group multiple dosing design.

To maintain blinding and double dummy, sotagliflozin and its matching placebo tablets (including packaging) and empagliflozin and its matching placebo capsules (including packaging) will be blinded and indistinguishable.

In accordance with the double-blind, double dummy design, the Investigators and all clinical site staff as well as Sponsor's clinical trial team members will remain blinded to study treatment on sotagliflozin /placebo and empagliflozin / placebo and will not have access to the randomization (treatment codes) except under exceptional medical circumstances. Consequently, the double blind, double dummy will be maintained.

The site pharmacist and his/her assistant, if necessary, will be responsible for allocation of the double blind, double dummy treatments to the patients. For this purpose the pharmacist will receive from the Sponsor the :

- Randomization list allocating the patients to the two treatment arms (one with sotagliflozin + empagliflozin placebo and one with sotagliflozin placebo + empagliflozin).
- Two packaging lists, one for sotagliflozin and its matching placebo and one for empagliflozin and its matching placebo, respectively, to link the blinded treatment numbers to the treatments.

Sotagliflozin / matching placebo tablets and empagliflozin/ matching placebo capsules kits will be delivered by the Sponsor to the local site pharmacists, as well as the unblinded randomization list and the packaging lists. In order to keep the blind, IMP will be stored under the responsibility of the pharmacist.

The IMPs is readily labelled with the blinded treatment numbers. The pharmacist needs to prepare re-grouping of treatment according to the randomization list, using the two packaging lists to allocate appropriate treatment numbers according to the randomization code. The re-grouped, blinded IMP will be provided to the Investigator / clinical personnel, only indicating the 4 treatment numbers prepared per patient, as well as the order how to be used for randomization.

For further details, please refer to the pharmacy manual.

The administration of investigational medicinal product (IMP) will be performed in accordance to the patient randomization list.

The pharmacist and his/her assistant will confirm and guarantee not to disclose the unblinded randomization list and packaging lists to anybody and will keep it in a locked area which is not accessible for Investigator, the study site and Sponsor's clinical trial team members.

In order to keep the blind, no unblinded IMP will be provided to the Investigator or other members of the clinical team at the site.

While the pharmacist/assistant is preparing the treatments, no other person should have access to the room in which the preparation takes place.

The Investigator, the study site and Sponsor's clinical trial team members will not have access to the randomization (treatment) code except under circumstances described in [Section 8.8](#).

For further information, please refer to the pharmacy manual.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients are randomized to either:

- Treatment group A: sotagliflozin 400 mg QD.
- Treatment group B: empagliflozin 25 mg QD.

with a 1:1 ratio.

A randomized patient is defined as a patient who signed the informed consent and has been allocated to a randomized treatment.

A patient cannot be randomized more than once in the study.

Before randomizing a patient on Day 1, the Investigator or designee should check if the patient complies with all inclusion/exclusion criteria. Patients will be then assigned a randomized treatment in a preplanned, chronological order.

Potential replacement patients will receive the same treatment as the withdrawn patient.

8.6 PACKAGING AND LABELING

Sotagliflozin 200 mg tablets or their matching placebo will be provided by the Sponsor in bottles. Empagliflozin 25 mg capsules or their matching placebo will be provided by the Sponsor in boxes.

Packaging will be undertaken in accordance with the administration schedule.

The appropriate number of packages will be dispensed (please refer to [Section 1.2](#)).

The content of the labeling is in accordance with the local regulatory specifications and requirements.

Storage conditions and use-by-end date are part of the label text.

Treatment labels will indicate the treatment number (used for treatment allocation and reported in the e-CRF.)

8.7 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing IMP provided by the Sponsor in a secure and safe place in accordance with local regulations, labeling specifications, policies and procedures.

Control of storage conditions for IMP provided by the Sponsor, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi IMP should be managed according to the rules provided by the Sponsor.

Storage conditions are available on the IMP labels.

Sotagliflozin or its matching placebo tablets should be stored between 15°C and 30°C (59°F to 86°F).

Empagliflozin capsules or its matching placebo tablets should be stored between 2°C and 30°C (36°F to 86°F).

Refer to pharmacy manual for more information.

8.8 RANDOMIZATION CODE BREAKING DURING THE STUDY

Please refer to [Section 9.7](#).

In case of an adverse event (AE), the code will not be broken except in the circumstances when knowledge of the IMP is essential for treating the patient. If possible, a contact should be initiated with the Sponsor's monitoring team or medical expert before breaking the code.

For each patient, code-breaking material that contains the name of the treatment is supplied as envelopes. It is to be kept in a safe place on site throughout the clinical trial. The Sponsor will retrieve all code-breaking material (opened or sealed) on completion of the clinical trial.

If the blind is broken, the Investigator will document the date of opening and reason for code breaking in source data.

The code could be broken by the Sponsor during the study conduct as per internal procedure. If any information is considered to help the evaluation of the safety, it should be available before unblinding.

8.9 RESPONSIBILITIES

The Investigator, the clinical site pharmacist, or other personnel allowed to store and dispense IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All IMPs shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP provided by the Sponsor (deficiency in condition, packaging, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure.

A potential defect in the quality of IMP provided by the Sponsor may be patient to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP provided by the Sponsor to a third party, allow the IMP provided by the Sponsor to be used other than as directed by this clinical trial protocol, or dispose of IMP provided by the Sponsor in any other manner.

8.10 CONCOMITANT MEDICATION

The use of concomitant medication should not be allowed during the study unless specified in the inclusion criteria or study procedures or medically required. However, if a specific treatment is required for any reason, an accurate record must be entered in the eCRF, including the name of the medication (INN), daily dosage, and duration of use. The Sponsor must be informed within 2 working days via email or fax, with the exception of treatment of headache.

The patients should be on stable treatment with ACE inhibitor or ARB for at least 4 weeks (ie, no change in drug, no dose adjustment); metformin as s diabetic comedication should be stable for at least 3 months.

Patients with these treatments are not allowed to be included in this clinical study:

- -thiazides, spironolactone or loop diuretics.
- -insulins, DPP-IV inhibitors, GLP-1 agonists, sulfonylureas (SUs), SGLT2 inhibitors, glitazones or meglitinides ("glinides").

8.11 TREATMENT ACCOUNTABILITY AND COMPLIANCE

- Compliance of IMP/NIMP:
 - During in-house days, the IMP will be administered under direct medical supervision, and an appropriate record will be made in the source data by the Investigator or his/her delegate, in the other days the patient has to record the IMP administration in the diary,
 - The Investigator records the dosing information on the appropriate page(s) of the case report form,
 - Plasma drug assay results, if relevant.
- Accountability of IMP/NIMP provided by the Sponsor:
 - The Investigator counts the number of tablets and capsules, remaining in the returned packs, and then fills in the treatment log form,
 - The monitoring team in charge of the study then checks the case report form data by comparing them with the IMP and appropriate treatment log forms.

8.12 RETURN AND/OR DESTRUCTION OF TREATMENTS

For IMP provided by the Sponsor:

IMPs reconciliation and detailed treatment log of the remaining and destroyed Investigational Product will be established by the pharmacist and countersigned by the Investigator and the monitoring team, but only after official database lock. Any documentation potentially leading to an unblinding must be stored confidential under locked condition with restricted controlled access until official code breaking of the study after database lock.

The Investigator (or his/her delegated pharmacist) will not destroy the unused Investigational Product once the IMP reconciliation is achieved and unless the Sponsor provides written authorization. A potential defect in the quality of Investigational Product may be patient to initiation of a recall procedure by the Sponsor. In this case, the Investigator (or his delegated pharmacist) will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

For NIMP not provided by the Sponsor:

Tracking and reconciliation must be completed by the Investigator according to the system proposed by the Sponsor.

The destruction can be performed at site depending on IMP specificities and local requirements or IMP can be returned to the Sponsor for destruction.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PHARMACODYNAMIC PARAMETERS

9.1.1 Main endpoints

- Urine:
 - 24h urinary glucose excretion,
 - Further 24h urine parameters:
urine volume, electrolytes (sodium, potassium, calcium, magnesium, phosphate), pH, creatinine, uric acid, urea; albumin, proteins, ketones (β -hydroxybutyrate, total ketone bodies).
- Feces (collection period 48h):
 - Fecal sodium, potassium, chloride,
 - SCFAs (butyrate, propionate, acetate) and glucose excretion,
 - Also average volume and weight/day (incl. water contents),
 - pH/bicarbonate,
 - Firmicutes:Bacteroidetes ratio.
- 14 hour plasma profiles of glucose/insulin/intact pro-insulin/C-peptide/glucagon/GLP1 (active and total), PYY and pancreatic polypeptide (PP) over 14 hours after standardized meals (MMTT) at breakfast, lunchtime and dinner, performed at baseline and on the last day of treatment.

9.1.2 Further endpoints

- Average mean, systolic and diastolic 24h blood pressure from ABPM, change from baseline.
- Pulse wave velocity:
 - Carotid-radial pulse wave velocity and,
 - Carotid-femoral pulse wave velocity and,
 - Radial augmentations index.
- Echocardiography:
 - Velocity time index (VTI) over left ventricular outflow tract (LVOT),
 - Left ventricular end-diastolic diameter (LVEDD),
 - Left ventricular ejection fraction (LVEF),
 - Tissue Doppler imaging (TDI) with (E/e') ratio and (E/A) ratio,
 - Diastolic filling patterns.

- Cardiovascular laboratory panel (serum/plasma):
 - PRA (plasma renin activity), AT1/2 (angiotensin 1/2), aldosterone,
 - NT-proBNP, CT-pro vasopressin (Copeptin),
 - Erythropoietin, hematology.
- Fasting metabolic laboratory panel (serum/plasma):
 - FPG, plasma insulin + intact proinsulin, C-peptide, glucagon,
 - Plasma acetate, propionate; triglycerides, FFA,
 - β -hydroxybutyrate, total ketone bodies.
- Average mean, av. systolic and av. diastolic blood pressure (ABPM) at daytime (6 am. until 11 pm.) and during night (11 pm. until 6 am.).
- Seated SBP/DBP diurnal profile under in-house conditions; on Day -3 and Day 54;
- Seated SBP/DBP single measurement on out-patients visits and on the mornings of Day -1, Day 1, Day 56, and Day 57.
- Plasma volume (by indocyanine-green method)
- Following parameters from fractionated 24h urine collection:
 - Urinary glucose excretion,
 - Urine volume, electrolytes (sodium, potassium, calcium, magnesium, phosphate), pH,
 - Creatinine, uric acid, urea,
 - Albumin, proteins,
 - Ketones (β -hydroxybutyrate, total ketone bodies).

Four urinary fractions are collected over 24h as described in [Section 1.3](#).

- SMPG diurnal profile on Days -1 and 56; at least once per week during out-patients treatment period.
- Fasting SMPG on all in house days (beyond Days -1 and 56 who have a 5-point profile) and at least twice per week during out-patients treatment period.
- CGM: average diurnal glucose.

Further CGM parameters:

- Percent (%) of time in plasma glucose range of 80-140 mg/dL (4.4-7.8 mmol/L).
- Percent time above the upper limit (>140 mg/dL; >7.8 mmol/L) of glycemic range (%time in hyperglycemia).
- Percent time below the lower limit (<80 mg/dL; <4.4 mmol/L) of glycemic range (%time in hypoglycemia).
- Further CGM based parameters may be derived and full details will be specified in the Statistical Analysis Plan (SAP).
- Additional PD parameters may be added if needed to evaluate the objectives of the study.

9.1.3 Assessment methods

9.1.3.1 24H Urine collection

The 24H urine collections are performed on Day -1 and Day 56. The overall collection starts after the first void in the morning of Day -1/Day 56 and continues until the first void in the morning of Day 1/Day 57, inclusively.

The 24H urine collection is fractioned for each meal of the day. The 1st fraction starts after the first void in the morning and collects until a last void prior to lunch (T0H-T5H), inclusively. The 2nd fraction starts with lunch and ends with a last void prior to dinner (T5H-T10H). The 3rd fraction starts with dinner and lasts until a last void prior to the bedtime snack (T10H-T14H). The 4th fraction starts with the bedtime snack and lasts until the first void in the next morning, inclusively (T14H-T24H).

Patients have to be instructed by medical personnel to void a last time prior to each meal within 15 minutes prior to the start of the respective meal.

For the parameters to be measured, please see [Section 9.1.1](#).

9.1.3.2 48H Feces Collection

The feces collections will be performed over 48 hours from Day -2 at 00:00H until Day -1 at 24:00H, and from Day 55 at 00:00H until Day 56 at 24:00H.

The details of the stool sampling will be described in a separate lab manual.

The stools have to be put on dry ice and have to be kept at -80°C until analysis. The number of samples to be taken from the stool per excretion will be described in the laboratory manual.

For the parameters to be measured, please see [Section 9.1.1](#).

9.1.3.3 High-calorie Meal Challenge Tolerance Test

All the meals during the two in-house periods must be fully standardized with exactly matching contents and amounts on matching days and time of the two in-house periods, ie, meals on Day -5 have to match meals on Day 52, on Day -4 have to match Day 53 etc.

After the scheduled dosing and the standardized breakfast on Day -1 and Day 56, a high-calorie mixed meal of a size as specified in the FDA guidance for industry “Food-Effect Bioavailability and Fed Bioequivalence Studies” will be given at lunchtime around 1 p.m, ie, 5 hours after IMP dosing. The meal will contain approximately 1000 calories (kcal) with about 150, 500, and 350 calories from protein, carbohydrate, and fat, respectively, and has to be identical on Day -1 and Day 56. The contents should match the common standards for a lunch in the country of the site and must contain about 50% fraction of large carbohydrates over total carbohydrates. Further specifications will be written in a separate document (35).

Prior to the start of the meals of Day -1 and Day 56 and at various timepoints after the meals, venous blood samples will be taken to assess glucose, insulin, intact proinsulin, C-peptide, glucagon, active and total GLP1 and PYY. Time points are as described in the flow chart in [Section 1.3](#) and include breakfast, lunch, dinner, and the bed time snack, which are all standardized meals. The contents of all meals on these two days (D-1, D56) have to be provided by the dietician, with carbohydrates, fat, protein contents.

From blood sampling at each time point, the parameters as described in [Table 1](#) will be analyzed. Assuming 14 blood sampling time points per profile, patients will have a blood volume of 182 mL drawn once each, at baseline and at end of treatment.

Table 1 - Summary of blood sampling for the post-meal profiles on Day -1 and Day 56

| Postprandial profile of metabolic parameters | Parameter analysed from one sample | Volume matrix | Volume Blood (ml) |
|----------------------------------------------|--------------------------------------|------------------------|-------------------|
| NaF plasma | glucose | 1.2 ml | 2.5 |
| Serum | insulin, C-peptide, pro-insulin | 2 aliquots each 0.6 ml | 2.5 |
| P800 plasma | glucagon, GLP1 active and total, PYY | 3 aliquots each 1.3 ml | 8 |

Table 2 - Number of blood sampling for post-prandial profiles test

| | NaF plasma | Serum | P800 plasma |
|------------------------------|------------|---------|-------------|
| By patient / Day -1 | 14 | 14 | 14 |
| By patient / Day 56 | 14 | 14 | 14 |
| Total by patient | 28 | 28 | 28 |
| Total for study (n patients) | 28 * 40 | 28 * 40 | 28 * 40 |

9.1.3.4 ABPM

The variability of ABPM has been shown to have a smaller within-patient SD as compared to seated BP measurements ([14](#)). Therefore, this methodology has been selected to evaluate the effect on blood pressure.

The 24-hr blood pressure will be measured using an ambulatory blood pressure monitor. The 24-hour blood pressure monitoring will be performed during both in-house periods on the days indicated, starting at 08:00 a.m. prior to breakfast until 24 hours later.

Measurements will be made in the hours from 07:00 to 23:00 (daytime) every 15 min and every 30 minutes in the period from 23:00 to 07:00 (nighttime). To be valid, the full 24-hour recording has to include a minimum of 80% of valid blood pressure readings (ie, 65 readings out of 81 planned), and not missing more than 2 hours of consecutive measures during daytime or 4 hours of consecutive measures during night time.

The first two days of the recordings in both periods (D-5, D-4, D52, D53) are not to be used for PD analysis. Only the last 3 days of these periods can be used for PD analysis, ie, D-3, D-2, D-1, D54, D55, D56). For the safety analyses all ABPM measurements will be evaluated.

9.1.3.5 Pulse Wave Velocity

Pulse wave velocity will be assessed by the Investigator during the in-house days at baseline (D-2) and on treatment (D55) at matching times of the day. The device to be used is (Sphygmocor XCEL; or equivalent device) and parameters that will be measured are carotid-radial pulse wave velocity, carotid-femoral pulse wave velocity and radial augmentations index at minimum.

9.1.3.6 Echocardiography

An echocardiography will be assessed by the Investigator during the in-house days at baseline (D-3) and on treatment (D54) at matching times of the day. The Investigator will use the same device (GE Vivid E9, or equivalent device) for the baseline and the on-treatment measurements.

The minimum parameters to be recorded are velocity time index (VTI) over left ventricular outflow tract (LVOT), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), tissue Doppler imaging (TDI) and the diastolic filling patterns (32).

At screening an echocardiography is performed to exclude any significant cardiac disease or abnormality. This examination has to be performed according to the national medical standards at the site.

9.1.3.7 Seated SBP/DBP diurnal profile

Repetitive seated blood pressure measurements will be performed on Day -3 and on Day 54 to compare the effect size detectable with this method to ABPM measurements on an exploratory basis.

On these two days, there will be 5 measurements performed over the day, 1 prior to breakfast (0H), 1 prior to lunch (5H), 1 two hours after lunch (7H), 1 prior to dinner (10H), 1 at bedtime (14H).

For each seated blood pressure measurement, the patient will have 3 measurements taken while seated over 15 minutes (min. 5 minutes between each reading). Prior to the first measurement, the patient should remain seated at rest for at least 5 minutes. The value for analysis will be the mean of these 3 measurements.

On further selected days, seated blood pressure will be measured only in the morning before breakfast, i.e. on Day -1, Day 56. On Day 1 and Day 57 seated blood pressure will be measured in the morning predose/ before breakfast. Also, seated blood pressure will be measured on the out-patient visits (no diurnal profiles).

For safety measurements of blood pressure (supine position) please refer to [Section 9.2.2](#).

9.1.3.8 Plasma Volume Measurement

The plasma volume will be estimated by means of the indocyanine-green method as described before (30).

On Day -3 (baseline) and on Day 54 (on treatment), patients will be given an intravenous bolus injection of 0.25 mg/kg indocyanine-green over 5 seconds into a large arm vein. Blood samples (2 mL heparin plasma) will be collected from the contralateral arm every 30 seconds over the period from 2 to 5 minutes after the bolus injection (7 samples). The special handling of the samples during processing, such as protection from light, will be described in a lab manual.

Plasma indocyanine-green concentrations will be determined using a validated high-performance liquid chromatography (HPLC) analytical method at MLM Medical Labs GmbH, Dohrweg 63, 41066 Moenchengladbach, Germany.

The decline in indocyanine-green concentration over time will be used to back-extrapolate to the status after injection. A physiologically based mathematical model of indocyanine-green kinetics will be used then to estimate the plasma volume (30).

9.1.3.9 Fasting pharmacodynamic blood samplings

The lab parameters as listed in Table 3 and Table 5 are taken twice from each patient in fasting conditions during the in-house periods, once on Day -1 as baseline and once on Day 56 (predose) for on-treatment assessments.

Table 3 - Summary of blood sampling for the cardiovascular panel

| CV parameter panel | Parameter analysed from one sample | Volume matrix | Volume Blood (ml) |
|--------------------|---------------------------------------|------------------------|-------------------|
| P800 plasma | AT 1 | 1 ml | 2 |
| EDTA plasma | PRA, AT2 | 3 aliquots each 1.3 ml | 8 |
| Serum | aldosterone, NT-proBNP, Copeptin, EPO | 4 aliquots each 1.0 ml | 8 |
| Hematology tube | HCT, Hb, FBC | | 2.7 |

Table 4 - Number of blood samples for the fasting cardiovascular panel

| | EDTA plasma | Serum | P800 plasma |
|------------------------------|-------------|--------|-------------|
| By patient / Day -1 | 1 | 1 | 1 |
| By patient / Day 56 | 1 | 1 | 1 |
| Total by patient | 2 | 2 | 2 |
| Total for study (n patients) | 2 * 40 | 2 * 40 | 2 * 40 |

Table 5 - Summary of blood sampling for the fasting metabolic panel

| Fasting metabolic parameter panel: | Parameter analysed from one sample | Volume matrix | Volume Blood (ml) |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--------------------------|
| NaF plasma | glucose, propionate/acetate | 2 aliquots each 1.2 ml | 5 |
| Serum | insulin, C-peptide, pro-insulin, triglycerides, FFA (low bench top stability), β -hydroxybutyrate (low bench top stability), total ketone bodies (low bench top stability) | 2 aliquots each 1.2 ml | 5 |
| P800 plasma | glucagon | 1 ml | 2 |

Table 6 - Number of blood samples for the fasting metabolic panel

| | NaF plasma | Serum | P800 plasma |
|------------------------------|-------------------|--------------|--------------------|
| By patient / Day -1 | 1 | 1 | 1 |
| By patient / Day 56 | 1 | 1 | 1 |
| Total by patient | 2 | 2 | 2 |
| Total for study (n patients) | 2 * 40 | 2 * 40 | 2 * 40 |

9.1.3.10 Continuous Glucose Monitoring

During the two in-house periods patients will have their glucose monitored with a Continuous Glucose Monitoring (CGM) System. The device to be used by the site is a DexCom system, placing a subcutaneous sensor abdominally.

The first two days of the recordings in both periods (D-5, D-4, D52, D53) are not to be used for PD analysis. Only the last 3 days of these periods can be used for PD analysis, ie, D-3, D-2, D-1, D54, D55, D56). For the safety analyses all CGM measurements will be evaluated.

Patients will be blinded to the CGM measurements and have to use during the in-house periods the SMPG for glucose monitoring.

Parameters to be analyzed from the CGM recordings are:

- Average diurnal glucose exposure.
- Percent (%) of time in plasma glucose range of 80-140 mg/dL (4.4-7.8 mmol/L).
- Percent time above the upper limit (>140 mg/dL; >7.8 mmol/L) of glycemic range (%time in hyperglycemia).
- Percent time below the lower limit (<80 mg/dL; <4.4 mmol/L) of glycemic range (%time in hypoglycemia).

- Diurnal glucose stability as measured by mean amplitude of glucose excursions (MAGE).
- Further parameters will be specified in the SAP.

9.1.4 Assessment schedule

The assessment timing can be found in the period flow chart ([Section 1.3](#)).

9.2 SAFETY

Assessments for safety include AEs, clinical laboratory assessments, physical examination, ECG, weight and vital signs.

The following safety endpoints will be assessed:

- Adverse events, AEs leading to discontinuation from the IMP, adverse events of special interest (AESIs), Events of Special Interest (EOSIs), SAEs and deaths.
- Hypoglycemia (severe, documented symptomatic, or asymptomatic).
- Clinical laboratory results, vital signs and ECG results.

9.2.1 Baseline demographic characteristics:

Baseline demographic characteristics will consist of:

1. Age (years).
2. Height (cm).
3. Body mass index.
4. Race/ethnicity.
5. Gender.
6. Duration of T2DM (Month/ year of Diabetes diagnosis).
7. Medications to treat T2DM (and start date).
8. Year / month of diagnose of hypertension.
9. Medications to treat hypertension (with start and end date, as applicable).
10. Start of ACE inhibitor or ARB treatment (start date).

Patient race or ethnicity will be collected in this study because analysis of results according to race/ethnicity are required by several health authorities (eg, black population for FDA in United States, Japanese population for the PMDA in Japan or Chinese population for the CFDA in China).

9.2.2 Safety assessment at screening, at baseline and during the study

The tolerability investigations at baseline and during the study will consist of:

1. Physical examination:
 - At screening: cardiovascular system, heart and respiratory auscultation, thyroid, abdomen, nervous system, skin and mucosae, and musculo-skeletal system and peripheral arterial pulse; pupil, knee, Achilles, and plantar reflexes; peripheral lymph nodes and abdomen examination, only findings relevant to the study are to be documented.
 - At Day -5, Day 52 and end of study: physical examination (includes at a minimum: heart and respiratory auscultation; peripheral arterial pulse; pupil, knee, Achilles, and plantar reflexes; peripheral lymph nodes and abdomen examination).
2. Body weight (kg).
3. Auricular body temperature.
4. Vital signs measurements for safety evaluation (heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine resting position and – at screening – also after 3 minutes in standing position). The supine measurements are performed in triplicate with the mean values being entered into the CRF. For screening, all 3 values are entered into the CRF and have to be within the range given in the inclusion criteria.
At some time points, only a single seated blood pressure measurements is scheduled, which has to be performed after 5 minutes in seated position.
For repetitive seated blood pressure measurements for a pharmacodynamics blood pressure profile, please refer to [Section 9.1.3.7](#).
5. Laboratory tests (in fasting conditions at least for 10 hours for blood samples):
 - Hematology: red blood cell count, hematocrit (incl. HbA1c), hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
 - Coagulation: international normalized ratio, and activated partial thromboplastin time.
 - Biochemistry:
 - Plasma/serum electrolytes: sodium, potassium, chloride, calcium; bicarbonate,
 - Liver function: AST (aspartate aminotransferase), ALT (alanine aminotransferase), alkaline phosphatase, gamma-glutamyl transferase, total and conjugated bilirubin,
 - Renal function: urea, creatinine, uric acid,
 - Metabolism: glucose (fasting), albumin, total proteins, total and HDL cholesterol, triglycerides,
 - Potential muscle toxicity: creatine phosphokinase (CPK). If elevated, analyze CK-MB.

6. Archival blood sample: a 15 mL (or three 5 mL) blood sample(s) will be collected into a dry, red topped tube, decanted at room temperature during 30 minutes then centrifuged at approximately 1500 g for 10 minutes at 4°C; the serum will then be transferred into 3 storage tubes, which will be immediately capped and frozen in an upright position at -20°C. This sample will be used if any unexpected safety issue occurs to ensure that a pre-administration baseline value is available for previously non-assessed parameters (eg, serology). If this sample is not used, the Investigator will destroy it after the Sponsor's approval.
7. Serology tests: hepatitis B antigen, hepatitis C antibodies, anti-HIV1 and anti-HIV2 antibodies.
8. Urinalysis: proteins, glucose, erythrocytes, leucocytes, ketone bodies, creatinine, uric acid, and pH:
 - Quantitative: Glucose, ketone bodies, creatinine, uric acid, pH: these parameters are analyzed quantitatively from each urine sample.
 - Qualitative: A dipstick is to be performed on a freshly voided specimen for qualitative detection of proteins, erythrocytes and leukocytes using a reagent strip.
 - Secondary quantitative: A quantitative measurement for protein, erythrocytes, and leucocytes count will be required in the event that the urine sample test is positive for any of these parameters by urine dipstick (eg, to confirm any positive dipstick parameter by a quantitative measurement).
9. Urine drug screen: amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.
10. Alcohol breath or plasma test.
11. If female, beta-HCG (beta-human chorionic gonadotropin) blood tests.
12. If postmenopausal female, plasma follicle-stimulating hormone.
13. Adverse events, spontaneously reported by the patient or observed by the Investigator, will be monitored;
14. Standard 12-lead ECGs (safety ECGs) are recorded after at least 10 minutes in supine position using an (type of recorder and company to be added) electrocardiographic device. The electrodes will be positioned at the same place for each ECG recording throughout the study.

Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:

- A single 12-lead ECG (25 mm/s, 10mm/mV) printout with heart rate, PR, QRS, QT, QTc automatic correction evaluation, QTc Fridericia (by the ECG device), including date, time, and number of the patient, signature of the research physician, and at least 3 complexes for each lead. The Investigator's medical opinion and automatic values will be recorded in the e-CRF. This printout will be retained at the site.

- A digital storage that enables eventual further reading by an ECG central laboratory: each digital file will be identified by theoretical time (day and time DxxTxxHxx), real date and real time (recorder time), Sponsor study code, patient number (ie, 5 digits), and site and country numbers, if relevant. The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (ie, FDA 21 CFR, part 11).

9.3 PHARMACOKINETICS

9.3.1 Sampling times

The sampling times for PK blood collection can be found in the period flow chart ([Section 1.3](#)).

One PK profile will be taken from each patient at end of treatment on Day 56 in a blinded manner. Only those who have been on sotagliflozin will be analyzed. Thus, the bioanalytical team will be unblinded and they have to ensure to not communicate the individual treatment assignments to any member of the Clinical Trial Team.

9.3.2 Number of pharmacokinetic samples

Table 7 - Number of plasma samples

| | Sotagliflozin |
|-------------------------------------------------------|---------------|
| By patient | 8 |
| Total by patient | 8 |
| Total for study (20 patients receiving sotagliflozin) | 8*20 |

9.3.3 Sample handling procedure

Special procedures for collection, storage, and shipment are provided in [Appendix E](#) of the protocol.

The sample handling procedure is summarized in [Table 8](#) (see below).

Table 8 - Summary of handling procedures

| Sotagliflozin/ Sotagliflozin-3-O-glucuronide | |
|----------------------------------------------|------------------------------------------------|
| Blood sample volume | 2 mL |
| Anticoagulant | K2 EDTA |
| Handling procedures | See Appendix E of the protocol |
| Plasma aliquot split | 1 aliquot |
| Plasma storage conditions | -70°C |
| Plasma shipment conditions | dry ice |

9.3.4 Bioanalytical methods

Table 9 - Summary of bioanalytical method

| Sotagliflozin/ Sotagliflozin-3-O-glucuronide | |
|----------------------------------------------|----------------------------------|
| Matrix | Plasma |
| Analytical technique | LC-MS/MS |
| Lower limit of quantification | 2ng/mL parent/10ng/mL metabolite |
| Assay volume | 0.05 mL |
| Site of bioanalysis | Covance Indianapolis |
| Method reference | LLGHPP |

9.3.5 Pharmacokinetic parameters

The following pharmacokinetic parameters will be calculated, using noncompartmental methods from plasma sotagliflozin and sotagliflozin-3-O-glucuronide concentrations obtained in steady state. The parameters will include, but may not be limited to the following.

Table 10 - List of pharmacokinetic parameters and definitions

| Parameters | Drug/Analyte | Definition/Calculation |
|--------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| C_{max} | Sotagliflozin/ sotagliflozin-3-O-glucuronide | Maximum plasma concentration observed |
| t_{max} | Sotagliflozin/ sotagliflozin-3-O-glucuronide | First time to reach C_{max} |
| C_{trough} | Sotagliflozin/ sotagliflozin-3-O-glucuronide | Plasma concentration observed before administration during repeated dosing |
| AUC_{τ} | Sotagliflozin/ sotagliflozin-3-O-glucuronide | Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (τ) |

| Parameters | Drug/Analyte | Definition/Calculation |
|-------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| V_{ss}/F | Sotagliflozin | Steady-state volume of distribution: $V_{ss}/F = CL_{ss} / F \times MRT$ |
| CL_{ss}/F | Sotagliflozin | Apparent total body clearance of a drug in steady-state from the plasma calculated using the following equation: $CL/F = \frac{Dose}{AUC_{\tau}}$ |
| $R_{met}^{*}AUC_{\tau}$ | Sotagliflozin/ sotagliflozin-3-O-glucuronide | Metabolic ratio calculated using the following equation: $R_{met}^{*}AUC_{\tau} = \frac{AUC_{\tau_{metabolite}}}{AUC_{\tau_{parent}}}$ With metabolite cc and parent sotagliflozin |
| $R_{met}^{*}C_{max}$ | Sotagliflozin/ sotagliflozin-3-O-glucuronide | Metabolic ratio calculated using the following equation: $R_{met}^{*}C_{max} = \frac{C_{max_{metabolite}}}{C_{max_{parent}}}$ With metabolite sotagliflozin-3-O-glucuronide and parent sotagliflozin |

9.4 DNA SAMPLES

9.4.1 Mandatory drug metabolizing enzymes DNA samples

A blood sample will be collected to investigate allelic variants of other drug metabolizing enzymes (DMEs), such as UGT1A9, and/or drug transporters as intrinsic factors associated with PK or PD variability of sotagliflozin and sotagliflozin-3-O-glucuronide.

The Sponsor has included safeguards for protecting patient confidentiality. This sample will be used only for this specific analysis and then it and the extracted DNA will be destroyed upon completion of this analysis and the clinical study report, so no further information can be obtained from it.

Special procedures for collection, processing, storage and shipping of DME DNA samples are described in the DME Laboratory manual created by Covance Indianapolis.

9.4.2 Optional pharmacogenetic DNA sample

For those patients who signed the optional pharmacogenetic informed consent form, a blood sample will be collected at the study visit as specified in the study flow chart and this sample will be stored.

This sample may be used to determine a possible relationship between gene polymorphisms and response to treatment with sotagliflozin, how the body processes sotagliflozin and possible side effects to sotagliflozin.

This blood sample will be transferred to a site that will, on behalf of Sanofi, extract DNA from the sample and that is managed by Covance, Switzerland.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID (de-identification code) that is different from the patient ID. This “double coding” is performed to separate a patient’s medical information and DNA data.

The clinical study data (coded by patient ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored for up to 15 years from the completion of the clinical study report.

Special procedures for storage and shipping of DNA pharmacogenetic samples are described in the laboratory manual.

9.5 SAMPLED BLOOD VOLUME

Table 11 - Sampled blood volume

| Type | Volume per sampling | Number of samplings | Total |
|------------------------------------------------|---------------------|---------------------|---------------|
| Serology tests (serum) ^a | 0 | 1 | 0 mL |
| Hematology (plasma EDTA) | 2.7 | 7 | 18.9 mL |
| Coagulation (Citrates) | 3 | 5 | 15 mL |
| Biochemistry at screening (serum) | 7.5 | 1 | 7.5 mL |
| Biochemistry during study (serum) | 4.9 | 4 | 19.6 mL |
| HbA1c (plasma EDTA), at screening ^b | 0 | 1 | 0 mL |
| β-HCG (included in biochemistry sample) | - | - | - |
| FSH (included in biochemistry sample) | - | - | - |
| Archival sample | 15 | 1 | 15 mL |
| Optional Pharmacogenetics (full blood) | 6 | 1 | 6 mL |
| Genotyping for UGT1A9 | 3 | 1 | 3ml |
| Pharmacodynamics fasting metabolic panel | 12 mL | 2 | 24 mL |
| Pharmacodynamics CV panel | 18 mL | 2 | 36 mL |
| Pharmacodynamics postprandial profile | 13 mL | 28 | 364 mL |
| Pharmacodynamics indocyanine green | 2 mL | 14 | 28 mL |
| Pharmacokinetics sotagliflozin | 2 mL | 8 | 16 mL |
| Total | | | 553 mL |

^a included in the biochemistry at screening

^b included in the haematology sample

Of note, this blood volume will be drawn over a 10-14 weeks period. Additional samples may be needed if any laboratory result is outside of the normal range or for safety purposes.

9.6 FUTURE USE OF SAMPLES

The pharmacodynamic and pharmacokinetic samples, as well as the safety samples will be collected at the visit specified in the study flow chart and these samples will be stored. These samples may be used for other research purposes (excluding genetic analysis) related to cardiovascular and metabolic characteristics than those specified in the present study.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers than the one used during the study (ie, patient ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data.

All these samples will be destroyed after completion of all analyses and the CSR.

9.7 MEASURES TO PROTECT BLINDING OF THE TRIAL

Please also refer to [Section 8.8](#).

The bioanalyst and pharmacokineticist responsible for the sample analysis and pharmacokinetic evaluation will be unblinded. They will, however, agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule. The preliminary pharmacokinetic data available during the course of the study will refer to mean data with descriptive statistics and individual data without revealing any individual randomization numbers or patient numbers.

Nevertheless, for safety reason, the treatment code will be unblinded for reporting to the Regulatory Authority of any suspected unexpected serious adverse drug reaction and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

10 PATIENT SAFETY

The Investigator is the primary person responsible for taking all clinically relevant decisions on safety issues.

If judged necessary, the opinion of a Specialist should be envisaged in a timely manner (eg, acute renal failure, convulsions, skin rashes, angioedema, cardiac arrest, electrocardiographic modifications, etc.).

10.1 ADVERSE EVENT MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.2 DEFINITIONS OF ADVERSE EVENTS

10.2.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Adverse events will be graded according NCI-CTCAE v4.03 (3) and classified by system organ class (SOC) / preferred term (PT) according the last available version of the MedDRA dictionary. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the intensity of the adverse drug/biologic experience using the CTCAE general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

10.2.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient 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.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event:
 - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN, or development of drug dependence or drug abuse.

10.2.3 Adverse event of special interest

An **adverse event of special interest** (AESI) is an adverse event (serious or nonserious) of scientific and medical concern, specific to the IMP or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

10.3 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.3.1 General guidelines for reporting adverse events

All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol, are to be recorded on the corresponding page(s) or screen(s) of the case report form for included patients. For screen failed patients, recording in the case report form is only performed in case of SAE occurring during the screening period or in case of AE when some screening procedures expose the patient to safety risks (eg, any substance administered as pretreatment or for phenotyping, invasive tests performed or chronic treatment interrupted).

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity (see definitions in [Section 10.2.1](#)), action taken with respect to IMP/NIMP, corrective treatment/therapy given, additional investigations performed (eg, in the case of dermatologic lesions photographs are required), outcome, and Investigator's opinion as to whether there is a reasonable possibility that the AE was caused by the IMP/NIMP.

In order to ensure the safety of the patients, the Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team.

When treatment is prematurely discontinued, patients are to be assessed using the procedure planned for the end-of-study visit, including a pharmacokinetic sample if appropriate as defined by the protocol.

Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs in the eCRF only if:

- Symptomatic, and/or,
- Requiring either corrective treatment or consultation, and/or,
- Leading to IMP/NIMP discontinuation or modification of dosing, and/or,
- Fulfilling a seriousness criterion, and/or,
- defined as an AESI.

10.3.2 Guidelines for reporting serious adverse events

In the case of a SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send the notification to the monitoring team after approval by the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.

- A back-up plan is used (using paper flow) when the eCRF system does not work.
- Back-up plan.
- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) in the case report form to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical trial protocol.
- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further documentation should be sent to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.
- Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by the Investigator to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.3.3 Guidelines for reporting adverse events of special interest

The need for specific monitoring, documentation, and management of AESI are described in this section.

For each defined AESI, consider carefully the need to collect additional specific information that would impact the study and/or the case report form design, such as:

- Preexisting related condition or lifestyle of interest for the AE (eg, habits, cardiovascular risk factor, etc).
- Expected list of associated signs and symptoms.
- Corrective actions (eg, treatment discontinuation, concomitant treatment, etc).
- Diagnostic actions (eg, test(s) or procedure(s) results, etc).
- Additional descriptive factors.
- Sequelae.

For AESI, the Sponsor is to be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.3.2](#), even if a seriousness criterion is not met, using the corresponding pages of the case report form (to be sent) or screens in the eCRF.

The AESIs for this study are:

1. Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP.

Pregnancy occurring in a female patient included in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.2.2](#)),

- A) In the event of pregnancy in a female patient, IMP should be discontinued,
 - B) Follow-up of the pregnancy in a female patient or in a female partner of a male patient is mandatory until the outcome has been determined (see [Appendix A](#)).
2. Symptomatic overdose (serious or nonserious) with IMP/noninvestigational medicinal product (NIMP):
- A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and resulting in clinical symptoms and/or signs accompanied by administration of more than twice the intended daily dose within a 24-hour period. It will be recorded in the e-CRF as an AESI with immediate notification “Symptomatic OVERDOSE (accidental or intentional)” in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.

(Please note that an Asymptomatic overdose with the IMP/NIMP, accidental or intentional, defined as administration of more than twice the intended daily dose within a 24-hour period, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient, not based on accountability assessment. It will be recorded as an AE “Asymptomatic OVERDOSE, accidental or intentional.”).

3. ALT increase $\geq 3X$ ULN (refer to related flowchart in [Appendix C](#)).

10.3.4 Events of Special Interest (EOSIs)

An EOSI is a serious or non-serious AE of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. These events should be reported on the specific e-CRF page and will only qualify for expedited reporting when serious (fulfilling SAE criteria).

The EOSIs for this study are:

1. MACE (cardiovascular death, myocardial infarction, or stroke) and other specific CV events (eg, heart failure leading to hospitalization).
2. Severe hypoglycemia (see [Section 10.4.1.1](#)).
3. Venous thrombotic events (including venous thrombosis deep and pulmonary embolism).
4. Pancreatitis.
5. Bone fracture.
6. AEs leading to amputations.
7. Diabetic Ketoacidosis (DKA).
8. Malignancies of special interest (breast, bladder, renal cell, Leydig cell tumor of the testis, pancreatic, prostate, and follicular thyroid cancer).

9. Genital mycotic infections (to include vulvovaginal candidiasis in females and candida balanitis in males).
10. Urinary tract infection.
11. Diarrhea.
12. Volume depletion with serious consequence (orthostatic hypotension, orthostatic collapse fall, fracture).
13. Renal events, to include 50% decline in eGFR, end stage renal failure defined as eGFR <15 mL/min/1.73m², renal death.

If an EOSI fulfills the criteria of an SAE, reporting should be performed according to the instructions for reporting of SAEs (see [Section 10.3.2](#)). Otherwise, reporting should follow the instructions for an AE (see [Section 10.3.1](#)).

10.3.5 Guidelines for management of specific laboratory abnormalities

Once the patient is included in the clinical trial, the following laboratory abnormalities must be monitored, documented, and managed according to the related decision charts in [Appendix C](#).

- Neutropenia.
- Thrombocytopenia.
- Increase of ALT.
- Acute renal impairment.
- Increase in CPK suspected to be on non-cardiac origin and not related to an intensive physical activity.

10.4 SAFETY INSTRUCTIONS FOR EOSI OF HYPOGLYCEMIA

10.4.1 Hypoglycemia

- During the study, diabetic patients are instructed to document any hypoglycemic episodes in their study diary. The hypoglycemia will be reported in the specific e-CRF page with onset date and time, symptoms and/or signs, the SMPG value if available, and the treatment. If the event fulfills SAE criteria, hypoglycemia will also be reported as an SAE.
- Hypoglycemia is categorized according to the ADA workgroup on hypoglycemia classification ([36](#)) and summarized in [Figure 1](#).

10.4.1.1 Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma.

Self-monitored plasma glucose values may not be available, 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.

Note: “requiring assistance of another person” means that the patient could not help himself or herself to treat the hypoglycemia. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident. A severe hypoglycemic incident should be confirmed by the Investigator.

Any hypoglycemic event which leads to unconsciousness, coma, or seizure should also be reported as an SAE.

10.4.1.2 Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤ 3.9 mmol/L (≤ 70 mg/dL).

Clinical symptoms that are considered to result from a hypoglycemic episode are eg, increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.

10.4.1.3 Asymptomatic hypoglycemia

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 3.9 mmol/L (≤ 70 mg/dL).

Note: low plasma glucose values without symptoms or signs should not be reported more than once within 30 minutes. Repeated low glucose values within a short period could be due to malfunction of the device, error testing or following up a low glucose reading. The Investigator should try not to document false low SMPG values or redundant low glucose values as asymptomatic hypoglycemic event. Further clarification with the patients is needed.

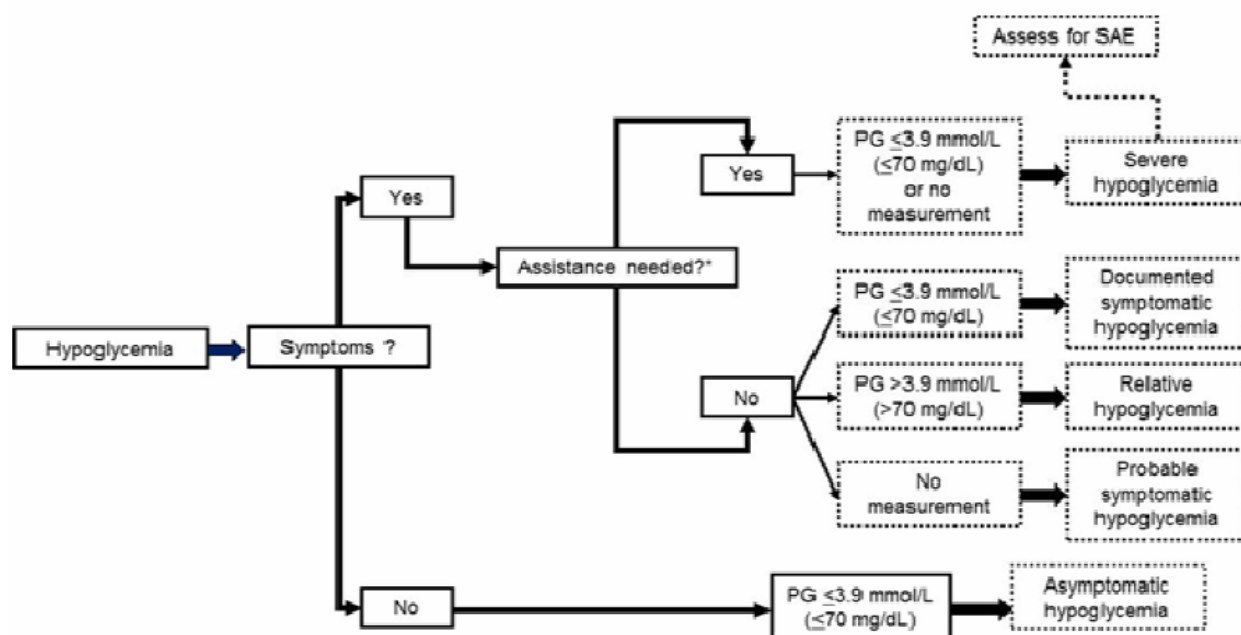
10.4.1.4 Probable symptomatic hypoglycemia

Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L [≤ 70 mg/dL]), ie, symptoms treated with oral carbohydrate without a test of plasma glucose.

10.4.1.5 Relative hypoglycemia

Relative hypoglycemia is an event during which the patient reports typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration > 3.9 mmol/L (> 70 mg/dL).

Figure 1 - Hypoglycemia classification in Study PDY15010



10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the Regulatory Authorities, IRB/IECs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the Regulatory Authorities, according to local regulations.

Adverse events that are considered as expected events will be specified by the reference safety information (Investigator brochure). The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

The study will be immediately stopped in case of any serious event which leads to hospitalization of a study participant and could be considered related to the study product and/or study procedures. Patients will be informed about the study suspension, the reason for the suspension and any necessary instructions. Once it is confirmed that it is safe for the study to continue, patients will receive all available information allowing him to confirm his decision to continue or not in the study.

11 HANDLING OF PATIENT WITHDRAWAL

11.1 LIST OF TREATMENT WITHDRAWAL CRITERIA

Refer to [Appendix C](#) for IMP-discontinuation criteria.

Refer to [Section 10.3.3](#) for cases in which AESI lead to treatment discontinuation.

Pregnancy will lead to permanent treatment discontinuation in all cases if applicable (Refer to [Section 10.3.3](#)).

11.2 REASONS FOR TREATMENT WITHDRAWAL

- The patient may withdraw from the treatment if they decide to do so, at any time and irrespective of the reason, or upon the Investigator's decision or at the specific request of the Sponsor.
- However, withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits. Patient who withdraws should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Such information about the reason of patient's withdrawal will be filled in in the appropriate eCRF page.
- In case of withdrawal, preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing. The informed consent for the study should note that although a patient is free to leave the study and stop taking study medication, the Investigators hope the patient will remain for follow up status evaluations.

11.3 REPLACEMENT OF PATIENTS

In case of a patient drop-out prior to treatment completion, a possible replacement will be decided on between PI and sponsor. Patients who are withdrawn due to treatment-related AEs will not be replaced.

11.4 TREATMENT WITHDRAWAL FOLLOW-UP PROCEDURE

All study treatment withdrawals should be recorded by the Investigator on the appropriate case report form pages or screens for eCRF when considered as confirmed.

If possible, patients are to be assessed using the procedure planned for the end-of-study visit, including a pharmacokinetic sample if appropriate.

For any patients who fails to return to the site, the Investigator should make every effort to recontact the patients (eg, contact the patient's family or private physician, review available registries or health care database), and to determine his/her health status, including at least his/her vital status. Attempts to contact the patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients withdrawn from the study must not be reincluded in the study. Their inclusion numbers must not be reused.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

12.1.1 Screening procedures

Screening procedures will be carried out within 30 days prior to, but not later than 2 days prior to the first admission to the unit. The patient will receive information on the study objective(s) and procedures from the Investigator. The patient will have to sign the informed consent prior to any action related to the study.

The screening visit will include the investigations listed in the Study Flow Chart ([Section 1](#)) and detailed in [Section 9.2](#).

Rechecking of any parameters at screening is to be limited to 2 times.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for the run-in period. Patients will receive a patient number according to the chronological order of admission to the unit on Day -5.

The 12 digit patient number consists of 3 components (eg, 276 0001 00001, 276 0001 00002, 276 0001 00003, etc), of which the first 3 digits (276) are the country number, the middle 4 digits are the site number and the last 5 digits are the patient incremental number within the site. The patient number remains unchanged and allows the patient to be identified during the whole study.

Only screen failed patients described in [Section 10.3.1](#) will have a patient number and will be recorded in the case report form.

12.1.2 Inclusion procedures

The inclusion will be carried out prior to first dosing on Day 1. The inclusion procedures and investigations will be carried out during the run-in period (Day-5 – Day1 predose) and will include the investigations listed in the Study Flow Chart ([Section 1](#)) and detailed in [Section 9](#).

Patients who comply with all inclusion/exclusion criteria will be assigned just before the IMP administration on Day 1:

- Treatment number (corresponding to one of the 2 treatments) in a preplanned order following the randomization list.

Rechecking of any baseline parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions. Results of a rechecked value should be known before the inclusion. The last value should be considered as the baseline value and reported in the case report form.

If a patient is finally enrolled, a DME DNA blood sample, and an optional DNA sample for possible further genomic analyses (provided appropriate consent has been obtained), as well as an archival blood sample will be taken on Day 1 pre administration.

12.1.3 Description by type of visit

Treatment period(s)

Please refer to the period flow chart in [Section 1](#).

The patients will be participated in one of the treatments arm (A or B) as parallel-group multiple dosing study design.

After the screening (Day -35 to Day -7) , an initial in-house period (Day -5 to Day -1) is to evaluate pharmacodynamic baseline parameters under standardized conditions, patients will be randomized (on Day 1) 1:1 to an 8 weeks (Day 1 to Day 56) multiple dosing treatment of 400 mg sotagliflozin QD or empagliflozin 25 mg QD.

Patients will return for a second in-house period to the unit in the last 5 days (Day 52 to Day 56) of treatment for re-analyses of all PD assessments on treatment under the same standardized conditions.

For the 5-days run-in period with baseline PD assessment the patients are admitted to the unit on Day -5. They receive standardized meals 3 times a day plus a standardized snack at bedtime during these days. The ABPM and CGM are set up for the time of the in-house stay. On specific days, the CV baseline assessment will be performed, ie, pulse wave velocity (Day-2) and echocardiography (Day-3), please refer to the flowchart. On Day -1 the further pharmacodynamic baseline assessments are performed starting at 08:00 a.m. with fractioned 24h urine collection, blood sampling for post-prandial glucose and insulin/glucagon profiles. Feces collection is performed over 48 hours (Days -2 and -1). In the morning of Day 1 the collection period ends and the first dose of IMP is given prior to breakfast. Thereafter the patients are released from the unit.

They continue dosing once daily for 56 days (Days 1 through 56), with at least 3 out-patients visits, one between Days 3-10, one between Days 11-28, one between Days 29 and 49, at least 7 days apart.

On Day 52 the on-treatment PD in-house assessment period starts with admission to the unit and the same schedule of standardized meals as at baseline. On specific days, echocardiography (Day54) and pulse wave velocity (Day 55) are assessed again. On Day 56 the on-treatment PD assessments will be performed with identical schedule as at baseline on Day -1. In the morning of Day 57, the collection period ends and the patients can be discharged after breakfast.

For practical reasons, approximately 45 minutes before starting the PK sampling on Day 56, an indwelling catheter may be inserted in a peripheral vein of the forearm in order to obtain blood samples. Between samplings, the catheter will be locked with a mandrel.

Discharge procedures

Patients will be discharged on Day 1 and day 57, after a complete review of the available safety data by the Investigator.

Ambulatory period(s)

After institutionalization, patients should immediately contact the Investigator or one of the clinical unit managers in the event of any unexplained symptom or any unexpected effect or event occurring during the study. For this reason, patients will be informed that they can contact the clinical unit by telephone 24 hours a day. Patients must give the Investigator a telephone number where they can be contacted in an emergency. Patients must carry with them, during ambulatory study period(s), the patient card indicating the study number and the emergency telephone number provided by the study site.

End-of-study visit (EoS)

Patients will return for an EoS visit between 7 to 14 days after last dosing. The Investigator will ensure that based on all available data, the patient can be safely released from the study.

12.1.4 Study restriction(s)

Throughout the out-patients treatment period, patients will be asked to take their breakfast within approximately 15 minutes after administration of study drug.

From 1 day before admissions to the unit until check-out on Day 1/Day 57, patients should refrain from drinking alcohol, tea, coffee, chocolate, quinine, or caffeine-containing beverages.

Patients should refrain from consuming poppy seeds 48 hours before the screening visit and then from 48 hours before admissions to the unit until check-out on Day 1/Day 57.

Consumption of citrus fruits and their juices is prohibited during the course of the patient's participation in the study from first admission to the unit.

Patients will be requested to follow a stable lifestyle for the duration of the study until the end-of-study visit.

12.2 DEFINITION OF SOURCE DATA

Evaluations recorded in the e-CRF must be supported by appropriately signed source documentation related but not limited to the following:

- Patient's diary with recording of SMPGs and hypoglycemia events, as well as dosing information.
- Agreement and signature of informed consent form with the study identification.
- Study identification (name).

- Patient number, confirmation of randomization, treatment batch number, dates and doses of study medication administration.
- Medical, surgical, diabetes history, including information on:
 - Demography, inclusion and exclusion criteria,
 - Last participation in a clinical trial,
 - Contraception method for WOCBP,
 - Previous and concomitant medication.
- Dates and times of visits and assessments including examination results.
- Vital signs, height, body weight, laboratory reports, Investigation results (eg, ECG traces, imaging reports), spirometry reports.
- Adverse events and follow-up:
 - In case of SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature treatment discontinuation (if any) and reason.
- Date of premature study discontinuation (if any) and reason.
- Nursing notes.
- Dietician's notes.
- Physician's notes.

13 STATISTICAL CONSIDERATIONS

The material in [Section 13](#) of the clinical trial protocol constitutes the statistical analysis plan for the study. Should this plan need revision during the study to accommodate clinical trial protocol amendments or to adapt to unexpected issues in study execution and data that affect planned analyses, a statistical analysis plan or statistical technical document will be issued prior to database lock or any interim analysis.

13.1 DETERMINATION OF SAMPLE SIZE

There was no formal sample size calculation performed for this study.

13.2 PATIENT DESCRIPTION

13.2.1 Disposition of patients

The total number of patients for each of the following categories will be presented:

- Patients screened (ie, having signed the informed consent).
- Screen failure patients and reason for screen failure.
- Patients entered in run-in period.
- Run-in failure patients and reason for run-in failure.
- Randomized patients: patients who signed the informed consent and have been assigned a treatment number.

A detailed description of patient accountability including count of patients randomized and treated (ie, randomized patients who received at least one administration of IMP), who did not complete the study along with the main reason for permanent treatment discontinuation, and patients who requested permanent treatment discontinuation, will be generated.

All withdrawals from the study, taking place on or after study drug intake, will be fully documented in the body of the clinical study report (CSR).

13.2.2 Protocol deviations

During the blinded review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment compliance, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the study team before database lock and listed in the Data Review and Surveillance Report, including missing data and study drug discontinuations, and classified as critical, major or minor deviations.

Individual deviations to inclusion and exclusion criteria as reported by the Investigator will be listed.

If any, major and critical deviations other than those involving inclusion/exclusion will be listed by patient and/or described in the body of the clinical study report.

13.3 ANALYSIS POPULATION

The number of patients included in each study population (safety population, pharmacokinetic population, pharmacodynamic population, Pharmacokinetic/Pharmacodynamic population if applicable) will be provided. All exclusions from any analysis populations will be fully documented in the CSR.

13.3.1 Safety population

All patients exposed to IMP (regardless of the amount of treatment administered) will be included in the safety population.

13.3.2 Pharmacokinetic population

All patients with no major or critical deviations related to IMP (eg, vomiting just after drug administration), and for whom PK data are considered sufficient and interpretable, will be included in the pharmacokinetic population.

13.3.3 Pharmacodynamic population

All patients with no major or critical deviations related to IMP (eg, vomiting just after drug administration) and/or pharmacodynamic (PD) procedures (e.g. test meals) and measurements, for whom the PD data are considered sufficient and interpretable will be included in the pharmacodynamic population.

13.3.4 Pharmacokinetic/Pharmacodynamic population

All patients exposed to sotagliflozin and being included in both the pharmacokinetic and the pharmacodynamic populations will be included in the pharmacokinetic/pharmacodynamic population.

13.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

13.4.1 Patient demographic characteristics, medical history and diagnoses

Continuous variables (age, weight) and qualitative variables (gender, race and body mass index [BMI]) will be summarized by descriptive statistics for the safety population and for additional population if relevant (eg, if many patients from the safety population are not part of the PD population).

T2DM disease history, hypertension disease history, including medication history for these diseases and baseline characteristics (HbA1c, years since diagnose of T2DM, years since start of treatment for T2DM, dose of metformin at screening, years since diagnose of hypertension, years since start of treatment for hypertension, current antihypertensive medications (drugs and regimens) at screening, average seated SBP and DBP at baseline (5 measurements taken on Day-2, eGFR at baseline) will be summarized in descriptive statistics by treatment group for the safety population and for the PK, PD populations, if relevant.

Previous medical or surgical history will be classified into primary system organ class (SOC) and high level term (HLT) using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group for the safety population and for the PK, PD populations, if relevant.

13.4.2 Baseline pharmacodynamic parameters

Baseline for PD parameters will be defined as the parameter value measured during the 5-days run-in period (from Day-5 to Day-1) prior to the first IMP dosing.

13.4.3 Baseline safety parameters

Baseline for safety parameters will be defined as the last available and evaluable parameter value before and closest to the first IMP dosing for laboratory data, vital sign parameters, and for 12-lead ECG parameters.

Baseline definitions specific to each type of safety parameter will be detailed in corresponding sections ([Section 13.8.2](#) to [Section 13.8.5](#)).

Baseline safety values will be presented along with subsequent safety values assessed during or after dosing.

13.5 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

A summary table presenting the exposure of treatment (ie, the number of days of administration) will be provided by treatment group for the safety population.

The following listings will be provided:

- Patients receiving IMP from specified batch.
- Randomization scheme.

13.6 PRIOR/CONCOMITANT MEDICATION/THERAPY

Medications will be coded according to the World Health Organization Drug Dictionary Drug Dictionary (WHO-DD), last available version before database lock). Medications that were stopped before the first IMP dosing and concomitant medications with the IMP will be listed separately by patient or summarized.

13.7 ANALYSIS OF PHARMACODYNAMIC VARIABLES

13.7.1 Description of pharmacodynamic variable(s)

Pharmacodynamic parameters are described in [Section 9.1](#).

Pharmacodynamic endpoints will be analysed as change from baseline to Week 8.

For 14 hour profiles of glucose/insulin/intact pro-insulin/C-peptide/glucagon/GLP1 (active and total), PYY and pancreatic polypeptide (PP) after MMTT, area under the concentration time curve (AUC) will be calculated using the linear trapezoidal rule. It will be determined using the real time of samplings, for the full 14 hour profiles and after each MMTT, at baseline and Week 8. Change from baseline will be then derived for each parameter and each MMTT.

For ABPM, average SBP and average DBP will be calculated as the mean of the corresponding 24-hour blood pressures measurement done every 15 minutes during daytime and every 30 minutes during nighttime. Mean daytime and mean nighttime will be also considered for SBP and DBP. Change from baseline to Week 8 will be then derived for each parameter.

For seated SBP and DBP, the mean of the 3 measurements will be calculated for each of the 5 assessments performed over the day (prior to breakfast, prior lunch, two hours after lunch, prior to dinner, bedtime). Change from baseline to Week 8 will be then derived for each parameter.

For CGM, the average diurnal glucose exposure will be calculated using the last 3 days of recordings of the run-in period (D-3, D-2 and D-1) and the last week of treatment (D54, D55 and D56) separately. Change from baseline to Week 8 will be then derived.

Further details of pharmacodynamics parameters will be described in the SAP.

13.7.2 Main analysis

The following analysis will be performed for the main endpoints ([Section 9.1](#)).

The continuous PD endpoints (change from Baseline to Week 8) will be analyzed by the ANCOVA model with treatment groups (Sotagliflozin, Empagliflozin) as fixed effects, and baseline values as a covariate.

Adjusted mean change from Baseline to Week 8 for each treatment group will be provided from the model, as well as the between-group difference and/or ratio (comparing sotagliflozin versus empagliflozin) and the 95% CI for the difference.

Descriptive statistics and graphs will be provided by treatment.

13.7.3 Further analysis/analysis of further variables

The same analysis as described in [Section 13.7.2](#) will be performed on the further endpoints.

13.8 ANALYSIS OF SAFETY DATA

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, graphics) and if needed on statistical analysis (appropriate estimations, hypothesis tests). The safety analysis will be conducted according to the sponsor's document "Analysis and reporting of safety data from Clinical Trials through the Clinical Study Report" (BTD-009536).

The potentially clinically significant abnormality (PCSA) values (BTD-009536 appendices - PCSA list for Phase 2/3 studies (oncology excepted)) are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, vital signs and ECG parameters.

All the safety analyses will be performed using the safety population.

For all safety data, the observation period will be divided into three segments:

- The **pretreatment period** is defined as the time between informed consent signature and the first IMP administration.
- The **TEAE period** is defined as the time from the first IMP administration up 7 days after the last IMP administration.
- The **post-TEAE period** is defined as the time starting after the TEAE period up to the final study end date.

13.8.1 Adverse events

13.8.1.1 Definitions

Adverse events will be coded to a "Preferred Term (PT)" and High Level Group Term (HLGT)", "High Level Term (HLT)" and primary "System Organ Class (SOC)" using the Medical Dictionary for Regulatory Activities (MedDRA, version currently in use by the sponsor at the time of database lock). Their severity will be graded according NCI-CTCAE v4.03.

They will be classified into predefined standard categories according to chronological criteria:

- **Pretreatment AEs:** AEs that occurred, worsened or became serious during the pretreatment period.
- **Treatment emergent AEs (TEAEs):** AEs that occurred, worsened or became serious during the TEAE period.
- **Post-TEAEs:** AEs that occurred, worsened or became serious during the post-TEAE period.

TEAEs will be assigned to the treatment received at the time of the AE onset.

If the onset date (or time) of an AE (occurrence, worsening or becoming serious) is incomplete or missing, then the AE will be considered as a TEAE unless a partial date (or time) shows it as a pre- or posttreatment event.

All AEs reported in the study will be listed, sorted by patient, onset date and time.

13.8.1.2 Treatment-emergent adverse events

The following TEAEs summaries will be provided by treatment for the safety population:

- Overview of TEAEs: number and percentage of patients with any TEAE, any severe TEAE, any serious TEAE, any TEAE leading to death (if any occurred), and any TEAE leading to permanent treatment discontinuation.
- Summary of TEAEs by primary SOC, HLGT, HLT, and PT.
- Summary of TEAEs by primary SOC and PT.
 - Number and percentage of patients with at least one TEAE,
 - Number of occurrences of TEAEs.

Patients presenting TEAEs will be listed sorted by primary SOC and PT.

13.8.1.3 Deaths, serious, and other significant adverse events

Any deaths, serious and other significant AEs will be listed.

13.8.1.4 Adverse events leading to treatment discontinuation

Any AEs leading to permanent treatment discontinuation will be listed.

13.8.1.5 Adverse events of special interest

Number (%) of patients experiencing treatment emergent AESI will be presented by AESI category and PT, sorted by decreasing incidence of PT within each AESI category.

13.8.2 Clinical laboratory evaluations

Baseline definition

The values to be used as the baselines will be the Day -5 assessment values. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baselines, provided they were done before the first IMP administration.

Abnormalities analyses

For parameters with laboratory ranges and/or abnormality criteria (PCSA), analysis will be performed using all postbaseline assessments done during the TEAE period, including all unplanned and rechecked values. Counts of patients with PCSAs according to baseline status will be presented by treatment. The same type of summary tables will be provided for out-of-normal laboratory range values.

Descriptive statistics

For parameters of interest (hematocrit, hemoglobin, serum sodium, bicarbonate, creatinine, uric acid, urea, fasting glucose, triglycerides, ketones (BHB and total ketones) in plasma and creatinine, uric acid, pH, glucose, ketones in urine), raw data and changes from baseline will be summarized in descriptive statistics, by treatment and scheduled time of measurement.

PCSA Listings

A listing of individual data from patients with postbaseline PCSAs will be provided; values will be flagged when outside the laboratory limits and/or when reaching the PCSA criteria.

A listing of liver function data for patients experiencing at least one of the following situations will be provided:

- ALT > 3ULN and total bilirubin >2 ULN during the study, with at least one of them being post first dose, irrespective of the definition of the TEAE period.
- Conjugated bilirubin >35% of Total bilirubin and Total bilirubin >1.5 ULN, on the same sample post first dose, irrespective of the definition for the TEAE period.

If any, a listing related to increase in ALT ≥ 3 ULN will be provided, including notably the information on drug intake, medical and surgical history, alcohol habits, and trigger factors, event details with ALT values, associated signs and symptoms.

Out-of-normal range definitions will be listed.

13.8.3 Vital signs

Heart rate (HR), systolic and diastolic blood pressures (SBP and DBP) will be analyzed as raw parameter value and change from baseline.

Body weight will be analyzed as raw parameter value and percent change from baseline and BMI will be analyzed as raw parameter value.

Baseline definition

The values to be used as baselines will be the Day -5 assessment values for heart rate and blood pressures and the Day-1 assessment values for body weight and BMI. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baselines, provided they were done before the IMP administration of the respective treatment phase, and in the same condition.

Abnormalities analyses

For all parameters, analysis will be performed using all postbaseline assessments done during the TEAE period, including all unplanned and rechecked values. Counts of patients with PCSAs will be presented by treatment, regardless of the baseline status.

Descriptive statistics

For heart rate and blood pressures, raw data and changes from baseline (supine position only) will be summarized in descriptive statistics by treatment and scheduled time of measurement.

For body weight, raw data and percent change from baseline will be summarized in descriptive statistics by treatment and scheduled time of measurement.

PCSA Listings

A listing of individual data from patients with postbaseline PCSAs will be provided; values will be flagged when reaching the PCSA criteria.

13.8.4 Electrocardiogram

ECG parameters (HR in bpm, QTc, QT, QRS and PR in msec) will be coming from automatic readings. All parameters will be analyzed as raw data and absolute change from baseline. In addition, for the abnormalities analysis, PR and QRS will be also analyzed as percent change from baseline.

Baseline definition

The values to be used as baselines will be the Day -5 assessment values. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baselines, provided they were done before the IMP administration of the respective treatment phase, and in the same condition.

Abnormalities analyses

For all parameters, analysis will be performed, using all postbaseline assessments done during the TEAE period, including all unplanned and rechecked values. Counts of patients with PCSAs will be presented by treatment, regardless of the baseline status.

Descriptive statistics

ECG parameters (raw data and absolute change from baseline) will be summarized in descriptive statistics by treatment and scheduled time of measurement.

13.8.5 Other related safety parameters

13.8.5.1 Body temperature

Raw data will be summarized in descriptive statistics by treatment and scheduled time of measurement.

13.9 ANALYSIS OF PHARMACOKINETIC DATA

13.9.1 Pharmacokinetic parameters

The list of pharmacokinetics parameters is listed in [Section 9.3.5](#).

13.9.2 Statistical analysis

Pharmacokinetic parameters of Sotagliflozin and Sotagliflozin 3-O-glucuronide will be summarized by descriptive statistics (such as mean, geometric mean, median, SD, SEM, CV, minimum, and maximum) under the responsibility of Pharmacokinetics Department, Sanofi.

13.10 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The relationship between main PD endpoints and sotagliflozin concentrations will be explored graphically, using scatterplots of the change from baseline to Week 8 in PD parameter versus concentration.

13.11 INTERIM ANALYSIS

In case of interim analysis for the purpose described in [Section 6.3](#), only descriptive statistics will be provided for parameters of interest, no statistical test will be performed.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH (International Conference on Harmonization) guidelines for Good Clinical Practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

14.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in, and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenetics analysis, the optional pharmacogenetics written informed consent form should be signed, name filled in, and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

The informed consent form and the optional pharmacogenetics informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

The written informed consent form and any other written information to be provided to patients should be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The patient or the patient's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the

trial. The communication of this information should be documented. In case of study suspension due to safety concerns, study patients will be informed of this study suspension and the reason for it. Once it is confirmed that it is safe for the study to continue, study patients will be asked to confirm their agreement to continue the study.

14.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the Health Authorities (Competent Regulatory Authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae, etc.) and the date of the review should be clearly stated on the written IRB/IEC approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Health Authorities (Competent Regulatory Authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the Health Authorities (Competent Regulatory Authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC and to Health Authorities (Competent Regulatory Authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the trial's outcome at the end of the clinical trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules).

The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the case report form, discrepancy resolution form, or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the case report forms. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements, and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the case report form entries against the source documents, except for the preidentified source data directly recorded in the case report form. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to original medical records which support the data on the case report forms (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate case report forms (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All case report forms should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (discrepancy resolution forms) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITE(S)

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

16.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the case report forms, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

16.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

16.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

16.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IEC/IRB or regulatory authorities in countries requiring this document.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

16.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

16.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total numbers of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

16.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

16.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of the study results to the Investigator.

16.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

The Investigator shall not use the name(s) of the Sponsor and/or of its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC written approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

18 BIBLIOGRAPHIC REFERENCES

1. Powell DR, Smith M, Greer J, Harris A, Zhao S, DaCosta C, et al. LX4211 Increases Serum Glucagon-Like Peptide 1 and Peptide YY Levels by Reducing Sodium/Glucose Cotransporter 1 (SGLT1)–Mediated Absorption of Intestinal Glucose. *The Journal of Pharmacology and Experimental Therapeutics*. 2013;345:250–9.
2. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium–Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport - From Bench to Bedside. *Diabetes Care*. 2015;38:2344–53.
3. Zambrowicz B, Ogbaa I, Frazier K, Banks P, Turnage A, Freiman J et al. Effects of LX4211, a dual sodium-dependent glucose cotransporters 1 and 2 inhibitor, on postprandial glucose, insulin, glucagon-like peptide 1, and peptide tyrosine tyrosine in a dose-timing study in healthy subjects. *Clin Ther*. 2013;35:1162-73.
4. Zambrowicz B, Freiman J, Brown PM, Frazier KS, Turnage A, Bronner J, et al. LX4211, a Dual SG LT1/SG LT2 Inhibitor, Improved Glycemic Control in Patients With Type 2 Diabetes in a Randomized, Placebo-Controlled Trial. *Clinical Pharmacology & Therapeutics*. 2012;92(2): 158-69.
5. Rosenstock J, Cefalu WT, Lapuerta P, Zambrowicz B, Ogbaa I, Banks P et al. Greater Dose-Ranging Effects on A1C Levels Than on Glucosuria With LX4211, a Dual Inhibitor of SGLT1 and SGLT2, in Patients With Type 2 Diabetes on Metformin Monotherapy. *Diabetes Care*. 2015;38:431–8.
6. Sands AT, Zambrowicz BP, Rosenstock J, Lapuerta P, Bode BW, Garg SK et al. Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes. *Diabetes Care*. 2015;38:1181–88.
7. Cariou B, Charbonnel B. Sotagliflozin as a potential treatment for type 2 diabetes mellitus. *Expert Opin Investig Drugs*. 2015; 24(12):1647-56.
8. Holt PR, Atillasoy E, Lindenbaum L, Ho SB, Lupton JR, McMahon D et al. Effects of Acarbose on Fecal Nutrients, Colonic pH, and Short-Chain Fatty Acids and Rectal Proliferative Indices. *Metabolism*. 1996;45(9):1179-87.
9. Weaver GA, Tangel CT, Krause JA, Parfitt MMI. Acarbose Enhances Human Colonic Butyrate Production. *The Journal of Nutrition*. 1997;127(5):717-23.
10. Dobbins RL, Greenway FL, Chen L, Liu Y. Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. *Am J Physiol Gastrointest Liver Physiol*. 2015;308:G946–54.
11. Pluznick J. A novel SCFA receptor, the microbiota, and blood pressure regulation. *Gut Microbes*. 2014;5(2):202–7.

12. Mortensen FV, Nielsen H, Mulvany MJ, Hesseløe I. Short chain fatty acids dilate isolated human colonic resistance arteries. *Gut*. 1990;31:1391-4.
13. Miyamoto J, Kasubuchi M, Nakajima A, Irie J, Itoh H, Kimura I. The role of short-chain fatty acid on blood pressure regulation. *Current opinion in nephrology and hypertension*. 2016;25(5):379-83.
14. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, et al. Empagliflozin Reduces Blood Pressure in Patients With Type 2 Diabetes and Hypertension. *Diabetes Care*. 2015;38(3):420–8.
15. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated Type 1 diabetes mellitus. *Cardiovascular Diabetology*. 2014;13:28.
16. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2015;17:1180–93.
17. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al : Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; 373:2117-28.
18. Bahne E, Hansen M, Brønden A, Sonne DP, Vilsbøll T, Knop FK. Involvement of Glucagon-like Peptide-1 in the Glucose-lowering effect of Metformin. *Diabetes Obes Metab*. 2016;18(10):955-61.
19. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with Type 2 diabetes. *Diabetes Obes Metab*. 2013;15(9):853-62.
20. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus. *Circulation*. 2014;129:587-97.
21. Weber MA, Mansfield TA, Alessi F, Iqbal N, Parikh S, Ptaszynska A. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin–angiotensin system blockade. *Blood Press*. 2016;25(2):93–103.
22. Empagliflozin [package insert]. Ridgefield, CT, Boehringer Ingelheim Pharmaceuticals, Inc., and Indianapolis, IN, Eli Lilly and Company; July 2016. p 1-25.
23. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl U, Woerle H. Empagliflozin reduces blood pressure in patients With type 2 diabetes and hypertension. *Diabetes Care*. 2015 Mar;38(3):420-8.
24. Lehmann A, Hornby PJ. Intestinal SGLT1 in metabolic health and disease. *Am J Physiol Gastrointest Liver Physiol*. 2016;310(11):887–98.

25. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM et al. Gut Dysbiosis Is Linked to Hypertension. *Hypertension*. 2015;65(6):1331-40.
26. Den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research*. 2013;54(9):2325-40.
27. Atlas SA. The Renin-Angiotensin Aldosterone System: Pathophysiological Role and Pharmacologic Inhibition. *Supplement to Journal of Managed Care Pharmacy* 2007;13(8, S-b):9-20.
28. Jacob M, Conzen P, Finsterer U, Krafft A, Becker BF, Rehm M. Technical and physiological background of plasma volume measurement with indocyanine green: a clarification of misunderstandings. *J Appl Physiol*. 2007;102(3):1235–42.
29. Jacob M, Chappell D, Conzen P, Finsterer U, Krafft A, Becker BF et al . Impact of the time window on plasma volume measurement with indocyanine green. *Physiol Meas* 2008;29(7):761–70.
30. Polidori D, Rowley C. Optimal back-extrapolation method for estimating plasma volume in humans using the indocyanine green dilution method. *Theoretical Biology and Medical Modelling*. 2014;11:33.
31. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness. A Scientific Statement From the American Heart Association. *Hypertension*. 2015;66:698-722.
32. Wang Y, Marwick TH. Update on Echocardiographic Assessment in Diabetes Mellitus. *Curr Cardiol Rep*. 2016;18(6):85.
33. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Euro Heart J*. 2013;34(28):2159–219.
34. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al.: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119(16):2250-94.
35. Melanson KJ, Greenberg AS, Ludwig DS, Blood Glucose and Hormonal Responses to Small and Large Meals in Healthy Young and Older Women. *Journal of Gerontology: Biological Sciences*. 1998;Vol. 53A; 4, B299-B305.

36. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005 May;28(5):1245-9.

19 APPENDICES

Appendix A. Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy.
 - Documented bilateral salpingectomy.
 - Documented bilateral oophorectomy.
3. Postmenopausal:
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

CONTRACEPTION GUIDANCE

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in [Section 7.2](#)):
 - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent,
 - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in [Table 12](#) when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (during the protocol-defined time frame).
- Refrain from donating sperm for the duration of the study and for [Table 12](#) after (study completion or the last dose of study treatment).

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in [Table 12](#).

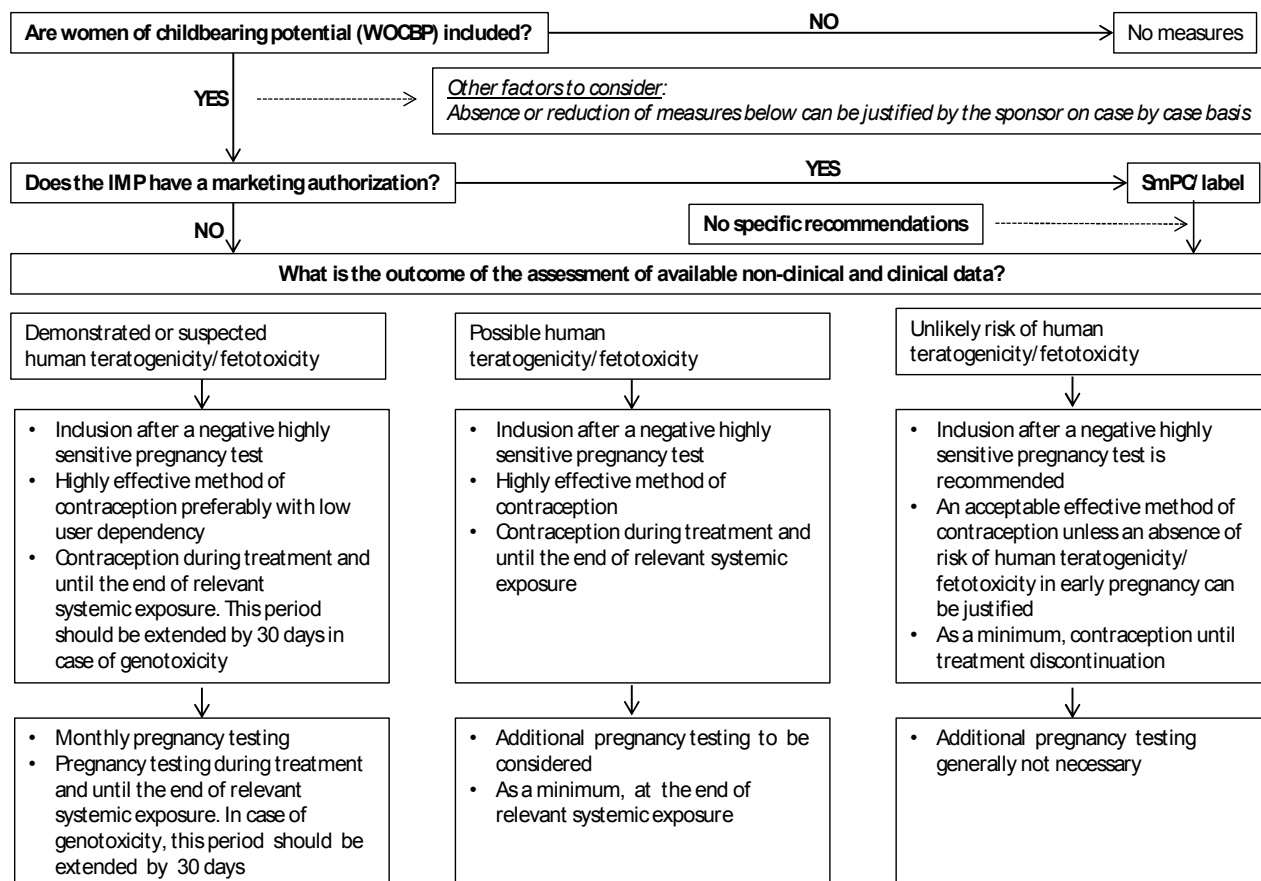
Table 12 - Highly Effective Contraceptive Methods

| |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Highly Effective Contraceptive Methods That Are User Dependent^a</p> <p><i>Failure rate of <1% per year when used consistently and correctly</i></p> <ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b. <ul style="list-style-type: none"> - Oral, - Intravaginal, - Transdermal. • Progestogen-only hormone contraception associated with inhibition of ovulation. <ul style="list-style-type: none"> - Oral, - Injectable. |
| <p>Highly Effective Methods That Are User Independent^a</p> <ul style="list-style-type: none"> • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> - Intrauterine device (IUD), - Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion. |
| <p>Vasectomized partner.</p> <p><i>Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not and less than 1 year after vasectomy, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.</i></p> |
| <p>Sexual abstinence.</p> <p><i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i></p> |
| <p>NOTES:</p> <p>^a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.</p> <p>^b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be utilized during the treatment period and for at least one month after the last dose of study treatment.</p> |

See guidance below:

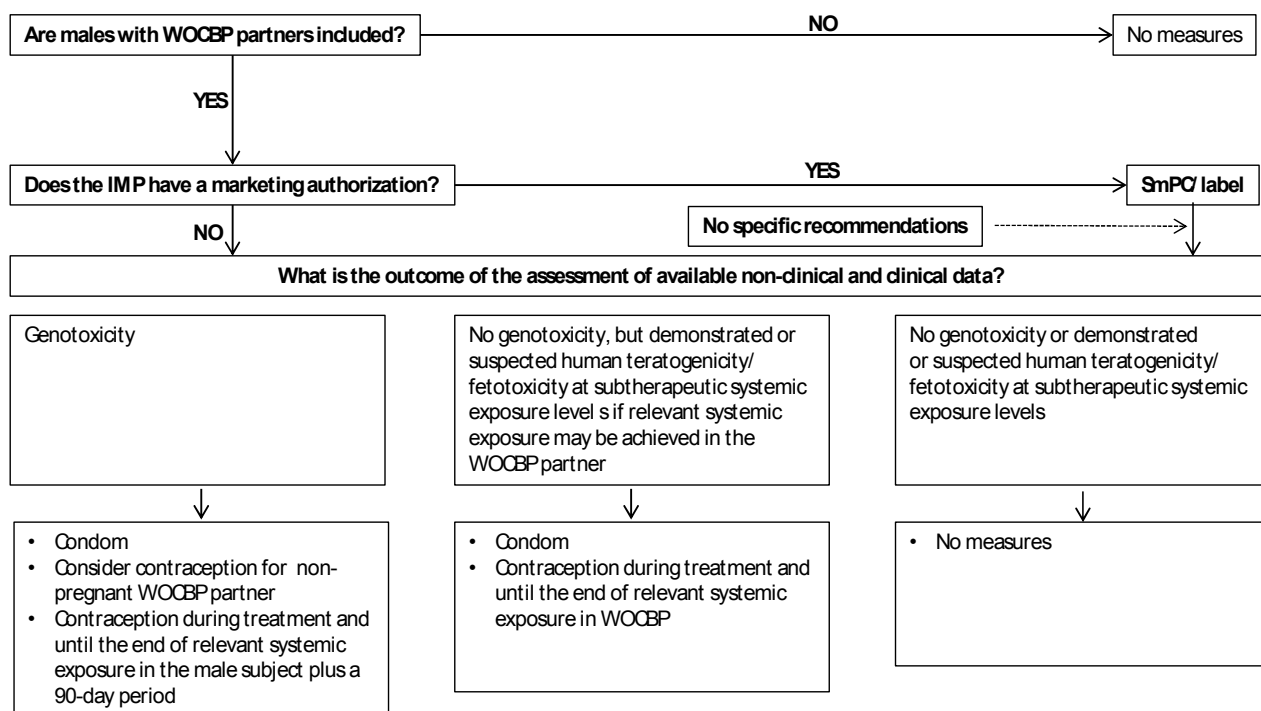
Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Women of Childbearing Potential (WOCBP)



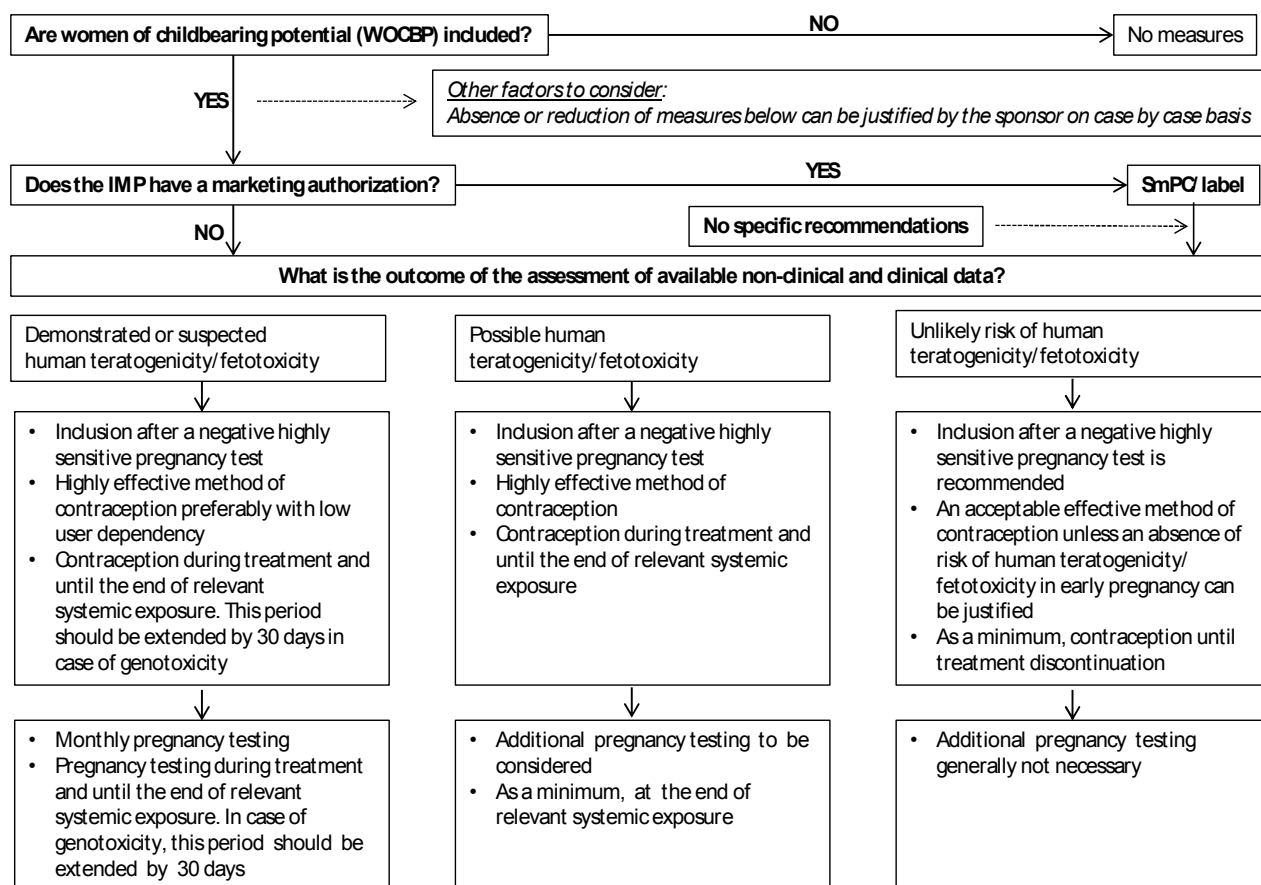
Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Males with WOCBP Partners



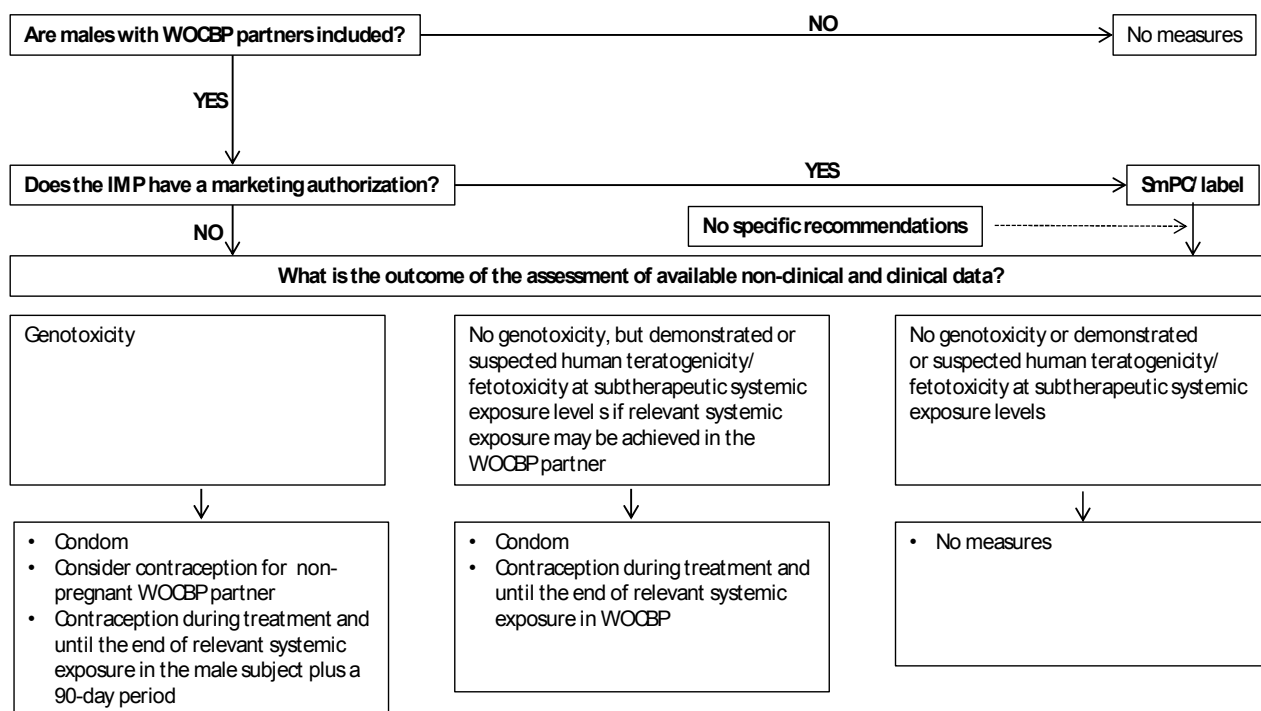
Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Women of Childbearing Potential (WOCBP)



Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Males with WOCBP Partners



Clinical Facilitation Group (September 2014) - Recommendations related to contraception and pregnancy testing in clinical trials

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will (discontinue study treatment or be withdrawn from the study or may request continuation of study treatment).

Appendix B. Recommendations on basic genitourinary hygiene, maintaining hydration and recognizing diabetic ketoacidosis

Patients with T2D are at risk for developing GU infections. The following guidelines should be communicated to females and uncircumcised males regarding GU infections. Patient communication cards will be printed with the following:

For females:

“The following advice may be useful in helping you to keep your bladder and urethra free from infection:

- Go to the toilet as soon as you feel the need to urinate, rather than holding it in.
- Wipe from front to back after going to the toilet.
- Practice good hygiene by washing your genitals every day, and before having sex.
- Empty your bladder after having sex.”

For uncircumcised males:

“The following advice may be useful in helping you to keep the foreskin free from infection:

- Wash the end of your penis and foreskin with soap and water (do not let soap get in the opening).
- After your shower or bath, dry the end of your penis and foreskin properly and replace the foreskin.
- Also, when you urinate, slide the foreskin back enough so that urine does not get on the foreskin-this helps to keep it clean.”

Maintaining Hydration:

Sodium-glucose cotransporter type 2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. All patients will be advised to maintain proper fluid intake and to consider increasing it if they sense greater thirst, more urine production, or if they feel dizzy or faint.

Patient communication cards will be printed with the following for patients with T2D:

“The following advice may be useful in helping you to maintain proper hydration and prevent dehydration:

- Dehydration is when your body loses too much fluid, frequently due to diarrhea or increased urination.
- Consider increasing the amount of fluids you drink if:
 - You sense greater thirst than usual,

- You have a dry mouth or cracked lips,
- You have a fever,
- You have diarrhea or vomiting,
- You urinate more frequently or in larger amounts than usual,
- You get up in the middle of the night to urinate (more than usual),
- You feel dizzy or light-headed,
- You exercise, or when it is hot outside”.

Recognizing DKA

Potential GI adverse events occurring with sotagliflozin may mask presenting symptoms of DKA. Patient communication cards will be printed with the following:

“If you have any of these symptoms on the list, then contact your study site immediately for assistance with managing your diabetes:

- Inability to maintain oral intake.
- Generalized weakness.
- Abdominal (belly) pain.
- Increased weight loss.
- Fever.
- Frequent urination, including at night.
- Fruity-scented breath.
- Confusion.
- Acute illness.
- Consistently elevated blood glucose.
- Feeling very thirsty or drinking a lot.
- Nausea or vomiting.
- Having trouble thinking clearly or feeling tired.

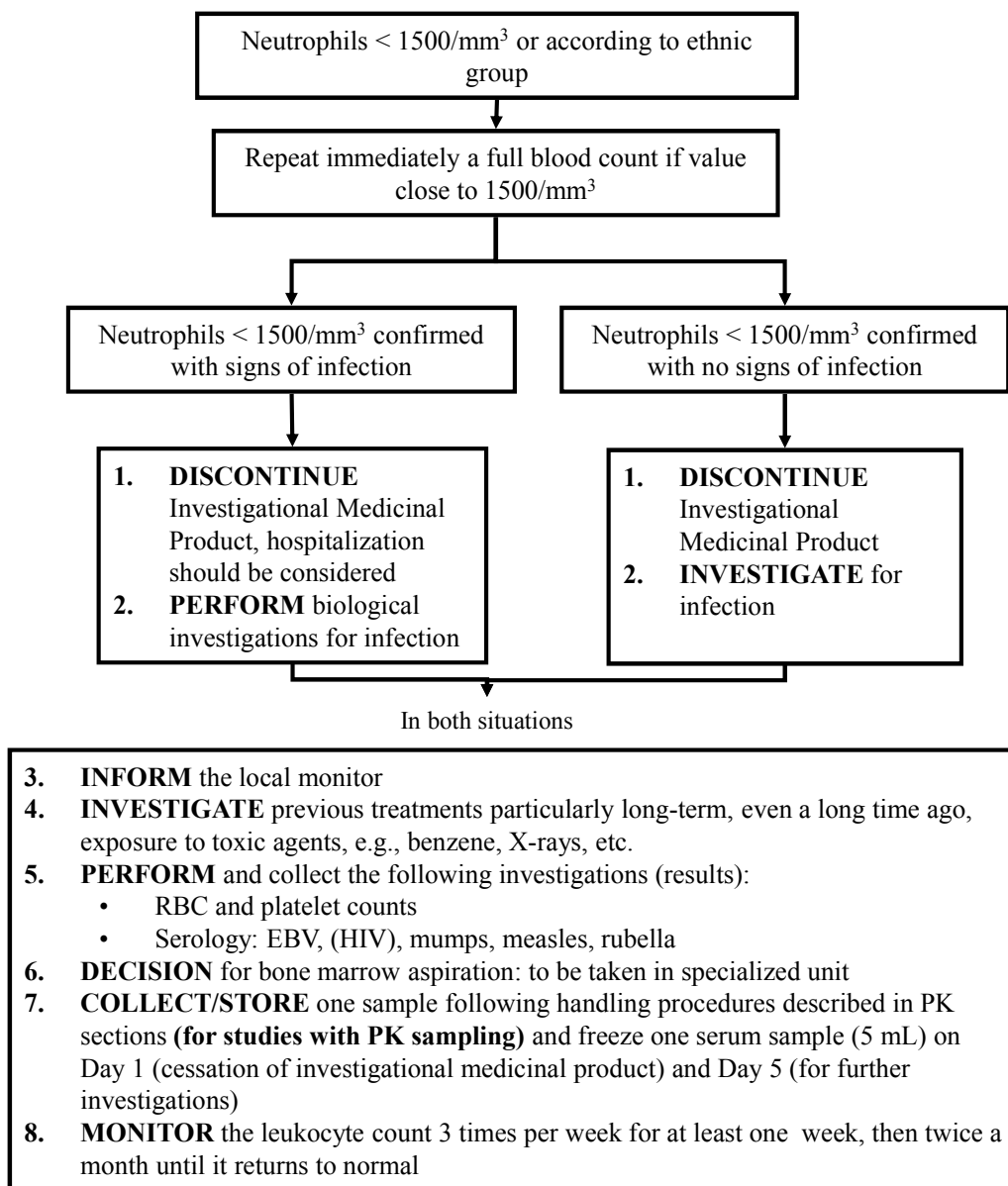
It is possible to have DKA even if your blood glucose is not elevated. Regardless of your blood glucose level, if you have any of these symptoms on the list, then contact your study site regarding the need to be evaluated for possible DKA, which will include specific blood testing. If your study site is closed and your study doctor is not available, go to the nearest emergency room for evaluation.

If you are scheduled for a procedure or surgery that requires you to not take any food or liquids, please contact your study doctor for instructions on continuing study drug. In such cases your study doctor may advise you NOT to take your study drug from the day prior to the procedure or surgery until after the procedure or surgery is complete, and you are taking food and liquids as you normally do.”

Whenever AE data is collected or the patient reports DKA or intercurrent illness (including infections), generalized weakness, increased weight loss, gastrointestinal symptoms including nausea, vomiting, or abdominal pain or other symptoms or signs that the Investigator believes may be consistent with DKA, then the site will determine if an assessment for DKA is appropriate. If laboratory testing confirms presence of metabolic acidosis, then the “Possible DKA” e-CRF will be completed.

Appendix C. Decision charts

NEUTROPENIA

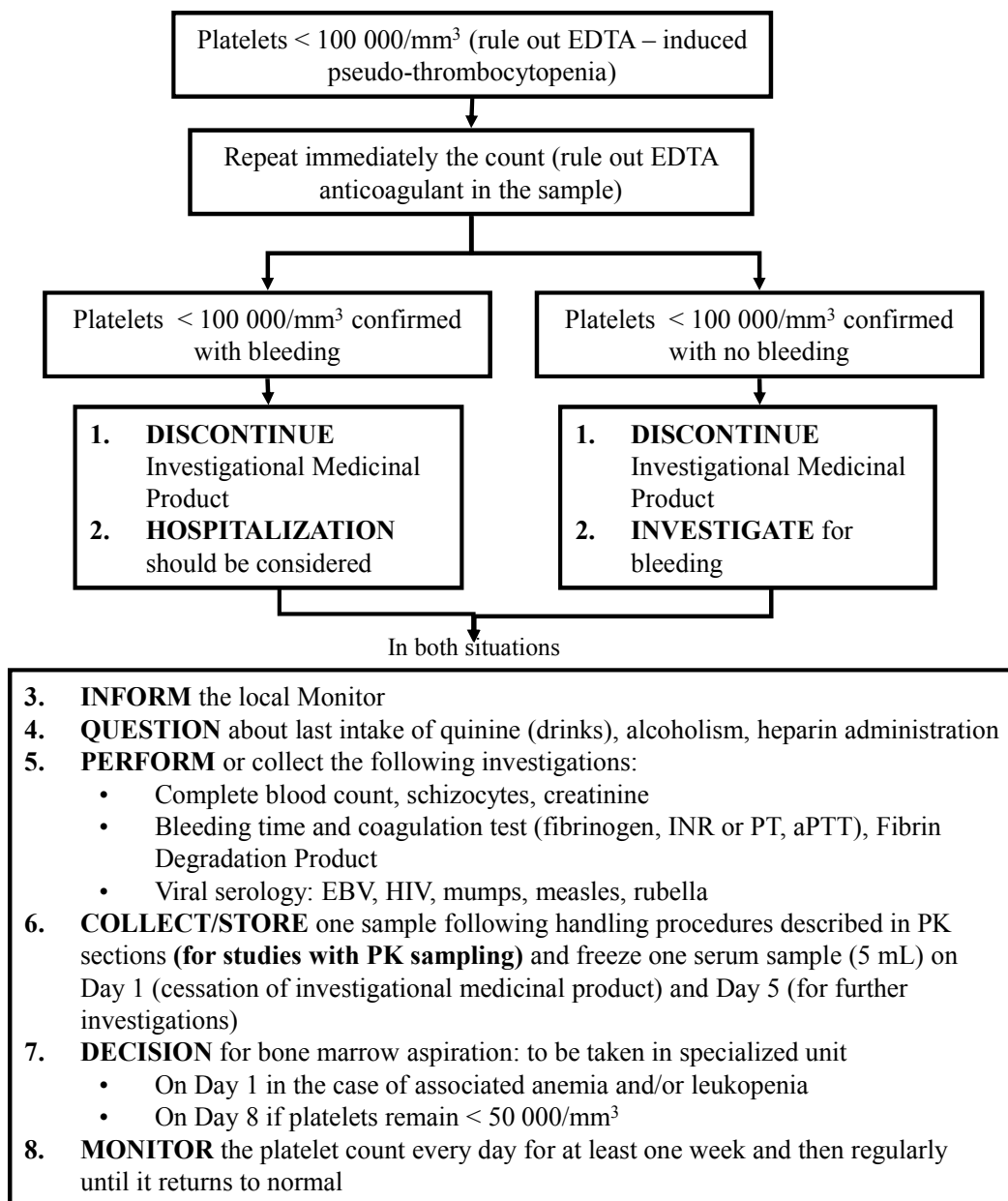


Note:

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm³

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in [Section 10.3.1](#) is met.

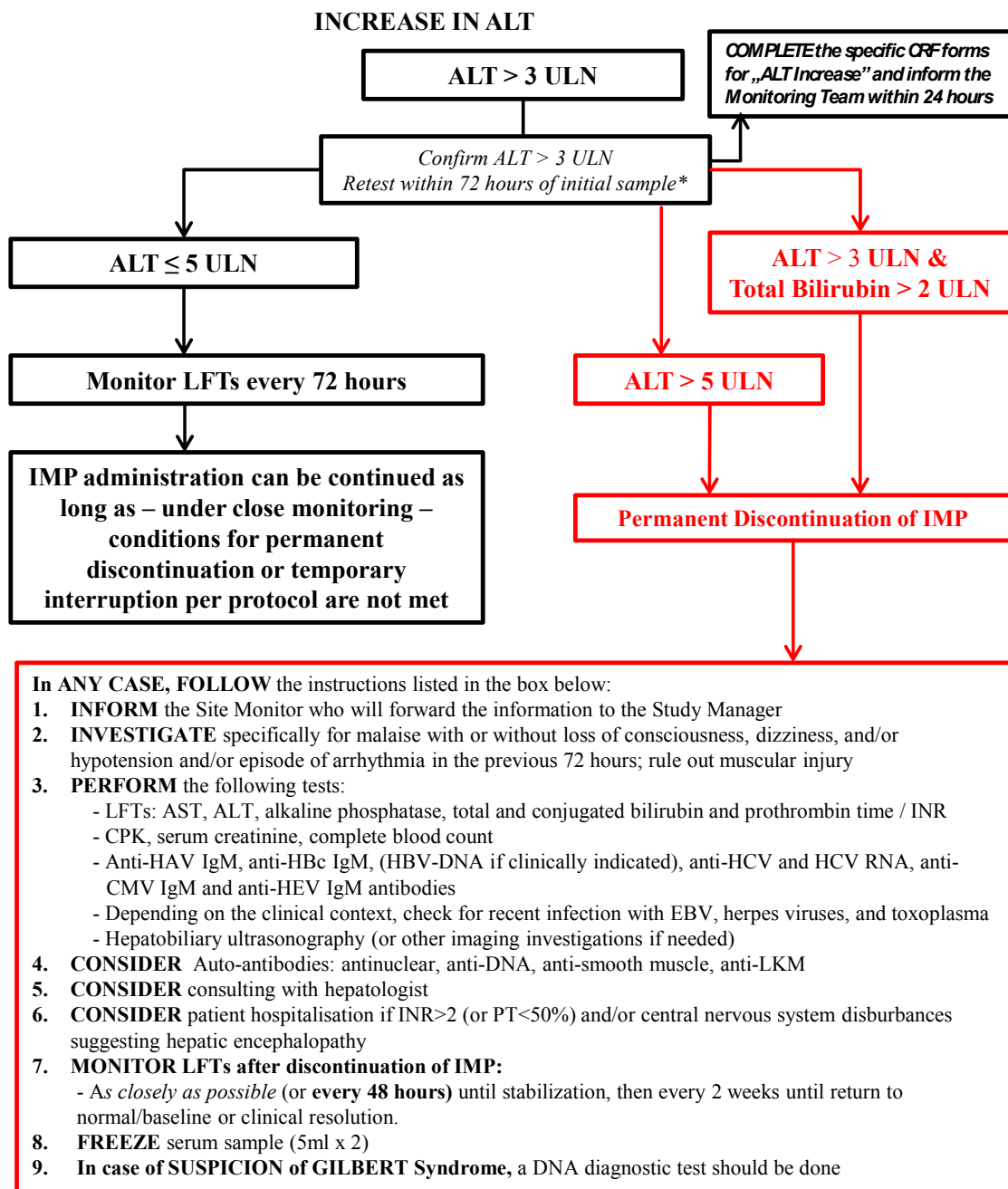
THROMBOCYTOPENIA



Note:

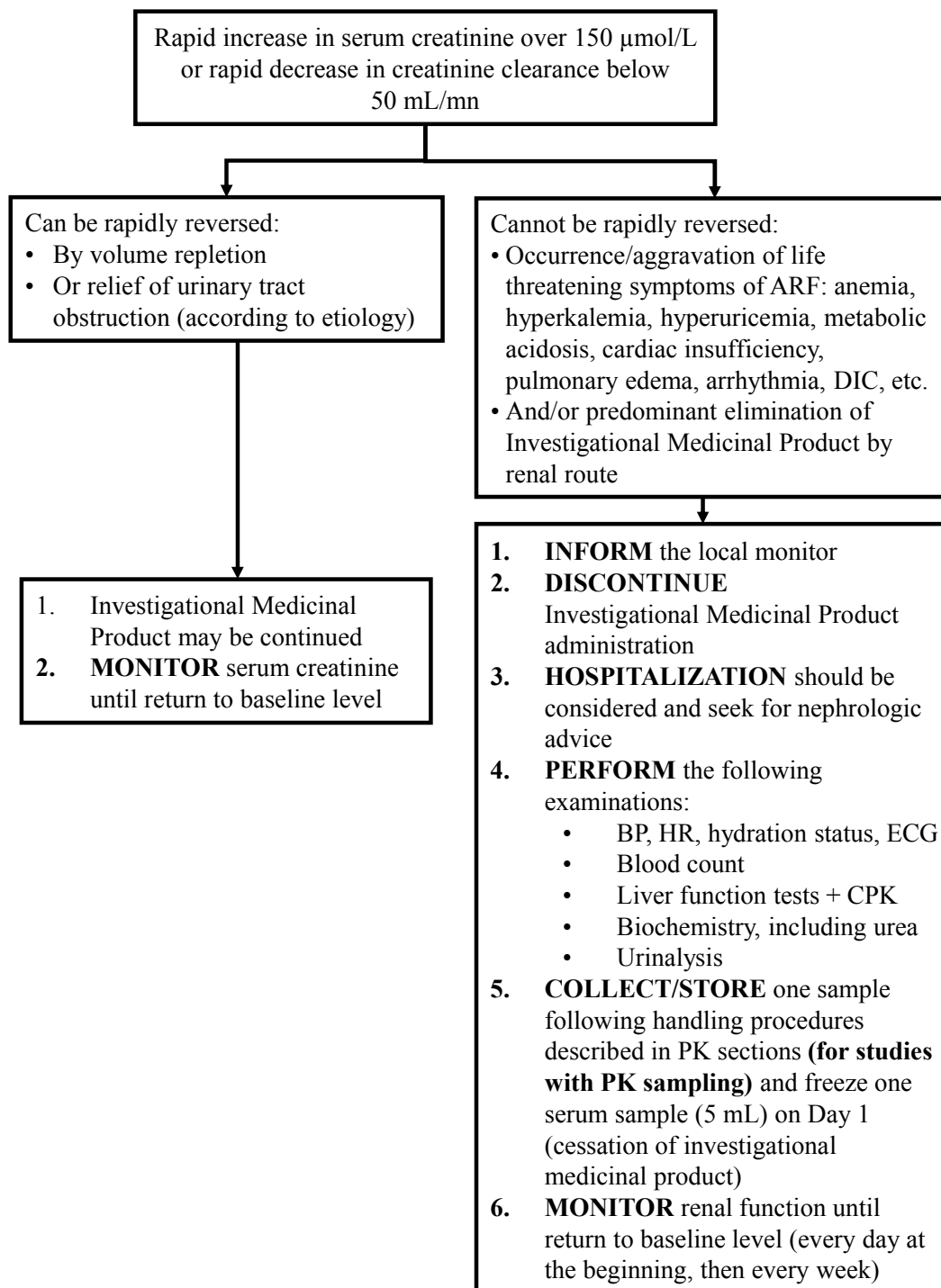
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in [Section 10.3.1](#) is met.



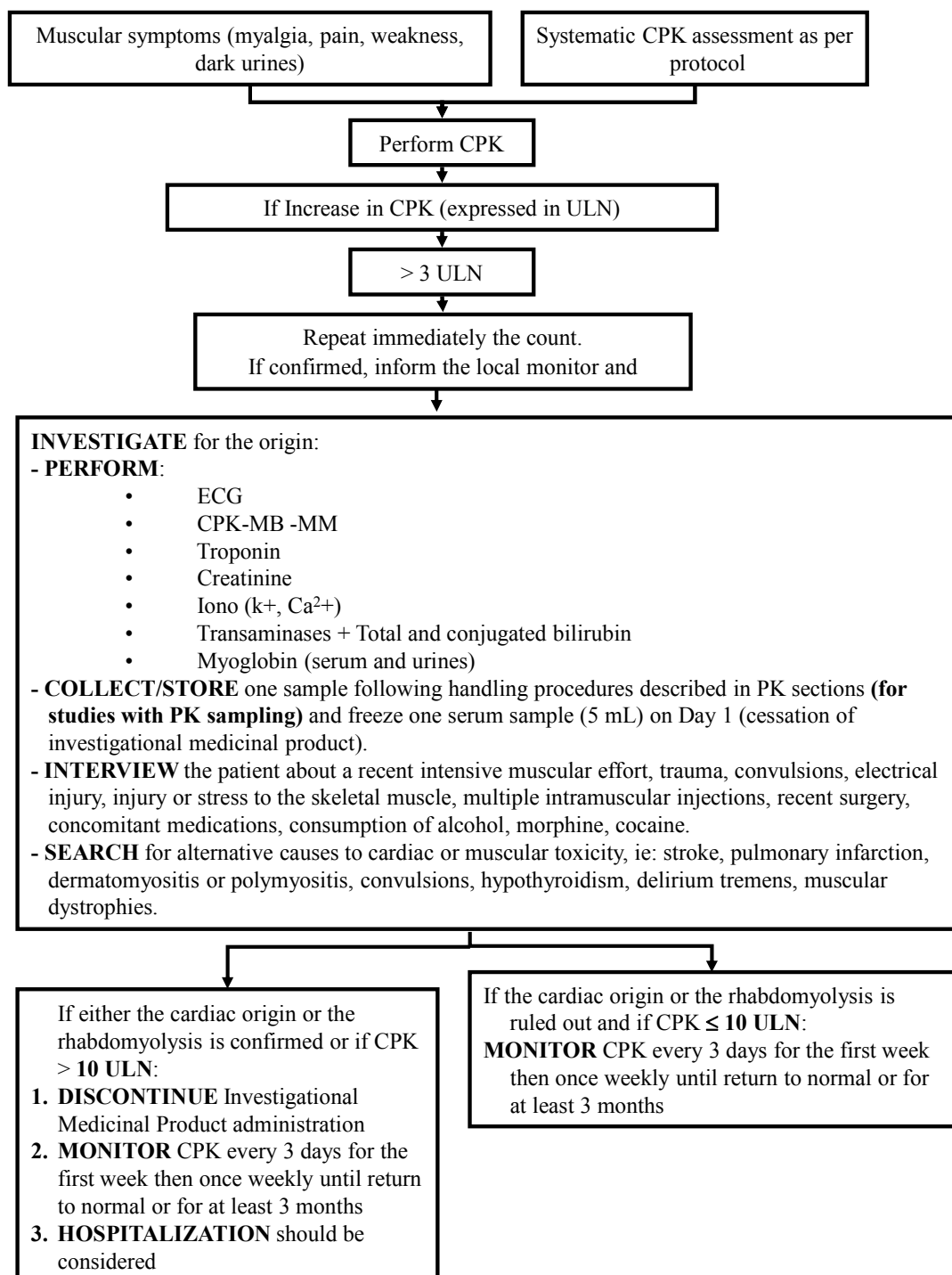
Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in [Section 10.3.1](#) is met.

ACUTE RENAL IMPAIRMENT



Acute renal failure is to be recorded as AE only if at least one of the criteria listed in [Section 10.3.1](#) is met

**INCREASE OF CPK SUSPECTED TO BE OF NON-CARDIAC ORIGIN
AND NOT RELATED TO AN INTENSIVE PHYSICAL ACTIVITY**



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in [Section 10.3.1](#) is met.

Appendix D. Blood Pressure and Pulse Rate monitoring

Equipment

1. Blood pressure measurements will be taken by an automated blood pressure monitor. Same equipment should be used throughout the study and should be calibrated as per manufacturer recommendation.
2. Bladder Length – Should nearly or completely encircle the patient's arm. For many adults, the standard "adult" size bladder is not long enough and the "large" size bladder is recommended.
3. Bladder Width – Should be at least 40% of the bladder length.

Patient Factors

Extraneous variables associated with the measurement of blood pressure (BP) should be minimized. These include:

- Food intake, caffeine-containing beverages, cigarette smoking, or strenuous exercise within 2 hours prior to measurement.
- Full urinary bladder.
- The patient should not talk while BP is being measured.

The proper sized cuff should fit snugly with the lower edge 2 to 3 cm above the antecubital fossa.

The patient should be allowed to sit quietly in a comfortably warm place (temperature around 25°C or 77°F) for 5-10 minutes with the arm supported at heart level, preferably with the cuff in place and with no restrictive clothing on the arm. The patient should be encouraged not to tense his or her muscles.

Determination of the arm with the highest blood pressure

At screening, BP should be measured in both arms after a 10 minute rest period in supine position and also after 3 minutes in standing position. The supine measurements are performed in triplicate with at least 1 minute between BP measurements with the cuff fully deflated between measurements.

The arm with the higher DBP in supine position will be determined at this visit by averaging the 3 DBP values from each side. Blood pressure should be measured in this arm throughout the study (unless a new issue develops that prohibits measurement of BP in that arm).

Measurement Technique

Vital signs measurements for safety evaluation (heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine resting position and – at screening – also after 3 minutes in standing position to reveal patients with orthostatic symptoms at baseline. The supine measurements of SBP, DBP and pulse rate are performed in triplicate with the mean values being

entered into the CRF. For screening, all 3 supine values are entered into the CRF and have to be within the range given in the inclusion criteria.

At some time points, only a single seated blood pressure measurements is scheduled, which has to be performed after 5 minutes in seated position.

Appendix E. Procedure for collection, handling, storage and shipment of sotagliflozin (and its metabolite) specimens plasma concentrations measurements.

1. SAMPLING SUPPLIES DESCRIPTION

| | |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plasma sotagliflozin specimens | Collection material: Blood collection tube with K2 EDTA allowing drawing for 2 mL of blood eg, BD vacutainer (Part no. 367846 or equivalent) |
| | Storage tube: 2 mL polypropylene, screw cap, flat base tubes (Sarstedt PN 72.694 or equivalent). |
| Miscellaneous | Centrifuge Collection material provided by Investigator site |
| | An import permit must accompany each shipment if applicable |
| | Dry ice single use |
| | Specimen labels and shipment documentation for all samples will be provided by the Investigator site |
| | Styrofoam shippers with boxes, shipping labels, Ziploc® storage bag, and any other necessary packaging supplies in order to comply with IATA Dangerous Goods Regulations, Packing Instructions 650 for shipment below 70°C. Plasma: Sample storage boxes (Base area: 136 x 136 mm; Height 50 mm; for 10x10 samples for Sarstedt Micro-Vial, code 72.694) |

2. COLLECTION/HANDLING/PROCESSING OF SAMPLES

Analytical methods used are extremely sensitive (eg, LC/MS-MS). All sampling procedures must be followed accurately.

Due to a high rate of haemolysis the following recommendations are made:

- Use venipuncture as the primary method to obtain blood samples.
- If indwelling catheters are required (poor veins, patient objects to multiple venipunctures, etc.), use vacutainers and no syringes to obtain samples.

2.1. Blood collection for sotagliflozin/sotagliflozin 3-O-glucuronide plasma samples

- **Collection schedule:** Per protocol.
- **Procedure.**
 - Ensure the blood collection tube is clearly and appropriately labeled,

- Collect 2 mL of blood, using the collection tube as indicated in Sampling Supplies Description section. **Note: The collection tube must be filled completely in order to obtain the correct ratio of blood to anticoagulant,**
- Gently invert tube at least 8 times permitting specimen to mix with tube's anticoagulant,
- The exact date and time of sample collection should be recorded on the case report form.

2.2. Plasma samples

- **Procedure – Plasma.**

- **Within an hour of blood collection**, centrifuge at 1500 g for 10 minutes at ambient temperature,
- Immediately following the centrifugation, transfer the top layer of human plasma with a fresh pipette into 1 prelabeled storage tube, being careful not to transfer blood cells,
- Ensure that all sample tubes are clearly and appropriately labeled,
- Immediately cap tubes and freeze the plasma in an upright position at -70 °C for storage.

- **Storage -70°C.**

Samples should be grouped according to patient in a storage container with individual compartments and sent to Bioanalytical laboratory (Covance BioA) for analysis (see Section 4 for shipping address).

- **Labeling of blood and plasma specimens**

Each sample must be labeled with the following minimum information:

| | |
|--------------------------------------------------------------|----------------------------------------------------------|
| Product code: | sotagliflozin |
| Protocol number: | PYD15010 |
| Patient number: | xxx-yyyy-zzzzz (country code-site code- patient code) |
| Sample number: | P00 to P07 (plasma) |
| Sample Day/Nominal timepoint of collection: hours/minutes | eg, D1 0h 0m |
| Compound assayed | PK Plasma Sotagliflozin |

3. PACKAGING AND SHIPMENT OF PHARMACOKINETICS SAMPLES

3.1 Shipment preparation, packaging and shipments

- Samples must be packaged according to IATA Dangerous Goods Regulations, Packing Instructions 650.
- Absorbent material must be placed in the Ziploc storage bag containing samples (See Section 2).
- All bagged samples are to be packed in dry ice in styrofoam shippers with enough dry ice to ensure that the samples remain frozen for a 48-hour period for intracontinental shipments and for a 72-hour period intercontinental shipments. The following table indicates the recommended amount of dry ice that should be used.

| Styrofoam shipper | Shipper: World Courier amount of dry ice | Shipper: other courier amount of dry ice |
|--------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Medium(15" X 13" X 12") (38 X 33 X 31 cm) | 10 lb (4.6 kg) | 20 lb (11.4 kg) |
| Large (15.4" X 22.5" X 15") (39 X 57 X 38 cm) | 20 lb (11.4 kg) | 40 lb (22.8 kg) |

- Place dry ice along the bottom of the styrofoam shipper.
- Place bagged samples on dry ice, add additional dry ice around the sides and top, and add lid.
- The styrofoam shipper should be placed in the cardboard box in which the shipper arrived.
- The fully completed and signed “Shipment Document” must be enclosed in a plastic resealable bag, and then placed on top of the styrofoam shipper between the lid and cardboard box.
- The World Courier waybill and other shipping documents are placed in a documents pouch on the exterior of the box.
- Seal cardboard box and place the “Dry Ice” and “UN3373” labels on the exterior of the cardboard box.
- The exterior of the box should be marked “RUSH – **BIOLOGICAL SUBSTANCE, CATEGORY B** SPECIMENS PACKED IN COMPLIANCE WITH IATA PACKING INSTRUCTIONS – STORED AT -70°C”.
- The INVESTIGATOR SITE must notify the shipment receiver (see shipment contact names and phone numbers in Section 4) **prior to shipment**, with date of shipment and any tracking information.
- **Ship samples to Sponsor only on Monday, Tuesday, or Wednesday for intracontinental shipments, only on Monday or Tuesday for intercontinental shipments, and not on the evening before a public holiday.**

- Specimens will be shipped to the contact names as indicated in Section 4 below, using the fastest possible courier (World Courier for intercontinental shipments is required).

3.2 Shipment Documentation

- The Investigator site must include a shipment manifest to each sample shipment, prepared from their database. The minimum information required in the manifest will be: Product code, Protocol number, patient number, Sample number, Aliquot, Period, Sample Day/Nominal time point of collection (hours/minutes), Compound assayed.

3.3 Acknowledgement of receipt

Upon receipt of the samples at the Bioanalytical laboratory an acknowledgment of receipt will be completed by the shipment receiver and will be sent back to the Investigator site (see Section 4 for contact names at Investigator site).

4. SHIPMENT CONTACT NAMES AND ADDRESSES

Shipment address:

Sample Management- Bioanalytical (Suite B)
Melanie.MccorTipton@Covance.com
Covance Bioanalytical Services, LLC
8211 SciCor Drive, Suite B
Indianapolis, IN 46214
USA

Prior to each shipment of samples, you must notify the dates and waybill number in advance by emailing a “Shipment Notification Form” and “shipment manifest” (excel-form) to:

Contact names

- **Covance Bioanalytical Services LLC (Shipment receiver).**

Melanie.MccorTipton@covance.com

Gregory.Hoback@covance.com

- **Sanofi – Sponsor.**

Amy.Obrien@sanofi.com

Elizabeth.jenkins@sanofi.com

- **Investigator site – Acknowledge of Receipt documentation.**

Anke.Schulze@charite-research.org

PDY15010 16.1.1 Protocol

ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm) |
|------------------|-----------------------------|--------------------------------------------|
| Ruetten, Hartmut | Clinical Approval | 09-Oct-2017 14:14 GMT+0200 |
| Jacob, Yves | Regulatory Approval | 09-Oct-2017 14:24 GMT+0200 |