Official Title: An exploratory, randomized, double-blind, placebo-controlled, parallel arm trial of the safety and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure

NCT Number: NCT03292653

Document Date(s): Protocol Version 2: 02 August 2019

AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: Sotagliflozin / SAR439954

An exploratory, randomized, double-blind, placebo-controlled, parallel arm trial of the safety and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure

STUDY NUMBER: PDY15079

VERSION DATE / STATUS: 01-Aug-2019 / Approved

Version Number:	2	EudraCT IND Number(s) WHO universal trial number:	2017-002774-39 IND [redacted] U1111-1190-7962
Date:	01-Aug-2019	Total number of pages:	124

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CLINICAL TRIAL SUMMARY

COMPOUND: SAR439954 STUDY No : PDY15079

TITLE	An exp oratory, random zed, doub e-b nd, p acebo-contro ed, para e arm tr a of the safety and pharmacodynam c act v ty of sotag f oz n n hemodynam ca y stab e pat ents w th worsen ng heart fa ure.
INVESTIGATOR/TRIAL LOCATION	Pr nc pa Invest gator; Dr. [redacted]. Mu t nat ona , mu t center, Up to 15 s tes for cohort 1 and 2. US on y, m ted number of centers 1-3 for cohort 3
STUDY OBJECTIVE(S)	**Primary objectives:** The pr mary object ve of th s study s the assessment of safety and to erab ty of sotag f oz n, added to the standard of care treatment, n hemodynam ca y stab e pat ents w th worsen ng of heart fa ure, compared to p acebo. A co-pr mary object ve of th s tr a s the est mat on of the effect of sotag f oz n, when added to the standard of care treatment, on changes n p asma vo ume, as assessed by d rect (nd cator d ut on) **and/or** nd rect (hemo-concentrat on) methods, n hemodynam ca y stab e pat ents w th worsen ng of heart fa ure, compared to p acebo. **Secondary objectives**: Exp ore the effect of sotag f oz n, added to standard of care treatment, on erythropo es s, as assessed by changes n p asma erythropo et n eve s, n hemodynam ca y stab e pat ents w th worsen ng of heart fa ure, compared to p acebo. Exp ore the effect of sotag f oz n, added to standard of care treatment, on changes n p asma NT-proBNP eve s, n hemodynam ca y stab e pat ents w th worsen ng of heart fa ure, compared to p acebo. **Other objectives**: Exp ore the effect of sotag f oz n compared to p acebo treatment, n hemodynam ca y stab e pat ents w th worsen ng of heart fa ure, on the fo ow ng endpo nts: Change n tota body water from base ne to 14 days Change n ur c ac d from base ne to 14 days Change n beta-hydroxybutyrate from base ne to 14 days Change n tota b ood vo ume from base ne to 14 days Change n red ce mass from base ne to 14 days Percentage of pat ents w th n 15% of dea b ood vo ume on study day 14 B ood pressure, s tt ng (SBP and DBP) at day 14 compared to base ne
STUDY DESIGN	A random zed, doub e-b nd, p acebo-contro ed, para e arm tr a of the safety, to erab ty and pharmacodynam c act v ty of sotag f oz n n hemodynam ca y stab e pat ents w th worsen ng heart fa ure. Study drug w be n t ated (e ther n the hosp ta or outpat ent fac ty) w th n 7 days fo ow ng comp et on of ntravenous d uret c therapy, and cont nued n an outpat ent

	sett ng for a tota of 14 days. An n t a cohort of pat ents (Cohort 1) w rece ve sotag f oz n 200 mg (approx mate n=10) or p acebo (approx mate n=5) ora y for 14 days. Fo ow ng safety mon tor ng and rev ew of Cohort 1 by the data mon tor ng comm ttee (DMC), Cohort 2 w rece ve sotag f oz n 400 mg (approx mate n=10) or p acebo (approx mate n=5) ora y for 14 days. Fo ow ng safety mon tor ng and rev ew of Cohort 2 by the DMC, conduct of cohort 3 w commence where pat ents w be a ocated to two arms, sotag f oz n 400 mg (approx mate n=17) or p acebo (approx mate n=17) ora y for 14 days.
STUDY POPULATION	Ma e and fema e pat ents, 18 years and o der w th worsen ng of heart fa ure requ r ng adm n strat on of ntravenous d uret cs.
Main selection criteria:	**Inclusion criteria:** **<u>Inclusion criteria at screening</u>** I 01. Wr tten nformed consent; I 02. 18 years of age or o der I 03. Pat ent adm tted to the hosp ta or had urgent v s t to emergency department or heart fa ure un t/c n c or nfus on center for Congest ve Heart Fa ure (CHF), def ned by: - Presence of ≥2 of the fo ow ng c n ca s gns and symptoms of congest on: jugu ar ve n d stens on, p tt ng edema n ower extrem t es greater than trace , dyspnea, ra es heard on auscu tat on, rad ograph c pu monary congest on, we ght ga n above h stor ca dry we ght of at east 5 bs. (2.27 kg) AND - Requ r ng treatment w th IV d uret cs I 04. Est mated g omeru ar f trat on rate (eGFR) ≥30 m /m n/1.73m^2 at the screen ng or random zat on v s t by the 4 var ab e Mod f cat on of D et n Rena D sease (MDRD) equat on I 05. Fema e subject must use a doub e contracept on method dur ng the study nc ud ng a h gh y effect ve method of b rth contro , except f she has undergone ster zat on at east 3 months ear er or s postmenopausa . I 06. Ma e part c pants, un ess vasectom zed and conf rmed ster e by sperm ana ys s, must use condoms dur ng the study and refra n from donat ng sperm up to 90 days after the day of ast dose. If the pat ent has a fema e partner of ch dbear ng potent a , the pat ent must wear a condom and fema e partner must use at east 1 h gh y effect ve method of b rth contro dur ng the study treatment per od and the Fo ow-up per od. **<u>Inclusion criteria at randomization</u>** I 07. Trans t on ng from ntravenous (IV) to ora d uret cs and

	ora d uret c treatment has been prescr bed or adm n stered I 08. Hemodynam ca y stab e, def ned as: -SBP ≥100 mmHg w th no requ rement for IV notropes or IV vasod ators **Exclusion criteria** E01. H story of Type 1 d abetes me tus E02. Appears un ke y or unab e to part c pate n the requ red study procedures, as assessed by the study Invest gator, study coord nator, or des gnee (ex: c n ca y-s gn f cant psych atr c, add ct ve, or neuro og ca d sease) or sect oned due to an off c a or court order E03. Tachyarrhythm a w th ventr cu ar rate> 130 bpm at the t me of screen ng, un ess determ ned to be c n ca y stab e by the nvest gator; or current adm ss on for worsen ng heart fa ure that s c ear y and pr mar y tr ggered by causes such as acute coronary syndrome, pu monary embo sm, cerebrovascu ar acc dent, heart va ve d sorders (such as severe aort c stenos s), as determ ned by the Invest gator E04. C n ca y s gn f cant myocard a nfarct on (MI) w th n past 1 month as determ ned by Invest gator and w th object ve ev dence from ECG, and/or card ac mag ng and/or coronary ang ography. Sma so ated e evat ons n tropon n that often accompany HF hosp ta zat on are not an exc us on, nor are c n ca y s gn f cant MIs that have been re-vascu ar zed w thout comp cat ons E05. Pat ents who recent y had or schedu ed to have card ac ntervent ons may be e g b e f: -Stab e 48 hours post procedure AND -Have d uret c treatment p anned for the durat on of treatment n th s study E06. Current use of or recent suspens on of d gox n therapy w th h gh eve s of d gox n (eve shou d be obta ned and must be <1.2 ng/mL) at screen ng. E07. H story of heart or k dney transp ant E08. D agnos s of hypertroph c obstruct ve card omyopathy E09. End-stage HF def ned as requ r ng eft ventr cu ar ass st dev ce nsert on, ntra-aort c ba oon p acement (IABP), or any type of mechan ca support dur ng the study per od E10. Pregnancy (demonstrated by serum pregnancy test at screen ng), breast-feed ng, or nab ty or refusa to undergo pregnancy test ng E11. Use of any nvest gat ona drug(s) or proh b ted therapy or sod um-g ucose co-transporter 2 (SGLT2) nh b tor 5 ha f- ves pr or to screen ng E12. Pat ents w th moderate or severe resp ratory, hepat c, neuro og ca , psych atr c, act ve ma gnant tumor or

	other major system c d sease (nc ud ng any d seases w th ev dence of ma absorpt on), mak ng mp ementat on of the protoco and/or the nterpretat on of the study resu ts d ff cu t E13. Known a erg es, hypersens t v ty, or nto erance to sotag f oz n or any nact ve component of sotag f oz n or p acebo (.e.,, m crocrysta ne ce u ose, croscarme ose sod um [d s ntegrant], ta c, s con d ox de, and magnes um stearate [non-bov ne]), un ess the react on s deemed rre evant to the study by the PI E14. Laboratory f nd ngs at the Screen ng V s t: a. A an ne am notransferase (ALT) or aspartate am notransferase (AST) >3 t mes the upper m t of the norma aboratory range (ULN) (1 repeat ab a owed) b. Tota b rub n >1.7 t mes the ULN (except n case of G bert's syndrome) (1 repeat ab a owed) c. Amy ase and/or pase > 3 t mes the ULN (1 repeat ab a owed) E15. Pat ents w th a severe or pers stent n sp te of opt ma treatment gen tour nary tract nfect on at t me of random zat on. E16. Pat ent s the Invest gator or any Sub- nvest gator, research ass stant, pharmac st, study coord nator, other staff or re at ve thereof d rect y nvo ved n the conduct of the protoco **Additional exclusion criteria for patients with diabetes** E17. H story of d abet c ketoac dos s or non-ketot c hyperosmo ar coma w th n 3 months pr or to the screen ng v s t E18. Lower extrem ty d abet c comp cat ons (such as sk n u cers, nfect on, osteomye t s and gangrene) dent f ed dur ng the Screen ng per od, and st requ r ng treatment at Random zat on
Total expected number of patients: **Expected number of sites:**	Approx mate y 64 pat ents comp et ng treatment w be enro ed. Up to 15 s tes
STUDY TREATMENT(s) **Investigational medicinal product(s)**	Sotag f oz n 200 mg (on y cohort 1): • 200 mg tab ets • Ora • 200 mg, adm n stered as one (1) 200-mg tab et p us one (1) p acebo tab et (dent ca to sotag f oz n 200 mg n appearance), once da y pr or to the f rst mea of the day for 14 days. Sotag f oz n 400 mg (cohorts 2 and 3): • 200 mg tab ets • Ora • 400 mg, adm n stered as two (2) 200-mg tab ets, once da y pr or to the f rst mea of the day for 14 days. P acebo (a cohorts):

Non investigational medicinal product(s) (NIMP)	• Tab ets dent ca n appearance to sotag f oz n 200 mg • Ora • P acebo adm n stered as two (2) p acebo tab ets, (dent ca to sotag f oz n 200 mg n appearance), once da y pr or to the f rst mea of the day for 14 days. **^{131}I-albumin**: Supp ed as ≤25µC n 1m at date of ca brat on. Each m conta ns: 10mg human a bum n (non-react ve to HBsAg) 16mg sod um d bas c phosphate 1.6mg sod um monobas c phosphate 0.4mg guan d ne hydroch or de Sod um ch or de 9mg benzy a coho Route of adm n strat on: Intravenous Dose reg men: 10mg (≤25 µC) adm n stered once on study Days 1 and 14. **Deuterium Oxide:** Formu at on; deuter um ox de 10 g / 10 mL pre-ster zed v a or ora syr nge w th t p cap for entera adm n strat on Route of adm n strat on: Ora Dose reg men: V a or Syr nge contents d uted to a vo ume of 100 mL n ster e water, adm n stered once on study Day 1 and 14
PRIMARY ENDPOINT(S) AND MAIN SECONDARY ENDPOINT(S)	**Primary endpoints:** Safety and To erab ty: Safety assessment nc ude: AEs, hypog ycem a (a Invest gator reported events, severe and/or documented symptomat c or asymptomat c), Events of Spec a Interest (EOSIs), Adverse Events of Spec a Interest (AESIs), AEs ead ng to d scont nuat on from the IMP, ser ous AEs (SAEs), and deaths. C n ca aboratory resu ts V ta s gns and e ectrocard ogram (ECG) resu ts. Pharmacodynam c: Changes n hemoconcentrat on from base ne to 14 days. Changes n p asma vo ume from base ne to 14 days. **Secondary endpoints:** Change n erythropo et n from base ne to 14 days Change n NT-proBNP from base ne to 14 days **Other endpoints:** Change n tota body water from base ne to 14 days Change n ur c ac d from base ne to 14 days Change n beta-hydroxybutyrate from base ne to 14 days Change n tota b ood vo ume from base ne to 14 days

	Change n red ce mass from base ne to 14 days Percentage of pat ents w th n 15% of dea b ood vo ume on study day 14 B ood pressure, s tt ng (SBP and DBP) at day 14 compared to base ne
ASSESSMENT SCHEDULE	Screen ng w occur when pat ents are hosp ta zed or had urgent v s t to emergency department or heart fa ure un t/c n c or nfus on center and treated w th ntravenous d uret cs for worsen ng heart fa ure. Random zat on (Day1) w take p ace w th n 7 days fo ow ng d scont nuat on of ntravenous treatment w th d uret cs. Base ne aboratory parameters, tota body water and p asma vo ume measurements, n t at on of IMP adm n strat on occur on Day 1. The f na assessment for hemoconcentrat on, tota body water and p asma vo ume changes w be on day 14+/-1 day.
STATISTICAL CONSIDERATIONS	**Pharmacodynamic endpoints** Descr pt ve stat st cs for the pharmacodynam c endpo nts, as raw data and change from base ne w be prov ded by treatment. S m ar y t me prof e p ots of mean ± SEM w be prov ded by treatment for a pharmacodynam cs endpo nts. **Safety** The safety ana ys s w be based on the rev ew of descr pt ve stat st cs (summary tab es) and nd v dua data for v ta s gns, rena funct on, adverse events (AEs) and other c n ca aboratory va ues and ECG parameters. Adverse events w be coded us ng Med ca D ct onary for Regu atory Act v t es (MedDRA) n an updated vers on ava ab e at the study, and the number of pat ents w th Treatment-Emergent Adverse Events (TEAEs) w be summar zed. Potent a y c n ca y s gn f cant abnorma t es (PCSAs) for c n ca aboratory, v ta s gn, and ECG data and out-of-norma range va ues for c n ca aboratory data w be f agged and summar zed n frequency tab es.
DURATION OF STUDY PERIOD **(per subject)**	- Screen ng: 1-21 days - Treatment per od: 14±1 days - Fo ow-up: 14±2 days Tota study durat on: 26 – 51 days
STUDY COMMITTEES	**Steering committee:** No **Data monitoring committee:** Yes **Clinical Endpoint Committees**: No

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendement	Date, version
Amended C n ca Tr a Protoco 03	A	01-Aug-2019, vers on 2 (e ectron c 7.0)
Protoco Amendment 03 (Canada)	Canada	18-Ju -2018, vers on 1 (e ectron c 1.0)
Amended C n ca Tr a Protoco 02	A	04-Mar-2018, vers on 1 (e ectron c 1.0)
Protoco Amendment 02	A	14-Mar-2018, vers on 1 (e ectron c 1.0)
Amended C n ca Tr a Protoco 01	A	09-Jan-2018, vers on 1 (e ectron c 1.0)
Protoco Amendment 01	A	28-Feb-2018, vers on 1 (e ectron c 1.0)
Or g na Protoco	A	05-Ju -2017, vers on 1 (e ectron c 1.0)

OVERALL RATIONALE FOR THE AMENDMENT

During the conduct of the first two cohorts of this study, it was determined through data from concurrent studies that the 200mg dose level would not be explored further as a therapeutic dose. To reduce the burden on patients, the 200mg dose level is being removed from cohort 3, and the study is being simplified without compromising patient safety or scientific merit.

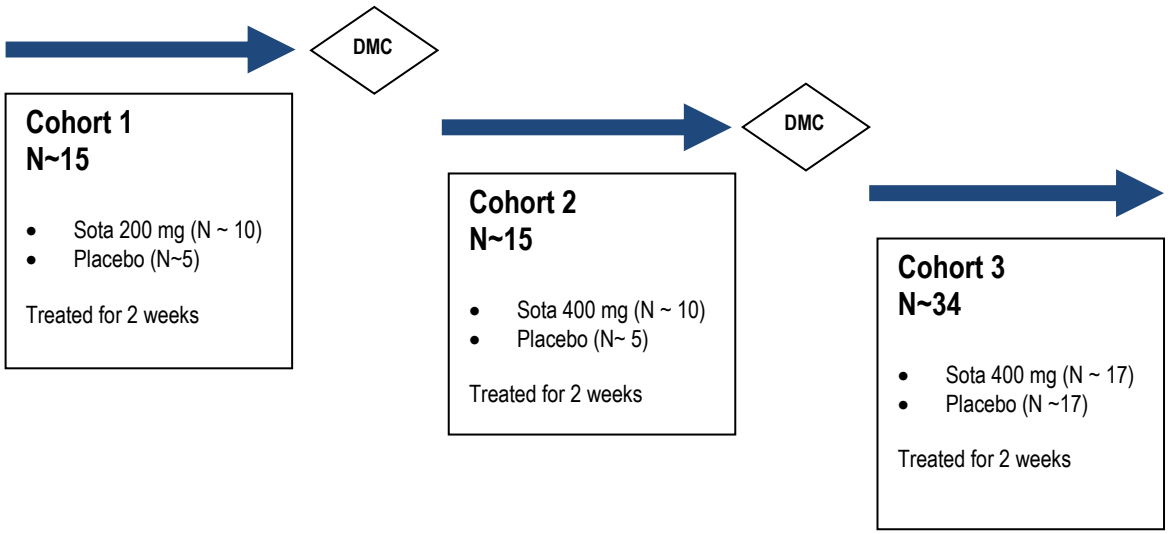
Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Sect on 1.1 Graph ca des gn (th s change was made to the c n ca tr a summary tab e), Sect on 6.1 Descr pt on of study (reca cu ated n tab e1), sect on 8.1 Number of pat ents p anned, 10.1.3 Assessment schedu e nc ud ng reca cu ated tab e 6	The 200mg arm was removed from cohort 3 w thout rep ac ng subjects	Reduce the tota number of subjects to 64. the sponsor s proceed ng deve opment w th 400mg dose on y
Sect on 1.4 f ow chart (cohort 3), sect on1.5 per od f owchart (cohort 3), sect on 13.1.3.4 V s t 3 and v s t 4, and numerous ment ons of v s t 3 and/or 4 n the text	In cohort 3 forgo V s t 4 v s t 3 w occur between Day 6 and Day 8 v s t, hence obv at ng one s te v s t. In order to prevent confus on the or g na v s t number ng w be kept as n cohort 1 and 2, n f owcharts and n text v s t 4 n cohort 3 w be devo d of any v s t act v ty.	Reduce the burden off the pat ent - trave ng to the s te
Sect on 10.3 Pharmacok net cs, nc ud ng reca cu at ng Tab e 9, Sect on 1.4 f ow chart (cohort 3), sect on1.5 per od f owchart (cohort 3)	PK assessments were removed from cohort 3.	PK samp ng mposed a substant a burden for pat ents part c pat ng n the tr a , and as a consequence, t was removed. PK s not a pr mary object ve n th s study; forgo ng PK samp ng s not comprom s ng ts sc ent f c va ue
C n ca tr a summary, Sect on 8.3 Exc us on cr ter a exc us on cr ter on 03	Current y: E03.Current adm ss on or v s t for Worsen ng HF that s c ear y and pr mar y tr ggered by causes such as tachyarrhythm a (examp e: susta ned ventr cu ar tachycard a, or atr a f br at on/f utter w th susta ned ventr cu ar response > 130 beats per m nute), acute coronary syndrome, pu monary embo sm, cerebrovascu ar acc dent, heart va ve d sorders (such as severe aort c stenos s), as determ ned by the Invest gator Changed to: E03.Tachyarrhythm a w th ventr cu ar rate> 130 bpm at screen ng, un ess determ ned to be c n ca y stab e by the nvest gator; or current adm ss on for worsen ng heart fa ure that s c ear y and pr mar y	C ar f cat on that tachycard a >130 at screen ng s grounds for exc us on

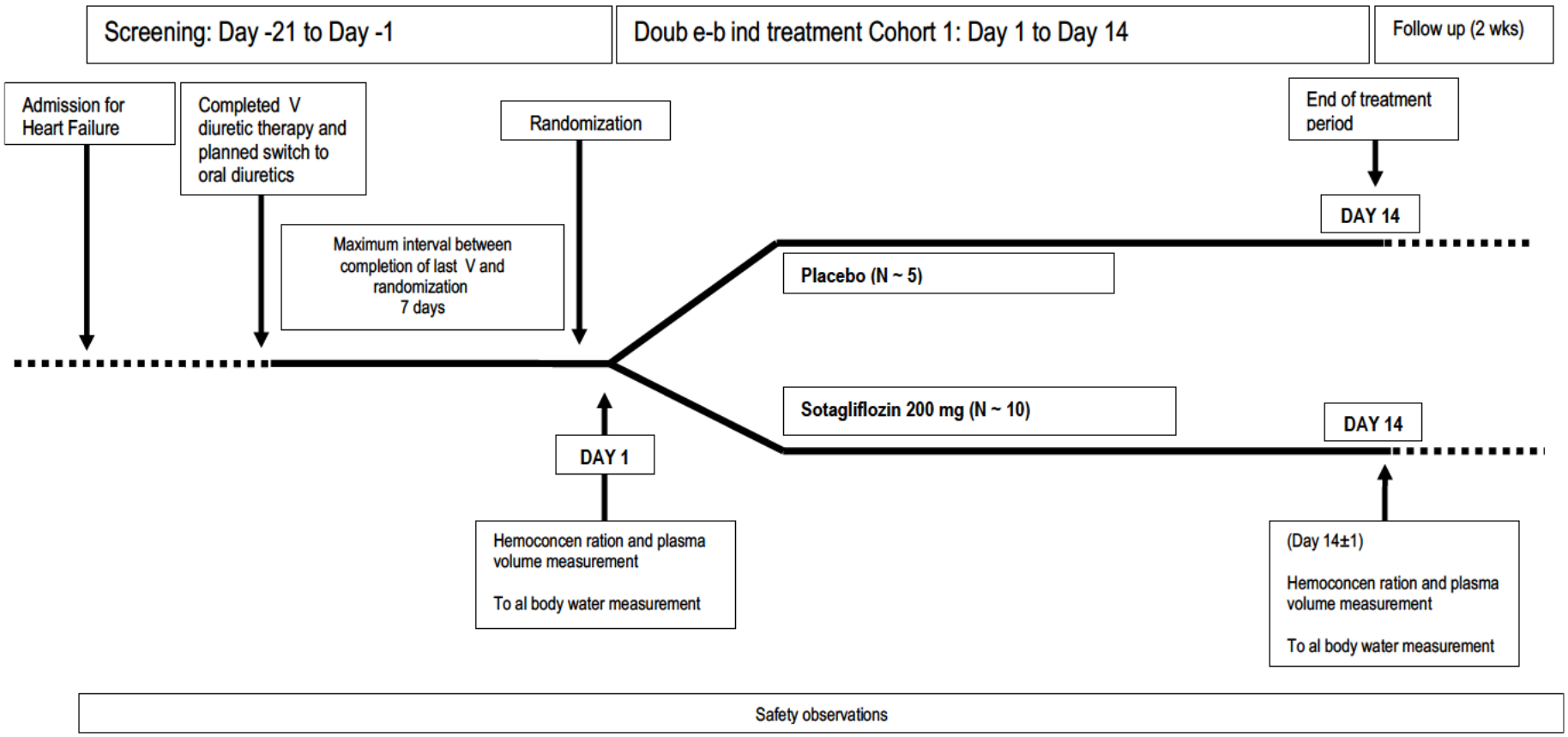
Section # and Name	Description of Change	Brief Rationale
	tr ggered by causes such as acute coronary syndrome, pu monary embo sm, cerebrovascu ar acc dent, heart va ve d sorders (such as severe aort c stenos s), as determ ned by the Invest gator	
Sect ons: C n ca tr a summary n stat st ca cons derat on and n study des gn A so; Sect on 14.10 Inter m ana ys s	Remove reference to nter m ana ys s	The IA was or g na y ntended to assess safety and to cons der whether the number of subjects needs to be ncreased go ng forward w th cohort 3. Accumu at ng favorab e safety data n the CHF n th s study and other ongo ng stud es w th arger number of subjects and onger exposure obv ated the need to study the ower dose of 200mg. There the number of the rema n ng subjects who are on 400 mg s too sma for a mean ngfu IA. Hence the IA was removed.
Sect on13.1.4 Study restr ct ons	In cohort 3 remove the requ rement to eat 15 m nutes after IMP adm n strat on	Invest gators not ce that th s s d ff cu t for the subjects to comp y and record feed ng t mes

1 FLOW CHARTS

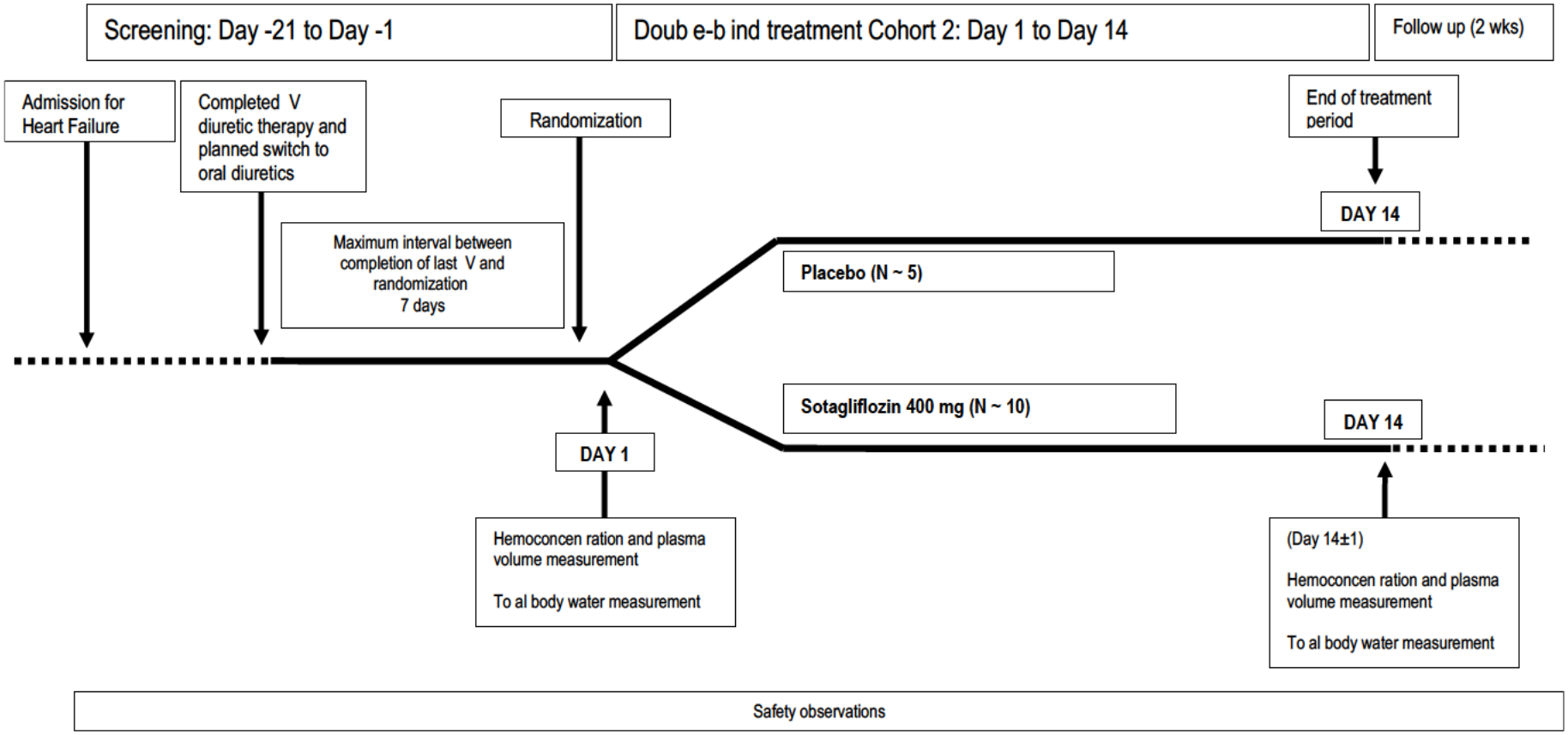
1.1 GRAPHICAL STUDY DESIGN



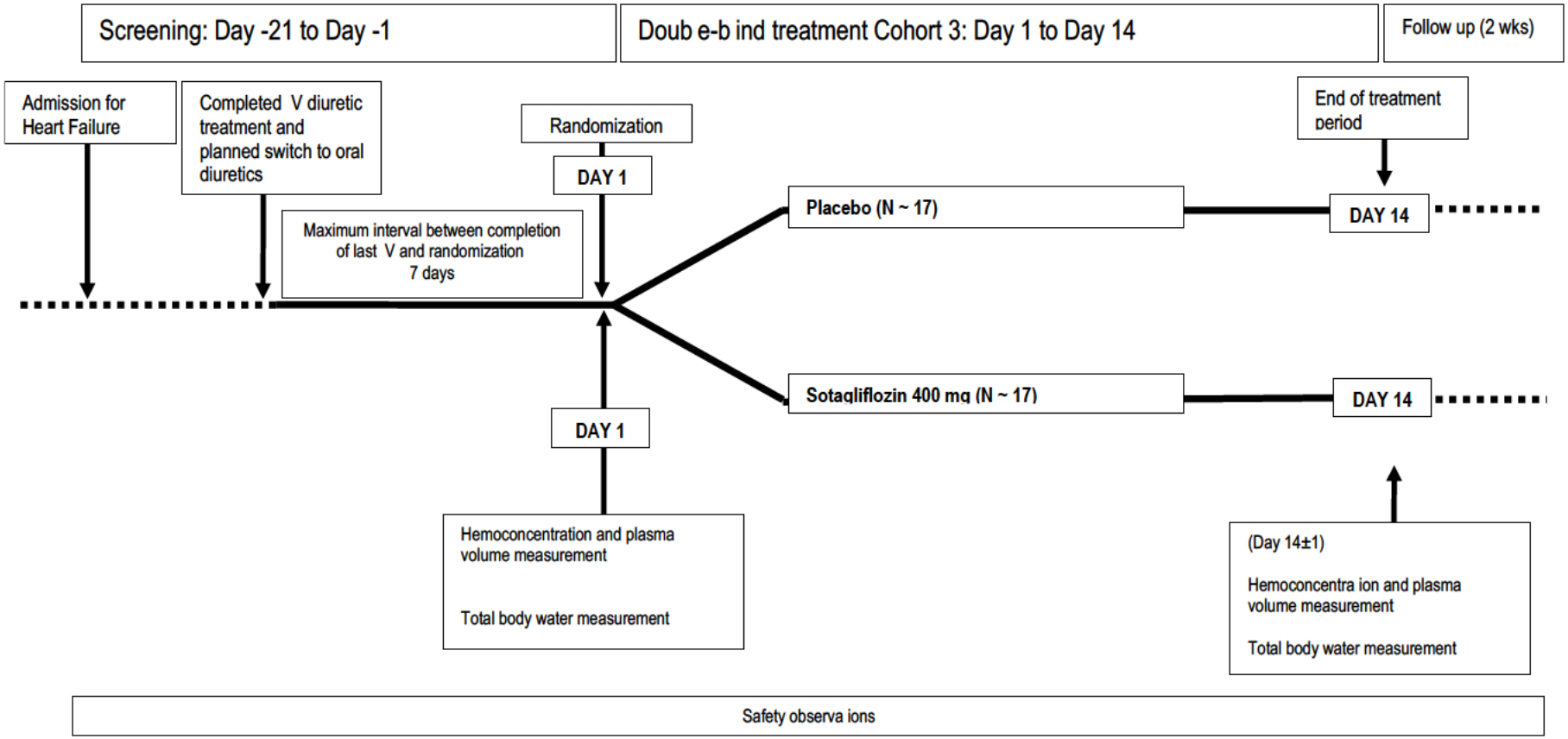
COHORT 1 (N~15)

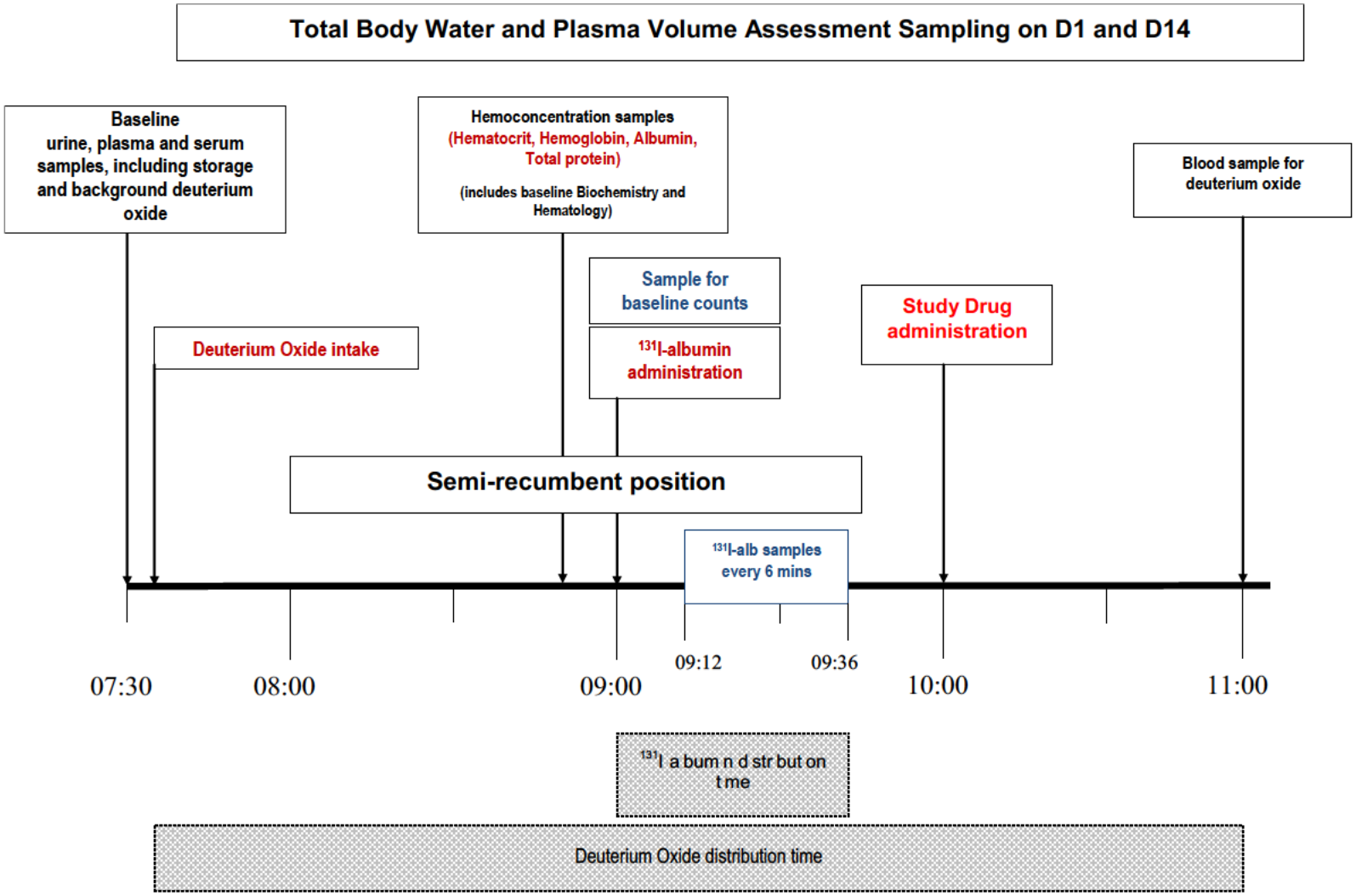

Screening: Day -21 to Day -1
Doub e-b ind treatment Cohort 1: Day 1 to Day 14
Follow up (2 wks)
Admission for Heart Failure
Completed V diuretic therapy and planned switch to oral diuretics
Maximum interval between completion of last V and randomization 7 days
Randomization
End of treatment period
DAY 14
Placebo (N ~ 5)
Sotagliflozin 200 mg (N ~ 10)
DAY 14
DAY 1
Hemoconcen ration and plasma volume measurement
To al body water measurement
(Day 14±1)
Hemoconcen ration and plasma volume measurement
To al body water measurement
Safety observations

COHORT 2 (N~15)


Screening: Day -21 to Day -1
Doub e-b ind treatment Cohort 2: Day 1 to Day 14
Follow up (2 wks)
Admission for Heart Failure
Completed V diuretic therapy and planned switch to oral diuretics
Maximum interval between completion of last V and randomization 7 days
Randomization
End of treatment period
DAY 14
Placebo (N ~ 5)
Sotagliflozin 400 mg (N ~ 10)
DAY 14
DAY 1
Hemoconcen ration and plasma volume measurement
To al body water measurement
(Day 14±1)
Hemoconcen ration and plasma volume measurement
To al body water measurement
Safety observations

COHORT 3 (N~34)


Screening: Day -21 to Day -1
Doub e-b ind treatment Cohort 3: Day 1 to Day 14
Follow up (2 wks)
Admission for Heart Failure
Completed V diuretic treatment and planned switch to oral diuretics
Randomization
DAY 1
Maximum interval between completion of last V and randomization 7 days
End of treatment period
Placebo (N ~ 17)
DAY 14
Sotagliflozin 400 mg (N ~ 17)
DAY 14
DAY 1
Hemoconcentration and plasma volume measurement
Total body water measurement
(Day 14±1)
Hemoconcentra ion and plasma volume measurement
Total body water measurement
Safety observa ions


Total Body Water and Plasma Volume Assessment Sampling on D1 and D14
Baseline urine, plasma and serum samples, including storage and background deuterium oxide
Hemoconcentration samples (Hematocrit, Hemoglobin, Albumin, Total protein)
(includes baseline Biochemistry and Hematology)
Blood sample for deuterium oxide
Sample for baseline counts
Study Drug administration
Deuterium Oxide intake
131I-albumin administration
Semi-recumbent position
131I-alb samples every 6 mins
09:12
09:36
07:30
08:00
09:00
10:00
11:00
131I albumin distribution time
Deuterium Oxide distribution time

1.2 STUDY FLOW CHART FOR COHORTS 1 AND 2

Phase	Screening	Treatment Period				Follow-up
VISIT	1	2	3	4	5 (EOT)	6 (EOS)
Day	D-21 to D-1[a]	D1	Between D3 and D6	Between D8 and D11	D14+/-1 [b]	Between D26 and D30
Informed consent[c]	X					
Discharge[c]	<------ X------>					
IRT contact	X	X			X	X
Visit at clinical site[d]		X	X[e]	X[e]	X[e]	X
Phone check/Visit at clinical site[g]						X
Inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Prior/concomitant medications	< ----------X---------- >					
Randomization[h]		X				
Meal[i]		X	X	X	X	
Diary[j] (daily): IP intake, concomitant medications, AE BP[k]		X	<----------X---------->			
Study treatment administration[l]						
IMP dispensing		X				
IMP administration		<---------- X---------->				
^{131}I-albumin injection (for plasma volume assessment)		X			X	
Deuterium oxide intake (for total body water assessment)		X			X	
Safety						
Physical examination[m]	X	X			X	
Height	X					
Body weight[n]	X	X			X	
Echocardiogram[o]	X					
[redacted]						
Vital signs[f], ECG[p]	X	X	X	X[p]	X	
Body temperature[q]	X	X			X	
Hematology[r]	X	X[t]			X[t]	
Biochemistry[s]	X	X[t]	X	X	X[t]	
Liver function (AST, ALT, ALP, GGT, total and conjugated bilirubin)	X	X	X	X	X	
Urine (Lab)		X	X	X	X	

Phase	Screening	Treatment Period				Follow-up
VISIT	1	2	3	4	5 (EOT)	6 (EOS)
Day	D-21 to D-1[a]	D1	Between D3 and D6	Between D8 and D11	D14+/-1 [b]	Between D26 and D30
β-HCG blood test[u]	X				X	
Plasma FSH[u]	X					
Adverse event collection	< ----------X---------->					
Pharmacokinetics						
Sotagliflozin pharmacokinetic plasma samples[v]		X	X	X	X	
Pharmacodynamics						
Blood collection for hemoconcentration samples [w]		X			X	
Blood collection for ^{131}I-albumin		X			X	
Blood collection for deuterium oxide		X			X	
Uric acid		X			X	
Erythropoietin		X			X	
NT-proBNP		X			X	
Beta-hydroxybutyrate		X			X	

[redacted]

a The laboratory evaluation closest to D1 will be used as the screening lab in case of discrepancies with prior labs. Oral hypoglycemic drugs and long-acting insulin should not be administered the morning of D1 or D14. If appropriate (for example, for patients admitted in the early morning hours), screening procedures may also take place on D1.

b Sites should adhere to D14 whenever possible

c Occasionally, a patient might be admitted, screened and randomized on the same day. In those cases, informed consent will also be sought during that day. In other cases, randomization may take place before discharge from hospital or admitting unit. If discharge is before D1, then the patient will come back to the site at D1 (Visit 2) for Randomization and IMP dispensing. For hospitalized patients eligible for discharge on study day D1, the timing of discharge is at the discretion of the treating physician but should not be less than 6 hours following administration of study drug. Patients that are not eligible for discharge, may complete all or part of the study as inpatients (hospital or other appropriate unit).

d Those visits need not be in an outpatient setting. For example, where mobility issues might cause restrictions, or patient is in a step-down unit or rehabilitation ward, the Investigator or designee could perform the Visit and relevant assessments and collect blood or urine samples at that setting. Visit 6 is the end of study visit (EOS). All patients will have a phone check at EOS. Patients may return to the clinical site if, in the judgment of the Investigator, may require a physical examination and additional investigations. A telephone call may also be scheduled soon after the End of Treatment Visit 5.

e IMP accountability and compliance check performed at end of treatment (EOT) Visit 5 and on visits planned at clinical site (Visit 3 and Visit 4)

f Vital signs: including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting (preferably sitting) resting position. For patients returning to the day unit for D1, they should stay in the unit. Their vital signs will be assessed at baseline and every 2 hours after administration of IMP. Patients should be monitored for at least 6 hours prior to discharge from the unit.

g Phone check will be to record any adverse events that occurred after study drug discontinuation, and to record daily BP readings since EOT Visit 5. Patients may return for a further visit (Visit 6) if in the opinion of the investigator they need a follow up examination and/or investigations.

h IRT contact for screening/randomization. Randomization within 7 days of discontinuation of IV diuretic therapy.

i Meals should be taken approximately 15 min after IMP administration throughout the study. On study day Visits 2 and 5, and Visits 3 and 4, patients should fast for approximately 6 hours prior to IMP administration.

j Diary dispensed on D1 (Visit 2). The diary will be reviewed and information recorded on eCRF. If the last follow up is by phone check, all relevant information will be captured and transcribed to the eCRF. Patients who may need to remain inpatients for some or all of the visits will also receive a diary. While inpatients, relevant data such as AE and IMP intake will be entered into the diary. For inpatients, BP and concomitant medications will be recorded in the patient source documents. Those who become eligible for discharge will also receive BP monitors and continue with diary updates on a daily basis.

k Patients will be taught how to perform the automated BP readings. Automated BP readings will be performed in triplicate, between 6 AM to 10 AM on a daily basis, starting D2 and ending at the last post-study follow up.

l Study treatment ends on Day 14 (EOT).

m Physical examination includes at a minimum: heart and respiratory auscultation; peripheral arterial pulse; pupil, and abdomen examination. All physical examinations in diabetic patients, including abbreviated physical examinations, will include examination of the lower extremities to evaluate for any evidence of foot ulcers or infection should be performed as part of the general physical examination and this examination should be documented on the e-CRF.

n All body weight measurements on scale provided by site staff.

o All patients must have a documented echocardiogram, either performed during current admission or within 12 months from the index hospitalization.

p ECG at Visit 2, Visit 3 and EOT Visit 5 only.

q Oral or tympanic body temperature.

r Complete blood count / hematocrit / hemoglobin.

s Creatinine, urea, electrolytes.

t For Visits 2 (Day 1) and 5 (Day 14±1), those samples will be obtained as part of the Hemoconcentration sampling, thus no additional samples for Hematology or Biochemistry are required. It is indicated here as a reminder that baseline hematology and biochemistry is done on Visits 2 and 5. For all other Visits, Hematology and Biochemistry samples are to be obtained as indicated.

u Beta-HCG test will be for all women of child-bearing potential as defined in the inclusion/exclusion criteria, and FSH to assess menopausal status when necessary.

v Pharmacokinetic samples taken on Visit 3 and Visit 4 are pre-dose drug treatment samples.

w Hemoconcentration is determined by measurement of hematocrit, hemoglobin, albumin and total protein. Baseline biochemistry (creatinine, urea and electrolytes) and hematology (CBC) is also determined from those samples.

1.3 PERIOD FLOW CHART (COHORT 1 AND 2)

VISIT		VISIT 2 and VISIT 5										VISIT 3		VISIT 4	
Day		D1 and D14(+/- 1 day)[a]										Between Day 3 and Day 6		Between Day 8 – and Day 11	
Time (hour/minute)	-3H	-2.5H	-2H	-1H	0H	0.5H	1H	3H	4H	5H	6H	-2.5 H	0H	-2.5H	0 H
Indicative clock time	7 am	7:30am	8 am	9:00 am	10 am	10:30am	11 am	1 pm	2 pm	3 pm	4 pm				
Discharge[b]											X				
Concomitant medications				<- ->											
Randomization[c]	X														
IMP accountability and compliance		<- - - - - - - - - - - - - - - - X - - - - - - - - - - - - - - - - - - ->										X		X	
Inclusion/Exclusion criteria[c]	X														
Meal[e]					X								X		X
Semi-recumbent position			<---------- X -------->												
Study treatment administration															
IMP administration					X								X		X
^{131}I-albumin injection				X											
Deuterium oxide intake[f]		X													
Safety															
Physical examination	X														
Vital signs	X					<------------------ ----X[g]----------------->						X		X	
Body weight[o]	X														
[redacted]															
ECG	X											X			
Urine (lab)		X										X		X	
Hematology				X[h]											
Biochemistry				X[h]								X		X	
β-HCG[i]		X													
Liver function (AST,ALT, ALP, GGT, total and conjugated bilirubin)[j]			X									X		X	
Adverse event collection					<------------------------------X--------------------------->										

VISIT		VISIT 2 and VISIT 5										VISIT 3		VISIT 4	
Day		D1 and D14(+/- 1 day)[a]										Between Day 3 and Day 6		Between Day 8 – and Day 11	
Time (hour/minute)	-3H	-2.5H	-2H	-1H	0H	0.5H	1H	3H	4H	5H	6H	-2.5 H	0H	-2.5H	0 H
Indicative clock time	7 am	7:30am	8 am	9:00 am	10 am	10:30am	11 am	1 pm	2 pm	3 pm	4 pm				
Pharmacokinetics															
Sotagliflozin plasma samples[k]		**Day 14:** P04							**Day 1:** P00 **Day 14:** P05		**Day 1:** P01 **Day 14:** P06	P02		P03	
Pharmacodynamics															
Blood collection Hemoconcentration,[l]				X											
Blood collection for ^{131}I-albumin				X[m]											
Blood collection for deuterium oxide[n]		X					X								
Uric acid		X													
Erythropoietin		X													
NT-ProBNP		X													
Beta-hydroxybutyrate		X													
[redacted]															

a Sites should adhere to D14 whenever possible

b For hospitalized patients eligible for discharge on study day D1,,the timing of discharge from the hospital is at the discretion of the treating physician but should not be less than 6 hours following the administration of study drug. Patients that are not eligible for discharge, may complete all or part of the study as inpatients (hospital or other appropriate unit). For patients returning to the day unit for D1, they should also stay in the unit and have their vital signs assessed every 2 hours after IMP administration and discharged not sooner than 6 hours after IMP administration. Laboratory tests may be performed in the hospital or outpatient unit, depending on whether the patient remains hospitalized.

c Day 1 only. IRT contact for randomization. The time is indicative, as randomization should take place after review of inclusion/exclusion criteria

[redacted]

e Meal to be taken within 15 minutes after administration of study drug.

f Deuterium oxide intake should take place after blood collection for baseline measurements.

g Vital signs: including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting (preferably sitting) resting position. For patients returning to the day unit for D1, they should stay in the unit. Their vital signs will be assessed at baseline and every 2 hours after administration of IMP. Patients should be monitored for at least 6 hours prior to discharge from the unit.

h For Visits 2 (Day 1) and 5 (Day 14±1), those samples will be obtained as part of the Hemoconcentration sampling, thus no additional samples for Hematology or Biochemistry are required. It is indicated here as a reminder that baseline hematology and biochemistry is done on Visits 2 and 5. For all other Visits, Hematology and Biochemistry samples are to be obtained as indicated.

i β-HCG performed at screening and D14 only

j Indicative time. Those samples can be obtained at the same time as the other samples are collected, eg, biochemistry.

k Pharmacokinetic samples at T(-2.5H) collected only on Visit 3, Visit 4 and Visit 5 (D14±1).

l Hemoconcentration is determined using the following: Hematocrit, hemoglobin, total protein and albumin. Baseline biochemistry (creatinine, urea, electrolytes) and complete blood count will also be determined from those samples

m One sample will be collected just before injection of ^{131}I-albumin (-1H, PD00) and further sample collection will start 12 min following the injection. Samples will then be collected every 6 minutes starting – 0H48min: -0H48min (PD01), -0H42min (PD02), -0H36min(PD03), -0H30min(PD04), -0H24min(PD05) min. For blood collection on D14 sample notation should be: -1H (PD06), -0H48min (PD07), -0H42min (PD08), -0H36min(PD09), -0H30min(PD10), -0H24min(PD11)

n Following administration of deuterium oxide, blood collection on D1: At -2.5H (PY00), 1H (PY01), and on Day 14: At -2.5H (PY02), 1H (PY03)

o All body weight measurements on scale provided by site staff

[redacted]

1.4 STUDY FLOW CHART COHORT 3 (FORGO VISIT 4 AND KEEP VISIT NUMBERING AS IN COHORT 1 AND 2)

STUDY FLOW CHART FOR COHORT 3 (forgo visit 4)

Phase	Screening	Treatment Period				Follow-up
VISIT	1	2	3	4	5 (EOT)	6 (EOS)
Day	D-21 to D-1[a]	D1	Between D6 and D8	Forgo	D14+/-1 [b]	Between D26 and D30
Informed consent[c]	X					
Discharge[c]	<------ X------>					
IRT contact	X	X			X	X
Visit at clinical site[d]		X	X[e]		X[e]	X
Phone check/Visit at clinical site[g]						X
Inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Prior/concomitant medications	< ----------X---------- >					
Randomization[h]		X				
Meal[i]		X	X		X	
Diary[j] (daily): IMP intake, concomitant medications, AE BP[k]		X	<----------X---------->			
Study treatment administration[l]						
IMP dispensing		X				
IMP administration		<---------- X---------->				
^{131}I-albumin injection (for plasma volume assessment)		X			X	
Deuterium oxide intake (for total body water assessment)		X			X	
Safety						
Physical examination[m]	X	X			X	
Height	X					
Body weight[n]	X	X			X	
Echocardiogram[o]	X					
Vital signs[f], ECG[p]	X	X	X		X	
Body temperature[q]	X	X			X	
Hematology[r]	X	X[t]			X[t]	
Biochemistry[s]	X	X[t]	X		X[t]	
Liver function (AST, ALT, ALP, GGT, total and conjugated bilirubin)	X	X	X		X	
Urine (Lab)		X	X		X	

Phase	Screening	Treatment Period				Follow-up
VISIT	1	2	3	4	5 (EOT)	6 (EOS)
Day	D-21 to D-1[a]	D1	Between D6 and D8	Forgo	D14+/-1 [b]	Between D26 and D30
β-HCG blood test[u]	X				X	
Plasma FSH[u]	X					
Adverse event collection	< ---------- X ---------->					
Pharmacodynamics						
Blood collection for hemoconcentration samples [v]		X			X	
Blood collection for ^{131}I-albumin		X			X	
Blood collection for deuterium oxide		X			X	
Uric acid		X			X	
Erythropoietin		X			X	
NT-proBNP		X			X	
Beta-hydroxybutyrate		X			X	
[redacted]						

a The laboratory evaluation closest to D1 will be used as the screening lab in case of discrepancies with prior labs. Oral hypoglycemic drugs and long-acting insulin should not be administered the morning of D1 or D14. If appropriate (for example, for patients admitted in the early morning hours), screening procedures may also take place on D1.

b Sites should adhere to D14 whenever possible

c Occasionally, a patient might be admitted, screened and randomized on the same day. In those cases, informed consent will also be sought during that day. In other cases, randomization may take place before discharge from hospital or admitting unit. If discharge is before D1, then the patient will come back to the site at D1 (Visit 2) for Randomization and IMP dispensing. For hospitalized patients eligible for discharge on study day D1, the timing of discharge is at the discretion of the treating physician but should not be less than 6 hours following administration of study drug. Patients that are not eligible for discharge, may complete all or part of the study as inpatients (hospital or other appropriate unit).

d Those visits need not be in an outpatient setting. For example, where mobility issues might cause restrictions, or patient is in a step-down unit or rehabilitation ward, the Investigator or designee could perform the Visit and relevant assessments and collect blood or urine samples at that setting. Visit 6 is the end of study visit (EOS). All patients will have a phone check at EOS. Patients may return to the clinical site if, in the judgment of the Investigator, may require a physical examination and additional investigations. A telephone call may also be scheduled soon after the End of Treatment Visit 5.

e IMP accountability and compliance check performed at end of treatment (EOT) Visit 5 and on visits planned at clinical site (Visit 3)

f Vital signs: including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting (preferably sitting) resting position. Orthostatic changes in blood pressure will be assessed once for all patients not limited by mobility issues (assess BP when supine or sitting for 10 mins and after 3 mins standing). For patients returning to the day unit for D1, they should stay in the unit. Their vital signs will be assessed at baseline and every 2 hours after administration of IMP. Patients should be monitored for at least 6 hours prior to discharge from the unit.

g Phone check will be to record any adverse events that occurred after study drug discontinuation, and to record daily BP readings since EOT Visit 5. Patients may return for a further visit (Visit 6) if in the opinion of the investigator they need a follow up examination and/or investigations.

h IRT contact for screening/randomization. Randomization within 7 days of discontinuation of IV diuretic therapy.

i Meals should be taken approximately 15 min after IMP administration throughout the study. On study day Visits 2 and 5, and Visits 3, , patients should fast for approximately 6 hours prior to IMP administration.

j Diary dispensed on D1 (Visit 2). The diary will be reviewed and information recorded on eCRF. If the last follow up is by phone check, all relevant information will be captured and transcribed to the eCRF. Patients who may need to remain inpatients for some or all of the visits will also receive a diary. While inpatients, relevant data such as AE and IMP intake will be entered into the diary. For inpatients, BP and concomitant medications will be recorded in the patient source documents. Those who become eligible for discharge will also receive BP monitors and continue with diary updates on a daily basis.

k Patients will be taught how to perform the automated BP readings. Automated BP readings will be performed in triplicate, between 6 AM to 10 AM on a daily basis, starting D2 and ending at the last post-study follow up.

l Study treatment ends on Day 14 (EOT).

m Physical examination includes at a minimum: heart and respiratory auscultation; peripheral arterial pulse; pupil, and abdomen examination. All physical examinations in diabetic patients, including abbreviated physical examinations, will include examination of the lower extremities to evaluate for any evidence of foot ulcers or infection should be performed as part of the general physical examination and this examination should be documented on the e-CRF.

n All body weight measurements on scale provided by site staff.

o All patients must have a documented echocardiogram, either performed during current admission or within 12 months from the index hospitalization.

p ECG at Visit 2, Visit 3 and Visit 5 (EOT) only.

q Oral or tympanic body temperature.

r Complete blood count / hematocrit / hemoglobin.

s Creatinine, urea, electrolytes.

t For Visits 2 (Day 1) and 5 (Day 14±1), those samples will be obtained as part of the Hemoconcentration sampling, thus no additional samples for Hematology or Biochemistry are required. It is indicated here as a reminder that baseline hematology and biochemistry is done on Visits 2 and 5. For all other Visits, Hematology and Biochemistry samples are to be obtained as indicated.

u Beta-HCG test will be for all women of child-bearing potential as defined in the inclusion/exclusion criteria, and FSH to assess menopausal status when necessary.

v Hemoconcentration is determined by measurement of hematocrit, hemoglobin, albumin and total protein. Baseline biochemistry (creatinine, urea and electrolytes) and hematology (CBC) is also determined from those samples.

1.5 PERIOD FLOW CHART (COHORT 3)

VISIT		VISIT 2 and VISIT 5										VISIT 3	
Day		D1 and D14(+/- 1 day)[a]										Between Day 6 and Day 8	
Time (hour/minute)	-3H	-2.5H	-2H	-1H	0H	0.5H	1H	3H	4H	5H	6H	-2.5 H	0H
Indicative clock time	7 am	7:30am	8 am	9:00 am	10 am	10:30am	11 am	1 pm	2 pm	3 pm	4 pm		
Discharge[b]											X		
Concomitant medications		<- ->											
Randomization[c]	X												
IMP accountability and compliance							<- - - - - - - X - - - - - - - - >						
Inclusion/Exclusion criteria[c]	X												
Meal[e]					X								X
Semi-recumbent position				<---------- X -------->									
Study treatment administration													
IMP administration					X								X
^{131}I-albumin injection				X									
Deuterium oxide intake[f]		X											
Safety													
Physical examination	X												
Vital signs	X							<---------------- X[g] ---------------->				X	
Body weight[o]	X												
[redacted]													
ECG	X											X	
Urine (lab)		X										X	
Hematology				X[h]									
Biochemistry				X[h]								X	
β-HCG[i]		X											
Liver function (AST,ALT, ALP, GGT, total and conjugated bilirubin)[j]			X									X	
Adverse event collection								<----------------------- X ----------------------->					

VISIT		VISIT 2 and VISIT 5										VISIT 3	
Day		D1 and D14(+/- 1 day)[a]										Between Day 6 and Day 8	
Time (hour/minute)	-3H	-2.5H	-2H	-1H	0H	0.5H	1H	3H	4H	5H	6H	-2.5 H	0H
Indicative clock time	7 am	7:30am	8 am	9:00 am	10 am	10:30am	11 am	1 pm	2 pm	3 pm	4 pm		
Pharmacokinetics[k]													
Pharmacodynamics													
Blood collection Hemoconcentration,[l]				X									
Blood collection for ^{131}I-albumin				X[m]									
Blood collection for deuterium oxide[n]		X					X						
Uric acid		X											
Erythropoietin		X											
NT-ProBNP		X											
Beta-hydroxybutyrate		X											
[redacted]													

a Sites should adhere to D14 whenever possible

b For hospitalized patients eligible for discharge on study day D1,,the timing of discharge from the hospital is at the discretion of the treating physician but should not be less than 6 hours following the administration of study drug. Patients that are not eligible for discharge, may complete all or part of the study as inpatients (hospital or other appropriate unit). For patients returning to the day unit for D1, they should also stay in the unit and have their vital signs assessed every 2 hours after IMP administration and discharged not sooner than 6 hours after IMP administration. Laboratory tests may be performed in the hospital or outpatient unit, depending on whether the patient remains hospitalized.

c Day 1 only. IRT contact for randomization. The time is indicative, as randomization should take place after review of inclusion/exclusion criteria [redacted]

e Meal to be taken within 15 minutes after administration of study drug.

f Deuterium oxide intake should take place after blood collection for baseline measurements.

g Vital signs: including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting (preferably sitting) resting position. Orthostatic changes in blood pressure will be assessed once for all patients not limited by mobility issues (assess BP when supine or sitting for 10 mins and after 3 mins standing). For patients returning to the day unit for D1, they should stay in the unit. Their vital signs will be assessed at baseline and every 2 hours after administration of IMP. Patients should be monitored for at least 6 hours prior to discharge from the unit.

h For Visits 2 (Day 1) and 5 (Day 14±1), those samples will be obtained as part of the Hemoconcentration sampling, thus no additional samples for Hematology or Biochemistry are required. It is indicated here as a reminder that baseline hematology and biochemistry is done on Visits 2 and 5. For all other Visits, Hematology and Biochemistry samples are to be obtained as indicated.

i β-HCG performed at screening and D14 only

j Indicative time. Those samples can be obtained at the same time as the other samples are collected, eg, biochemistry.

k Pharmacokinetic samples will not be collected for cohort 3.

l Hemoconcentration is determined using the following: Hematocrit, hemoglobin, total protein and albumin. Baseline biochemistry (creatinine, urea, electrolytes) and complete blood count will also be determined from those samples

m One sample will be collected just before injection of ^{131}I-albumin (-1H, PD00) and further sample collection will start 12 min following the injection. Samples will then be collected every 6 minutes starting – 0H48 min: -0H48 min(PD01), -0H42min(PD02), -0H36min(PD03), -0H30min(PD04), -0H24min(PD05) min. For blood collection on D14 sample notation should be: -1H (PD06), -0H48min (PD07), -0H42min (PD08), -0H36min(PD09), -0H30min(PD10), -0H24min(PD11)

n Following administration of deuterium oxide, blood collection on D1: At -2.5H (PY00), 1H (PY01), and on Day 14: At -2.5H (PY02), 1H (PY03)

o All body weight measurements on scale provided by site staff

[redacted]

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

AESI:	adverse event of special interest
CHF:	congestive heart failure
CV:	cardiovascular
DBP:	diastolic blood pressure
DMC:	Data Monitoring Committee
eGFR:	estimated glomerular filtration rate
EMPA-REG:	EMPAgliflozin-Remove Excess Glucose
EOSI:	event of special interest
GFR:	glomerular filtration rate
GI:	gastrointestinal
IB:	Investigator's Brochure
IMP:	investigational medicinal product
IRT:	interactive response technology
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	myocardial infarction
PD:	pharmacodynamic(s)
PK:	pharmacokinetic(s)
SAE:	serious adverse event
SBP:	systolic blood pressure
SGLT1:	sodium-glucose cotransporter type 1
SGLT2:	sodium-glucose cotransporter type 2
SUSAR:	suspected unexpected serious adverse reaction
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus
ULN:	upper limit of normal, upper limit of normal

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Sotagliflozin (Sanofi code SAR439954, Lexicon code LX4211) is an orally administered small molecule, the first dual inhibitor of sodium-glucose co-transporter 1 and 2 (SGLT1 and SGLT2), formulated as 75 mg and 200 mg coated tablets. The compound, a member of the pharmaceutical class of SGLT-inhibitors known as gliflozins, lowers blood glucose by decreasing and delaying SGLT1-mediated glucose absorption in the gastrointestinal (GI) tract as well as enhancing glucose excretion in the urine by reducing renal glucose re-absorption via action of SGLT2 in the kidney.

Sotagliflozin is being investigated as a therapy to improve glycemic control in adults with diabetes. In type 2 diabetes (T2DM) it is being developed as monotherapy or in combination with other classes of anti-diabetic agents. For type 1 diabetes (T1DM) it is being developed for adjunctive use with insulin.

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

4.2 RATIONALE

4.2.1 Study rationale

Recent clinical trial data support that SGLT2 inhibitors may reduce heart failure morbidity and mortality. The effects of the SGLT2 inhibitor empagliflozin on cardiovascular risk were studied in the EMPAgliflozin Remove Excess Glucose (EMPA-REG) trial (1). In EMPA-REG, patients with type 2 diabetes and established cardiovascular (CV) disease were randomized to placebo or empagliflozin with median treatment duration of 2.6 years. The primary outcome, a composite of death from CV causes, non-fatal myocardial infarction (MI) and non-fatal stroke, occurred in 12.1% of the placebo group and in 10.5% of the empagliflozin group for a hazard ratio of 0.86. The hazard ratio for cardiovascular death alone was 0.62, and this improvement in CV mortality was not a result of reduced MI or stroke, but rather was mediated by a reduction in heart failure hospitalization and death (hazard ratio for heart failure hospitalization was 0.65).

In EMPA-REG, empagliflozin was well-tolerated in patients with chronic heart failure. Patients who are hospitalized with worsening of heart failure are more susceptible to fluctuation in their hemodynamic state and their renal function and the safety and tolerability of SGLT inhibition in this setting is unknown. The mechanism of empagliflozin-mediated heart failure benefit is also unknown. One proposed mechanism is reduction in plasma volume (2). Patients with heart failure typically have increased total body water with the increase localized to the interstitial space and the vascular space. Acute and chronic therapy with diuretics can reduce plasma volume via natriuresis. Diuretics in current use block sodium absorption in the kidney leading to natriuresis, but also activate the counter-regulatory renin-angiotensin system which ultimately limits the degree of diuresis and reduction in plasma volume. In comparison, the SGLT2 inhibitor

dapagliflozin causes diuresis and compared to a thiazide diuretic, results in less activation of renin and greater volume reduction (3)(4). Sotagliflozin, by its inhibition of both SLGT1 and SGLT2, may reduce volume via both renal and GI mechanisms. The main objective of this study is to test the effects of combined SGLT1 and SGLT2 inhibition with sotagliflozin on hemoconcentration and plasma volume in patients with heart failure. Whereas empagliflozin has shown benefit in diabetic heart failure patients /non-diabetic patients with heart failure patients may also have favorable volume changes and may also benefit from SGLT inhibition, and thus both diabetic and non-diabetic heart failure patients will be enrolled.

4.2.2 Design rationale and risk assessment

Design: A parallel arm design was chosen for the comparison between sotagliflozin and placebo. A cross-over design was not considered feasible due to the physiologic changes typical of patients recently hospitalized with heart failure that would result in substantial period effect. A treatment duration of 14 days was selected as both the time required for maximum treatment effect on urinary sodium excretion and a feasible follow-up period for the selected heart failure patient population. The urinary sodium excretion is expected to be one of the determinants of plasma volume and thus the 14 day time-point should also reflect maximum plasma volume changes. Sodium excretion in the gastrointestinal tract may also impact plasma volume, although the magnitude and time-course are unknown.

Population: The population will include patients with pre-existing heart failure who have been hospitalized with worsening of their heart failure, and have been stabilized sufficiently to be switched from IV to oral diuretic therapy (post-worsening heart failure). Patients who present with worsening of heart failure are treated initially with IV diuretics due to reduced absorption of oral diuretics in the acute heart failure state (5). Once the signs and symptoms of worsening heart failure have improved, therapy is switched from IV to oral diuretic therapy in preparation for chronic outpatient treatment. The switch from IV to oral diuretic therapy represents a point in the clinical course when the signs and symptoms of volume overload have improved although the plasma volume remains increased and further reduction is achieved with oral diuretic therapy. This post-worsening population is more clinically stable and whereas volume overload persists, is suitable for assessing safety and pharmacodynamics (PD) efficacy of SGLT inhibition in heart failure. The limitations of this population include ongoing fluctuations of renal function and the limited published data on plasma volume change and hemoconcentration in this setting (6)(7)(8). Hemodynamic perturbations and pharmacotherapy during acute heart failure impact renal function and this period of flux makes renal function both vulnerable to toxic insults and difficult to assess for trends. Chronic kidney disease (CKD) is common in the heart failure population. It is anticipated that approximately 50% of patients with post-worsening heart failure may have an eGFR of <60mL/min/1.73m^2 (9). Sotagliflozin (400 mg) was well-tolerated in patients with stage 3 CKD for a period of 7 days. Patients with an eGFR of <30mL/min/1.73m^2 will be excluded from the study.

Dose: There are no published data to support the safety and tolerability of SGLT inhibition in patients who are hospitalized with worsening of heart failure. SGLT inhibition is known to reduce blood pressure and glomerular filtration rate (GFR) in healthy subjects and in patients with diabetes. Sotagliflozin causes a dose-dependent reduction in blood pressure.

It is not known whether or how GFR relates to the response to sotagliflozin. A recent meta-analysis of 11 phase 3 dapagliflozin studies suggests that its effects on BP, body weight, hematocrit, albuminuria, bicarbonate, pulse pressure, and uric acid are independent of eGFR levels (10). This *post hoc* analysis also showed that there is a poor relationship, which weakens further at lower eGFRs, between the change in HbA1c and the change with any of those parameters. To establish safety and tolerability, a submaximal dose of 200mg or placebo will be administered to the first 15 randomized post-worsening heart failure patients (randomized 2:1 sotagliflozin: placebo). Safety and tolerability, including effects on blood pressure and renal function, will be assessed by an independent data monitoring committee. Following safety review for the first cohort by Sponsor and DMC, the subsequent 15 patients will be randomized (2:1 ratio) to 400 mg sotagliflozin or placebo, with ongoing safety monitoring. Upon completion of cohort 2, and further safety review by the DMC and Sponsor, the remainder of patients will be randomized 1:1 to placebo or 400mg sotagliflozin.

4.2.3 Specific parameters rationale

Plasma volume and hemoconcentration: Pharmacodynamic endpoints that are likely to reflect heart failure benefit include those that are related to improvement in the volume overload that typically causes acute exacerbations. Vascular and extravascular volumes can be assessed in humans using the indicator dilution method. A known quantity and concentration of an indicator is administered, and subsequent plasma samples are taken. The dilution of the indicator is directly proportional to the volume of distribution. The standard approach to measurement of plasma volume is labelled human albumin, an indicator that remains primarily localized to the intravascular space (11)(12). The indicator dilution method using radiolabeled (^{25}I or ^{3} I) human albumin is the most accurate method for plasma volume measurement, and is commonly performed in hospitals or outpatient clinics (4). Changes in plasma volume can occur as a result of postural changes or alterations in sympathetic tone, necessitating a controlled testing environment. As plasma volume falls, stable intravascular constituents become more concentrated. This hemoconcentration has been used as an indirect assessment of plasma volume changes. Examples of intravascular components whose concentrations increase with reductions in plasma volume include hemoglobin, hematocrit, albumin and total protein (2)(3)(13). These biomarkers of plasma volume are easier to measure, require the same controlled testing environment used for plasma volume measurement, but may be more variable than plasma volume as a result of blood sampling and other interventions in the hospital setting.

Plasma volume may decline by as much as 25% with standard diuretic therapy in patients hospitalized with worsening heart failure (11). Plasma volume was measured after 12 weeks of treatment with the SGLT2 inhibitor dapagliflozin, the diuretic hydrochlorothiazide (HCTZ) or placebo in diabetic patients without heart failure. Whereas placebo-treated patients had a 5.2% increase and HCTZ-treated patients had a 2.8% increase, dapagliflozin-treated patients had a 7.3% reduction in plasma volume corresponding to a 10.1% further decrease compared to diuretic treatment (3). The intrasubject variability for plasma volume measurements using the radiolabeled albumin indicator dilution technique is low (14), but little is known about such measurements in patients hospitalized with post-worsening heart failure (11). Hospitalized post-worsening heart failure patients may have more variability in plasma volume than stable patients due to ongoing fluid shifts between the interstitial and intravascular spaces. Furthermore, as diuresis occurs and

plasma volume declines, the intravascular space may re-accumulate volume from the interstitial space. To investigate these potential sources of variability and capture such volume shifts participants will undergo measurement of total body water concurrently with plasma volume. The assessment for total body water also employs an indicator dilution method using deuterium oxide (D_2O) which is distributed within total body water. Deuterium is administered orally, its distribution time is approximately 2.5 hours, and is measured in plasma by nuclear magnetic resonance spectroscopy. The intrasubject variability for the method is low (15).

Heart failure is associated with anemia, and anemia has a negative impact on the prognosis of heart failure patients (16). Clinical trials are ongoing to determine whether anemia treatment improves outcome in heart failure patients. SGLT2 inhibition has been shown to augment release of erythropoietin, suggesting that hematocrit after SGLT2 inhibition may increase due to two distinct mechanisms; hemoconcentration and increased erythropoiesis (17). These different effects on hematocrit occur over different time-courses. The hemoconcentration effect may be detectable within several days, whereas erythropoiesis may require 4-8 weeks to detect (4)(18). Increased concentration of erythropoietin in plasma can be detected within hours following an hypoxic stimulus (19), and in diabetic patients erythropoietin concentrations increase within approximately 2 weeks of starting treatment with an SGLT2 inhibitor (3). Additional objectives of the study will be to determine whether sotagliflozin increases plasma concentrations of erythropoietin in heart failure patients, and explore the relationship with ketone body production as assessed by beta-hydroxybutyrate plasma levels.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is the assessment of safety and tolerability of sotagliflozin, added to the standard of care treatment, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

A co-primary objective of this trial is the estimation of the effect of sotagliflozin, when added to the standard of care treatment, on changes in plasma volume, as assessed by direct (indicator dilution) and/or indirect (hemoconcentration) methods, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

5.2 SECONDARY

Secondary objectives for this study are:

Explore the effect of sotagliflozin, added to standard of care treatment, on erythropoiesis, as assessed by changes in plasma erythropoietin levels, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

Explore the effect of sotagliflozin, added to standard of care treatment, on changes in plasma NT-proBNP levels, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

5.3 OTHER OBJECTIVES

A further objective for this study is to explore the effect of sotagliflozin compared to placebo treatment, in hemodynamically stable patients with worsening of heart failure, on the following endpoints:

- Change in total body water from baseline to 14 days
- Change in uric acid from baseline to 14 days
- Change in beta-hydroxybutyrate from baseline to 14 days
- Change in total blood volume from baseline to 14 days
- Change in red cell mass from baseline to 14 days
- Percentage of patients within 15% of ideal blood volume on study day 14
- Blood pressure, sitting (SBP and DBP), at day 14 compared to baseline

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a phase 2, multi-center, multinational, randomized, double-blind, placebo-controlled, parallel arm trial of the safety, tolerability and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure. Study drug will be initiated in the hospital or other appropriate setting such as heart failure or infusion unit, after completion of intravenous diuretic therapy, and continued in an outpatient setting for a total of fourteen days. The main pharmacodynamic endpoints studied are changes in plasma volume and total body water as measured by indicator dilution methods using 131-I-albumin and deuterium oxide, and hemoconcentration as measured by changes in hematocrit, hemoglobin, plasma total protein and plasma albumin levels.

An initial cohort of patients (Cohort 1) will receive sotagliflozin 200mg (n approximately10) or placebo (n approximately 5) for fourteen days. Following safety monitoring and review by the DMC, Cohort 2 will receive sotagliflozin 400mg (n approximately 10) or placebo (n approximately 5) orally for fourteen days. Following completion of Cohort 2 and review of safety and tolerability by the DMC, conduct of cohort 3 will commence where patients will be allocated to sotagliflozin 400 mg (n approximately 17) or placebo (n approximately 17) orally for fourteen days. This is summarized in Table 1.

Table 1 - Cohort randomization and allocation scheme

Cohort	Randomization	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Total N
1	2:1	10	0	5	15
2	2:1	0	10	5	15
3	1:1	0	17	17	34
Tota N		10	27	27	64

The graphical study design/flow charts are in Section 1.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each subject

- Screening period will be up to 21 days
- Treatment period is 14 1 days
- Follow up period will be 14 2 days
- Total study duration will approximately be 26-51 days

  However, subject participation could be prolonged in case of safety concerns (see Section 11.3.1).

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as the day of the last follow up contact for the last patient, including cases where the patient could not be contacted following recurrent attempts and within a reasonable amount of time since last visit/contact. In such cases, the patient will be considered a dropout, and the end of clinical trial will be the date of the last documented contact.

The Sponsor can terminate the trial prematurely based on the advice of the independent Data Monitoring Committee (DMC) or other unforeseen developments.

7 STUDY COMMITTEES

7.1 DATA MONITORING COMMITTEE (DMC)

A DMC with members who are independent from the Sponsor and the Investigators will meet on a regular basis, and will be responsible for:

- Review of accumulating clinical study safety data, and
- Making a recommendation to the Sponsor regarding the study and dose escalation from Cohort 1 to Cohort 2 and dose selection from Cohort 1 and 2 to Cohort 3 following the scheduled end of Cohort 1 and Cohort 2 meetings, or unscheduled meetings as triggered by safety signals.

Safety data to be reviewed will include all safety data considered relevant. Details describing the DMC processes and procedures are outlined in a separate DMC Charter. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data.

An expert review committee will also review all potential cases of DILIs in a treatment blinded manner to evaluate causality.

7.2 POTENTIAL OUTCOMES FOLLOWING DMC REVIEWS

Depending on the safety profile observed in Cohort 1, one of the following decisions will be taken for Cohort 2 and subsequently cohort 3:

- Dose administration may continue as scheduled in Section 9.4.
- OR a selected dose of 200, 400mg or both may be administered in - cohort 3 subsequent to DMC review, in balanced or unbalanced design
- Study may be stopped and Cohort 2 and 3 will not proceed.

Other safety parameters will be considered as well for decision making.

For safety purposes, the treatment of a specific patient may be unblinded before the next dose level is administered, after mutual agreement between the Sponsor and Investigator.

Similar outcomes and considerations as described above for the Cohort 1 review and its outcome, will also apply for the outcomes following review of Cohort 2.

7.2.1 Guidance for stopping rules

Discontinuation of IMP administration will be decided by the Investigator and/or the DMC. Patients re-hospitalized will discontinue IMP administration. In addition, IMP administration should be discontinued if in the opinion of the Investigator, and where appropriate following discussion with the Sponsor or urgent review by the DMC, IMP administration is associated with a serious AE or complications, or patient status deteriorates. Such cases might include a persistent decline of more than 50% in eGFR in the absence of any clinical improvement or development of new lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) in a diabetic patient requiring treatment.

8 SELECTION OF PATIENTS

8.1 NUMBER OF PATIENTS PLANNED

The study population will consist of male and female patients, 18 years and older, admitted to the hospital or heart failure unit or infusion center with worsening of heart failure requiring administration of intravenous diuretics, as per inclusion and exclusion criteria detailed below.

A subject who received treatment and prematurely ends his/her treatment will be replaced in order to have approximately 64 evaluable observations.

A patient should not be randomized more than once.

Re-screening is allowed once during the current hospitalization, if in the opinion of the investigator, the change in the clinical status of the patient allows inclusion in the trial. Patients that failed screening during the first encounter for this trial can be rescreened during subsequent hospitalizations or visits to the infusion or heart failure units.

A patient that requires re-hospitalization will be discontinued from IMP administration. Every effort will be made to follow up the progress of the patient and continue collection of relevant safety data, as appropriate and when applicable, and as judged by the Investigator with potential input from the DMC and Sponsor, as appropriate for each case, for the same follow up period (approximately 2 weeks) as for all other patients participating in the trial. In those cases, the follow up procedures and/or visit to clinical site should be followed as per study flow chart in Section 1.2. Only if judged appropriate by the Investigator and Sponsor, and in the absence of safety signals, the patient will be allowed to participate in some or all of the EOT study procedures.

For all patients, GFR will be calculated from the serum creatinine (sCr; mg/dL) and age (years) via the abbreviated Modification of Diet in Renal Disease (MDRD) equation (20):

$$GFR \quad 186 \quad (sCr)^{-} \quad ^{54} \quad (age)^{-0\,203} \quad (1.212\ if\ black) \quad (0.742\ if\ female)$$

8.2 INCLUSION CRITERIA

8.2.1 Inclusion criteria at screening

I 01. Written informed consent;

I 02. 18 years of age or older

I 03. Patient admitted to the hospital or had urgent visit to emergency department or heart failure unit/clinic or infusion center for Congestive Heart Failure (CHF), defined by:

- Presence of ≥2 of the following clinical signs and symptoms of congestion: jugular vein distension, pitting edema in lower extremities greater than trace , dyspnea, rales heard on auscultation, radiographic pulmonary congestion, weight gain above historical dry weight of at least 5 lbs (2.27 kg)

  AND

- Requiring treatment with IV diuretics

I 04. Estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m2 at the screening or randomization visit by the 4 variable Modification of Diet in Renal Disease (MDRD) equation

I 05. Female subject must use a double contraception method during the study including a highly effective method of birth control, except if she has undergone sterilization at least 3 months earlier or is postmenopausal.

I 06. Male participants, unless vasectomized and confirmed sterile by sperm analysis, must use condoms during the study and refrain from donating sperm up to 90 days after the day of last dose. If the patient has a female partner of childbearing potential, the patient must wear a condom and female partner must use at least 1 highly effective method of birth control

8.2.2 Inclusion criteria at randomization

I 07. Transitioning from intravenous (IV) to oral diuretics and oral diuretic treatment has been prescribed or administered

I 08. Hemodynamically stable, defined as:

- SBP ≥100 mmHg with no requirement for IV inotropes or IV vasodilators

8.3 EXCLUSION CRITERIA

E 01. History of Type 1 diabetes mellitus

E 02. Appears unlikely or unable to participate in the required study procedures, as assessed by the study Investigator, study coordinator, or designee (ex: clinically-significant psychiatric, addictive, or neurological disease), or sectioned due to an official or court order

E 03. Tachyarrhythmia with ventricular rate >130 bpm at screening, unless determined to be clinically stable by the investigator current admission for worsening heart failure primarily triggered by causes such as acute coronary syndrome, pulmonary embolism, cerebrovascular accident, heart valve disorders (such as severe aortic stenosis), as determined by the Investigator

E 04. Clinically significant myocardial infarction (MI) within past 1 month as determined by Investigator and with objective evidence from ECG, and/or cardiac imaging and/or coronary angiography. Small isolated elevations in troponin that often accompany HF hospitalization are not an exclusion, nor are clinically significant MIs that have been re-vascularized without complications

E 05. Patients who recently had or scheduled to have cardiac interventions may be eligible if:

- Stable 48 hours post procedure AND
- Have diuretic treatment planned for the duration of treatment in this study

E 06. Current use of or recent suspension of digoxin therapy with high levels of digoxin (level should be obtained and must be <1.2 ng/mL) at screening.

E 07. History of heart or kidney transplant

E 08. Diagnosis of hypertrophic obstructive cardiomyopathy

E 09. End-stage HF defined as requiring left ventricular assist device insertion, intra-aortic balloon placement (IABP), or any type of mechanical support during the study period

E 10. Pregnancy (demonstrated by serum pregnancy test at screening), breast-feeding, or inability or refusal to undergo pregnancy testing

E 11. Use of any investigational drug(s) or prohibited therapy or sodium-glucose co-transporter 2 (SGLT2) inhibitor 5 half-lives prior to screening

E 12. Patients with moderate or severe respiratory, hepatic, neurological, psychiatric, active malignant tumor or other major systemic disease (including any diseases with evidence of malabsorption), making implementation of the protocol and/or the interpretation of the study results difficult

E 13. Known allergies, hypersensitivity, or intolerance to sotagliflozin or any inactive component of sotagliflozin or placebo (i.e., microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicon dioxide, and magnesium stearate [non-bovine]), unless the reaction is deemed irrelevant to the study by the PI

E 14. Laboratory findings at the Screening Visit:

a) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of the normal laboratory range (ULN) (1 repeat lab allowed)

b) Total bilirubin >1.7 times the ULN (except in case of Gilbert's syndrome) (1 repeat lab allowed)

c) Amylase and/or lipase > 3 times the ULN (1 repeat lab allowed)

E 15. Patients with a severe or persistent in spite of optimal treatment genitourinary tract infection at time of randomization.

E 16. Patient is the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

8.3.1 Additional exclusion criteria for patients with diabetes

E 17. History of diabetic ketoacidosis or non-ketotic hyperosmolar coma within 3 months prior to the screening visit

E 18. Lower extremity diabetic complications (such as skin ulcers, infection, osteomyelitis and gangrene) identified during the Screening period, and still requiring treatment at Randomization

9 STUDY TREATMENTS

9.1 INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

The IMPs are sotagliflozin 400 mg, sotagliflozin 200 mg, and matching placebo. Patients will be provided with treatment kit according to the cohort number and the arm allocation in the cohort for the Double -Blind Treatment Period:

- Placebo kit: containing placebo tablets
- Or Sotagliflozin 200 mg kits: containing placebo tablets and Sotagliflozin 200 mg tablets
- Or Sotagliflozin 400 mg tablets: containing Sotagliflozin 200 mg tablets.

Table 2 - Summary of investigational medicinal products

IMP:	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo group
Name of IMP	Sotag f oz n (SAR439954)	Sotag f oz n (SAR439954)	P acebo
Pharmaceutical Form	Sotag f oz n (SAR439954) w be supp ed as 200 mg tab ets	Sotag f oz n (SAR439954) w be supp ed as 200 mg tab ets	P acebo w be supp ed as tab ets (dent ca to sotag f oz n n appearance)
Dose, timing, and route of administration	**Sotagliflozin 200 mg group**: One 200 mg tab et, taken ora y once da y, before the f rst mea of the day and One p acebo tab et, taken ora y once da y, before f rst mea of the day	**Sotagliflozin 400 mg group:** Two 200 mg tab ets, taken ora y once da y, before f rst mea of the day	**Placebo group:** Two p acebo tab ets, taken ora y once da y, before f rst mea of the day
Duration of treatment	14 days doub e-b nd Treatment Per od fo ow ng Random zat on	14 days doub e-b nd Treatment Per od fo ow ng Random zat on	14 days doub e-b nd Treatment Per od fo ow ng Random zat on
Storage conditions	Store between +15 C and +30 C (59 F and 86 F)		

9.2 NON-INVESTIGATIONAL MEDICINAL PRODUCTS

^{131}I-albumin:

Supplied as ≤25µCi in 1mL, at date of calibration. Each mL contains:

- 10mg human albumin (non-reactive to HBsAg)
- 16mg sodium dibasic phosphate
- 1.6mg sodium monobasic phosphate

- 0.4mg guanidine hydrochloride
- Sodium chloride
- 9mg benzyl alcohol

Route of administration: IV, see Laboratory manual for detailed instructions.

Dose: 10mg (≤25 µCi)

Deuterium Oxide:

Formulation; deuterium oxide 10 g / 10 mL presterilized vial or oral syringe with tip cap for enteral administration

Dose and Administration: The vial or syringe volume (10 mL) will be diluted to a final volume of 100 mL with sterile water. Patients will be asked to drink it all, under direct supervision. Details of the procedure for diluting the contents of the syringe and administration method are provided in the laboratory manual.

9.3 BLINDING PROCEDURES

9.3.1 Methods of blinding

To maintain blinding, sotagliflozin and the matching placebo tablets and packaging will be blinded and indistinguishable. During the double-blind Treatment Period for each cohort, each treatment package will be labeled with a number, which is generated by a computer program from Sanofi. Investigators will not have access to the randomization (treatment) code except under circumstances described in Section 9.3.2.

The randomization and the treatment allocation will be performed centrally by an IRT. The study biostatistician provides the randomization scheme to the IRT. Then, the IRT generates the subject randomization list from which it allocates treatment arms to the subject.

Details for the circumstances under which unblinded reports or data will be provided to DMC are provided in the DMC Charter.

9.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the subject.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking in source data. The identity of the unblinded personnel, how the code was broken, and the treatment kit number should also be recorded. The Sponsor should also be informed. If the code is broken by the Investigator (or other medical doctor in emergency situation), the patient must be withdrawn from IMP administration.

9.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number is generated centrally by Sanofi. The IMPs are packaged in accordance with this list.

At the Screening Visit, the Investigator or designee has to contact the IRT to receive the patient number. [redacted]

Before randomizing a subject on Day 1, the Investigator or designee should check if patients comply with all inclusion/exclusion criteria. At day 1, the IRT is contacted for randomization and corresponding allocation of treatments package. Patients are randomized to receive either sotagliflozin or placebo, according to the randomization scheme for each Cohort as described below:

Cohort 1:	Sotagliflozin 200 mg: Placebo	2:1
Cohort 2:	Sotagliflozin 400 mg: Placebo	2:1
Cohort 3 (as amended here):	Sotagliflozin 400 mg: Placebo	1:1

For each randomized patient, the IRT will allocate a treatment package number corresponding to the treatment group assigned.

A randomized subject is defined as a subject who is registered and assigned with a treatment kit number from the IRT, as documented in IRT.

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

A patient can be rescreened once in case of manageable exclusion as deemed by the Investigator. In these cases, a patient will need to sign a new ICF, be registered as a new patient in IRT, and assigned a new patient number in IRT (first Screening Visit is to be registered as a screen failure in IRT), and complete the Screening Visit procedures/assessments again.

Potential replacement patients will have a patient number assigned from IRT and the patient number that is replaced will be recorded in IRT and transferred to the case report form. Each patient will receive the same treatment and treatment sequence as the withdrawn patient. See also Section 12.3.

9.5 PACKAGING AND LABELING

Packaging will be undertaken in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The appropriate number of packages will be dispensed to cover up to the dispensing visit (please refer to Section 1.2). 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 eCRF).

9.6 STORAGE CONDITIONS AND SHELF LIFE

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

Control of IMP/NIMP storage conditions, especially control of temperature (e.g., refrigerated storage) and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The expiry date and storage conditions are written on the IMP/NIMP labels.

The IMP Sotagliflozin 400 mg or sotagliflozin 200 mg or placebo treatment kit should be stored between 15°C and 30°C (59°F and 86°F).

9.7 RESPONSIBILITIES

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

All IMP/NIMP 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/NIMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP/NIMP provided by the Sponsor (deficiency in condition, packaging, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP/NIMP provided by the Sponsor may be subject 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 or delegate, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP 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 in any other manner.

9.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).The IMP includes placebo and sotagliflozin 200 mg and 400 mg.

All concomitant medications should be documented on the concomitant medications and herbal therapies page of the e-CRF. This includes all non IMP treatments that are taken by the patients at any time during the clinical study, beginning Day 1.

Additionally, a history of all medications in the 3 months prior to Day 1 should be taken.

An accurate record of all concomitant medications must be entered in the eCRF, including the name of the medication (INN), daily dosage, and duration of use.

Doses of chronically administered medicines should be kept fixed during the trial if at all possible. Special consideration should be given to the following:

Digoxin

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. As this study assesses the safety of sotagliflozin for the first time in this patient population, it will have patients with supra-therapeutic levels (defined for the purposes of this study as >/ 1.2ng/ml) of digoxin at screening excluded from the trial. Patients that require digoxin during the study should have their plasma digoxin levels monitored.

Non-steroidal anti-inflammatory drugs (NSAIDS)

Concomitant use of NSAIDs increases the risk of acute renal injury and re-hospitalization in this patient population (21) and NSAIDs use during treatment for heart failure is contraindicated. Any NSAIDs use during the study would be at the discretion of the Investigator.

Anti-hypertensives

See also Section 9.12. Because sotagliflozin may reduce BP, adjustment of antihypertensive medication may be needed during the study in patients with hypertension, or following discontinuation of treatment with IMP.

Anti-diabetic medications

Sotagliflozin might reduce the need for insulin administration or other relevant medications in diabetic patients. Patients should monitor their blood glucose levels and adjust the dose and/or frequency of administration of relevant medication as required. Please refer to Section 11.5 for the management of hypoglycemic events.

Diuretics

Co-administration of IMP with loop and thiazide diuretics might lead to clinically significant volume depletion.

Modifications to the dose of the loop and/or thiazide diuretic might be necessary. The Investigator should consult with relevant experts (e.g., nephrologists) as appropriate. For patients with a systolic blood pressure <110 mm Hg at Randomization, the doses of any diuretic or other antihypertensive medication may be decreased in order to prevent possible hypotension.

9.9 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Compliance of IMP:

On Days 1 and 14, sotagliflozin 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.

Accounting and compliance for IMPs will be performed on, Visit 3 (between day 6 and day 8) and EOT Visit 5 (Day 14 1), or earlier in cases of discontinuation. The Investigator or his/her delegate will check the compliance to the study treatments based on the patient diary and will then complete the appropriate Site treatment and patient treatment log forms. Visual check on returned IMP will be performed by site staff. In addition the dosing information will be recorded on the appropriate pages of the e-CRF.

If compliance is inadequate as determined by the Principal Investigator (PI), patients will be trained again and mentored. If suboptimal compliance continues after training and mentoring, patients may be discontinued at the discretion of the PI after discussion with the Sponsor's medical monitor.

Missed doses of study medication can be made up if taken within 12 hrs. of the regularly scheduled time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis should not take a replacement dose.

9.10 PATIENT DIARY

Paper diaries will be used for this study. Information recorded into diary will document the compliance of IMP as well as other safety information (BP, Hypoglycemia, etc) and these recordings will be carefully reviewed also at each visit.

Patients will enter self-reported information starting at Visit 2 into their paper diaries and they will bring it back to the center at each following visit during the treatment and follow-up period). Patients will be instructed how to fill in it every day.

The diary includes sections for recording:

- Date and time of IMP dose
- Any change or new concomitant medication.
- Adverse events, including signs and symptoms suggesting occurrence of hypoglycemia
- Blood Pressure reading

9.11 RETURN AND/OR DESTRUCTION OF TREATMENTS

Patients are to return all in use or unused IMP at Visit 5 (or final assessment on-treatment visit in case of permanent premature discontinuation).All partially-used or unused IMPs will be retrieved by the sponsor CRO or delegate. Investigational medicinal product reconciliation must be performed at the site by the Investigator and the monitoring team using treatment log forms and documented on center IMP inventory countersigned by the Investigator and the monitoring team.

A written authorization for destruction will be given by the study team once the IMP reconciliation is achieved. This destruction can be performed at site depending on IMP specificities and local requirements or IMP can be returned to the Sponsor for destruction.

For NIMP not provided by the Sponsor (i.e., metformin or other oral anti-diabetic drugs), tracking and reconciliation is to be undertaken by the Investigator (or pharmacist if appropriate) according to the system proposed by the Sponsor.

9.12 POSTSTUDY TREATMENT

Patients will continue monitoring and recording their BP on a daily basis following discontinuation of IMP. At the follow up telephone check/onsite (only if required by investigator's clinical judgement) visit between day 26 and day 30, the patient will discuss entries in the diary, and any concerns with the investigator or his/her delegate. If, in the opinion of the investigator, the patient needs to attend for further examination and/or investigation, a follow up Visit (Visit 6) will be scheduled to meet the urgency and needs of patient treatment. If no further visit is scheduled, patients will be reminded to return their completed diaries.

10 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

10.1 ACTIVITY OR PHARMACODYNAMICS

10.1.1 Pharmacodynamic parameters

10.1.1.1 Primary endpoints

- Change in hemoconcentration from baseline to D14 as assessed by changes in hematocrit, hemoglobin, albumin and total protein, based on the assumptions made by Dill and Costill (22)
- Change in plasma volume in milliliters from baseline to D14 as assessed by the indicator dilution method using ^{3} I-labelled human albumin

10.1.1.2 Secondary endpoints

- Change in erythropoietin (mU/ml) from baseline to D14 measured by chemiluminescent enzyme-labelled immunometric assay
- Change in NT-proBNP (pg/mL) from baseline to D14 measured by standard electrochemiluminescence immunoassay

10.1.1.3 Other endpoints

- Change in total body water (mL) from baseline to D14 as assessed by the indicator dilution method using deuterium oxide
- Change in uric acid (mg/dL) from baseline to D14 as measured by standard assay
- Change in beta-hydroxybutyrate (µM) from baseline to D14 as measured by standard enzymatic colorimetric assay
- Change in red cell mass (mL) from baseline to D14, as derived from measurements of plasma volume (assessed by the indicator dilution method using ^{3} I-labelled human albumin) and hematocrit
- Change in total blood volume (mL) from baseline to 14 days, as assessed by the indicator dilution method using ^{3} I-labelled human albumin
- Percentage of patients within 15% of ideal blood volume on study day 14
- Blood pressure (sitting, SBP and DBP) at day 14, compared to baseline

10.1.2 Assessment methods

All eligible patients will have hemoconcentration samples obtained and total body water (deuterium oxide) assessment performed as per Section 10.1.2.1 below.

Sites that have the capacity to perform the additional plasma volume assessment by the ^{3} I-albumin method will follow the procedure described in Section 10.1.2.2.

Patients who decline measurement of total body water or plasma volume by the indicator dilution methods, or in cases where in the opinion of the Investigator technical issues might prevent successful completion of those techniques, may still participate in the study provided they have measurements of plasma volume by the indirect hemoconcentration method.

10.1.2.1 Hemoconcentration and Total Body Water estimation procedure on Day 1 and Day 14:

Hemoconcentration will be determined as previously described (22)(23), at all sites.

A new 18 or 20-gauge IV will be placed in a large vein, ideally the antecubital position, on the morning of day 1 and 14. Baseline urine, plasma and serum samples will first be collected.

All patients must have completed the last planned IV bolus or infusion therapy with diuretics.

It is recommended that procedures commence in the morning of D1. The actual start time may vary. The times provided below in Table 3 are indicative.

Total body water measurement, by the deuterium oxide dilution method, will also take place at all sites. Intake of the deuterium oxide solution will take place immediately after completion of the physical exam and baseline specimens at T0 (approximately 7:30 AM). One sample for measurement of deuterium concentration will be collected at baseline and the second one will be collected approximately 3.5 (10 min) hours after ingestion of the deuterium oxide solution.

At approximately 8 AM the subject will be asked to assume a semi recumbent position that will be comfortable to them for the next one and a half hours. The angle of the bed or chair should be at approximately 45º and will be recorded. At approximately 9:00 AM (after approximately one hour of recumbency) the blood samples for hematocrit, hemoglobin, albumin and total protein will be collected. The arm that the blood samples are being drawn from will not be in a dependent position and will be as close to the level of the right atrium as possible (to prevent hemoconcentration in the arm which can introduce substantial inaccuracy in the measurements). At approximately 10:00 AM the patient will receive the IMP. At approximately 11:00 AM, a blood sample for deuterium oxide determination will be obtained.

Table 3 - List of schedule of events for the hemoconcentration and total body water assessment procedure

Time points (from IMP intake)	***Day / Time***	***Procedure***
	D1 and D14	
T0 (-2.5 H)	7:30 am	Phys ca exam, v ta s gns, b ood and ur ne samp es, ECG Deuter um ox de ntake (mmed ate y after b ood samp e co ect on)
T1 (- 2 H)	8:00 am	Pat ent assumes sem -recumbent pos t on
T2 (-1 H)	9:00 am	Hemoconcentrat on samp es (Hematocr t, Hemog ob n, A bum n, and Tota Prote n). Pat ent a owed mob z ng.
T3 (0 H)	10:00 am	IMP adm n stered fo owed by breakfast
T4 (1 H)	11:00 am	B ood samp e for deuter um ox de

10.1.2.2 Plasma volume procedures on Day 1 and Day 14:

The procedure for plasma volume determination by the ^{3} I-albumin method will be performed at all sites with the capacity to do so.

The overall procedure and documentation are very similar to those described above, in Section 10.1.2.1. The schedule of events for ^{3} I-albumin IV administration, including the relevant sampling time points is as described below in Table 4. All times shown are indicative.

Intake of deuterium oxide will take place immediately after completion of the physical exam and baseline specimens at T0 (approximately 7:30 AM). The post-equilibration sample should be collected 3.5 hrs (10 min) following administration of the deuterium oxide solution.

At approximately 9:00 AM (after one hour of recumbency), and immediately after the samples for 'hemoconcentration' have been obtained, the patient will receive the ^{3} I-albumin injection. Further blood samples will be collected at 9:12 AM and then every 6 minutes for a total of 6 blood draws (including baseline). Samples should be collected as close to the specified time intervals as possible, however, small deviations (+/- 2 minutes) are acceptable as long as the actual time the sample collected is accurately recorded. A further sample for hematocrit determination will also be obtained at 9:36 AM, together with the final sample for ^{3} I-albumin determination.

Table 4 - List of schedule of events for the plasma and total body water volumes assessment procedures

***Time points (from IMP* intake)**	***Day/Time***	***Procedure***
	D1 and D14	
T0 (-2.5H)	7:30 am	Phys ca exam, v ta s gns, b ood and ur ne samp es, ECG. Intake of Deuter um ox de.
T1 (-2.0 H)	8:00 am	Pat ent assumes sem -recumbent pos t on
T2 (-1.0 H)	9:00 am	Hemoconcentrat on samp es (Hematocr t, Hemog ob n, A bum n, Tota Prote n) and samp e for background rad at on counts
		^{131}I-a bum n adm n stered IV
	9:12	P asma co ect on; Record t me
	9:18	P asma co ect on; Record t me;
	9:24	P asma co ect on; Record t me
	9:30	P asma co ect on; Record t me
	9:36	P asma co ect on; record t me; CBC
		Pat ent a owed mob z ng
T3 (0 H)	10:00 am	Sotag f oz n or p acebo adm n stered fo owed by breakfast
T4 (1 H)	11:00 am	P asma samp e for deuter um ox de

Table 5 - Summary of handling procedures for ^{131}I-albumin measurement samples samples

^{131}I-albumin measurement samples	
Blood sample volume	7 mL
Anticoagulant	K2 EDTA
Handling procedures	Samp es w be centr fuged for p asma preparat on. Immed ate y after centr fugat on the resu t ng p asma w be transferred to an appropr ate y abe ed tube and be frozen mmed ate y unt ^{131}I-a bum n measurements
Plasma storage conditions	-20ºC
Plasma shipment conditions	Samp es w be sh pped on dry ce.
Deuterium samples	
Blood Sample volume	3 mL
Anticoagulant	K2 EDTA
Handling procedures	Centr fugat on at 1000g for 10m ns at 4ºC
Plasma aliquot split	1m cryov a for Deuter um ox de
Plasma storage conditions	-20ºC
Plasma shipment conditions	Samp es w be sh pped on dry ce.

Further details for the collection, identification, storage, and shipment of ^{3} I-albumin and deuterium oxide samples are provided in the Laboratory manual.

10.1.3 Assessment schedule

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

Table 6 - Number of samples

	^{131}I-albumin	**Deuterium oxide**
By subject / D 1	6	2
By subject / D 14	6	2
Tota by subject	12	4
Tota for study (approx mate y 64 pat ents)	approx mate y 768	approx mate y 256

10.1.4 Assay methods

A brief outline of the bioanalytical assays is provided in the summary tables below.

Table 7 - Summary of assay method for ^{131}I-albumin

Analyte	^{131}I-albumin
Matr x	P asma
Ana yt ca techn que	Gamma counter (BVA-100 ana yzer)
Lower m t of quant f cat on	
Assay vo ume	1 mL
S te of b oana ys s	[redacted]
Method reference	Manzon et a . J Nuc Med Techno 2007; 35:55-63 (12)

Table 8 - Summary of assay method for deuterium oxide

Analyte	Deuterium oxide
Matr x	P asma
Ana yt ca techn que	NMR spectroscopy
Assay vo ume	0.2m
S te of b oana ys s	[redacted]
Method reference	Kha ed et a . Am J C n Nutr 1987; 45:1-6 (24)

10.2 SAFETY

Assessments for safety include AEs, clinical laboratory assessments, physical examination, ECG, weight and vital signs. An independent DMC will meet on a regular basis to review accumulating clinical trial safety data. Enrollment in Cohort 2 will only proceed following review of cases in Cohort 1 by the DMC, and similarly enrollment in Cohort 3 will only proceed following review of cases in Cohort 2 by the DMC.

Serum creatinine will be assessed at Baseline (Day 1, Visit 1) and on-site Visits 2, 3 and 4 (in cohort 3 on-site visit 4 was eliminated precluding any serum collection). A central laboratory will analyze samples and estimate change from Baseline in serum creatinine and eGFR. Renal safety will also be assessed on a regular basis by an independent expert, who may also be a member of the DMC.

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

10.2.1 Safety assessment at baseline and during the study

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

1. **Physical examination** (includes at a minimum: heart and respiratory auscultation; peripheral arterial pulse; pupil, and abdomen examination). All physical examinations in diabetic patients, including abbreviated physical examinations, will include examination of the lower extremities to evaluate for any evidence of foot ulcers or infection should be performed as part of the general physical examination and this examination should be documented on the e-CRF. New lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) requiring treatment should lead to permanent discontinuation of IMP.
2. **Body weight** (kg) and height (cm). Body weight should be obtained with patients wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.
3. **Oral or tympanic body temperature**;
4. **Vital signs**, including heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine or sitting resting position.

   Prior to discharge on Day 1 (T6H) and on EOT Day 14(1)(T6H), and on Visits 3 and 4 (only Visit 3 in cohort 3), orthostatic changes in blood pressure will be assessed once for all patients not limited by mobility issues (assess BP when supine or sitting for 10 mins and after 3 mins standing).
5. **Laboratory tests** (in fasting conditions for blood samples):

- **Hematology:** red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets, MCV, MCHC, RDW.
- **Biochemistry:**
  - Plasma/serum electrolytes: sodium, potassium, chloride, calcium.
  - Liver function: AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, total and conjugated bilirubin.
  - Renal function: urea, creatinine.
  - Pancreatitis: Amylase and Lipase
  - Potential muscle toxicity: creatine phosphokinase
  - Metabolism: glucose, albumin, total proteins.

6. **Urinalysis:** A urine sample will be collected and sent for quantitative measurement for glucose, protein, erythrocytes, and leucocytes count. Microbiological analysis will be requested in the presence of symptoms suggestive of urinary tract infection.
7. **If female and of child bearing potential, beta-HCG serum test.**
8. **If female without a clear history of menopause, plasma follicle-stimulating hormone.**

9. **Adverse events**, spontaneously reported by the subject or observed by the Investigator, will be monitored.
10. The **ECG** assessment of "normal" or "abnormal" will be analyzed. A 12-lead ECG record is performed locally at Visit 2, Visit 3 and Visit 5 (EOT) in cohorts 1 and 2, and 3. The 12-lead ECG should be performed after at least 10 minutes in supine position and, when possible, prior to the morning IMP administration. The Investigator should review the ECG and document the interpretation, sign and date it on the ECG print out and in the e-CRF. Each ECG trace is analyzed in comparison with the screening recorded trace. All original traces are kept as source data.

    Any new ECG abnormality should be rechecked for confirmation and reported as appropriate for that finding.

10.3 PHARMACOKINETICS

10.3.1 Sampling times

Sparse pharmacokinetic (PK) samples will be collected. PK samples will be collected only from patients in cohort 1 and 2. The sampling times for plasma collection can be found in the study and period flow charts (Section 1.2 and Section 1.3).

10.3.2 Number of pharmacokinetic samples

Table 9 - Number of plasma samples

	sotagliflozin
By subject	7
Tota by subject	7
Tota for cohort 1 and 2 on y (30 p anned)	210

10.3.3 Sample handling procedure

The sample handling procedure for the PK samples is summarized in Table 10 below.

Special procedures for collection, storage, and shipment are provided in the Laboratory manual.

Table 10 - Summary of handling procedures

	Sotagliflozin / Sotagliflozin-3-*O*-glucuronide
Blood sample volume	2 mL
Anticoagulant	K2 EDTA
Handling procedures	See Laboratory manua
Plasma storage conditions	-70°C or be ow
Plasma shipment conditions	dry ce

10.3.4 Bioanalytical methods

Table 11 - Summary of bioanalytical method

	Sotagliflozin/ Sotagliflozin-3-*O*-glucuronide
Matrix	P asma
Analytical technique	LC-MS/MS
Lower limit of quantification	2ng/mL parent/10ng/mL metabo te
Assay volume	0.05 mL
Site of bioanalysis	Covance Ind anapo s
Method reference	SA3GHPP

10.3.5 Pharmacokinetic parameters

No formal analysis of PK parameters will be performed. Single concentration-time-points will be subject to descriptive statistical analysis.

[redacted]

[redacted]

[redacted]

10.5 SAMPLED BLOOD VOLUME

Approximate sample blood volume is presented in the Table below (possible refinement/changes may occur). An additional PK sampling may occur to check the exposure in case of an expected AE:

Table 12 - Sampled blood volume

Type	Volume per sample	Sample number	Total
Hemato ogy	2 mL	5	10 mL
B ochem stry (LFTs, NT-proBNP and ur c ac d can be ana yzed off the same samp e, when app cab e)	4.5 mL	5	22.5 mL
β-HCG or FSH (when app cab e)	3.5 mL	Max 2	7 mL
^{131}I-a bum n (when app cab e)	7 mL	12	84 mL
Deuter um ox de	1 mL	4	4 mL
[redacted]			
Erythropo et n	2.5 mL	2	5 mL
Beta-hydroxybutyrate	2 mL	2	4 mL
Pharmacok net cs sotag f oz n*	2 mL	7	14 mL
[redacted]			
Total			
- male			177.5 mL*
- female			184.5 mL*
***Note: In cohort 3 pharmacokinetic sotagliflozin samples are not collected subtract 14 ml from each gender**			

Additional samples may be needed if any laboratory result is outside of the normal range or for safety purposes.

[redacted]

[redacted]

10.7 MEASURES TO PROTECT BLINDING OF THE TRIAL

Sites and Investigators should not perform unblinded analyses of urine samples during the trial.

Nevertheless, for safety reason, the treatment code will be unblinded for internal review and /or 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, DMC and/or the Sponsor.

11 SUBJECT 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.)

11.1 ADVERSE EVENT MONITORING

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

11.2 DEFINITIONS OF ADVERSE EVENTS

11.2.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a subject 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 and classified by system organ class (SOC) / preferred term (PT) according the last available version of the Medical Dictionary for Regulatory Activities (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.

11.2.2 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 subject 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 subject 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. Unblinding of suspected unexpected serious adverse reaction (SUSAR) by the Sponsor is described in Section 9.3.2.

11.2.3 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 the study by protocol amendment.

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 11.2.2),

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/non investigational 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 increased ≥ 3X ULN (refer to related flowchart in Appendix B)

11.2.4 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:

4. MACE (cardiovascular death, myocardial infarction, or stroke) and other specific CV events (eg, heart failure leading to hospitalization).
5. Severe hypoglycemia (see Section 11.5.1.1)
6. Venous thrombotic events (including venous thrombosis deep and pulmonary embolism)
7. Pancreatitis
8. Fracture bone
9. AEs leading to amputations
10. Diabetic Ketoacidosis (DKA)
11. Malignancies of special interest (breast, bladder, renal cell, Leydig cell tumor of the testis, pancreatic, prostate, and follicular thyroid cancer)
12. Genital mycotic infections (to include vulvovaginal candidiasis in females and candida balanitis in males)
13. Urinary tract infection
14. Diarrhea

15. Volume depletion with serious consequence (orthostatic hypotension, orthostatic collapse fall, fracture)
16. Renal events, to include 50% decline in eGFR, end stage renal failure, renal death defined as eGFR < 15 ml/min/1.73m^2

11.3 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

11.3.1 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. 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 11.2.1), 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 this study, the use of concomitant medication, as well as the nature of the disease and comorbidities, might make it difficult to assess causal relationships, as might for example be the case with renal function or shifts in blood pressure. In such cases, where the nature of the relationship cannot be determined by the investigator, the Global Safety Officer with input from other appropriate study team members and/or DMC will determine if there is a causal relationship.

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.

11.3.2 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 subject's identity is protected and the subject'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, subject 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 subject’s identity is protected and the subject’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 subject and considered by the Investigator to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

11.3.3 Guidelines for reporting adverse events of special interest

For AESI, the Sponsor is to be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 11.3.2, 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.

11.3.4 Guidelines for reporting events of special interest

If an EOSI fulfills the criteria of an SAE, reporting should be performed according to the instructions for reporting of SAEs (see Section 11.3.2). Otherwise, reporting should follow the instructions for an AE (see Section 11.3.1).

11.3.5 Guidelines for management of specific laboratory abnormalities

Once the subject is included in the clinical trial, the following laboratory abnormalities must be monitored, documented, and managed according to the related decision charts in Appendix B.

- Neutropenia
- Thrombocytopenia
- ALT increase
- Creatine phosphokinase (CPK) increase, suspected to be on non-cardiac origin and not related to an intensive physical activity

Renal function and the extent of renal injury that is commonly precipitated by intensive diuretic treatment in this patient population will be reviewed on a frequent basis by an independent renal expert, member of the Data Monitoring Committee (DMC), who shall communicate potential issues to the Sponsor. Overall renal safety in Cohorts 1 and 2 will be assessed by the DMC.

11.4 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.
- The following AESI to the Regulatory Authorities requiring such reporting:
  - Pregnancy
  - Symptomatic overdose
  - ALT increase >3 x ULN

Adverse events that are considered as expected events will be specified by the reference safety information provided in the Investigator's Brochure.

If required, unblinding of SUSARs will be the responsibility of the Sponsor.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

11.5 SAFETY INSTRUCTIONS FOR DIABETIC COMPLICATIONS

11.5.1 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 SMBG value if available, and the treatment. Unless the event fulfills SAE criteria, hypoglycemia will not be reported as an AE.

Hypoglycemia is categorized according to the ADA workgroup on hypoglycemia classification (25) and summarized in Figure 1.

11.5.1.1 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.

11.5.1.2 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.

11.5.1.3 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.

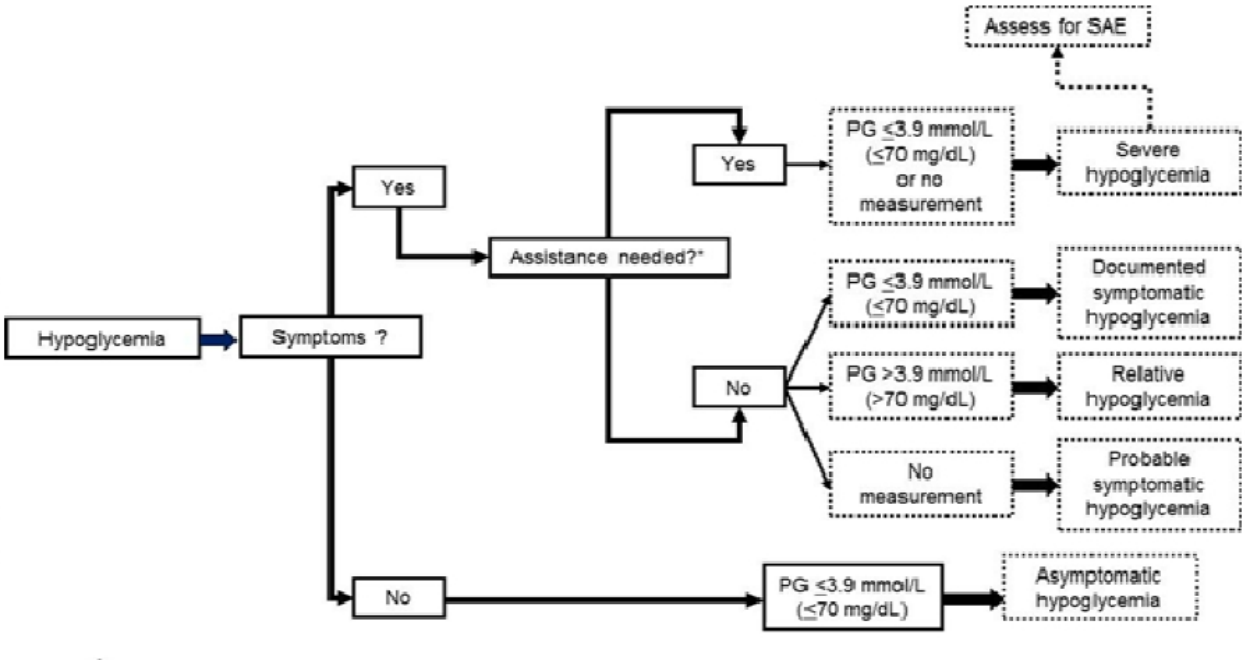
11.5.1.4 Probable symptomatic hypoglycemia

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]), i.e., symptoms treated with oral carbohydrate without a test of plasma glucose.

11.5.1.5 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 PDY15079



11.5.2 Instructions for the management of DKA in diabetic patients

Diabetic ketoacidosis, including atypical (euglycemic) DKA, is the most serious emergency in patients with T1D and T2D. It is possible that GI or other AEs occurring with sotagliflozin may mask presenting symptoms of DKA. Because sotagliflozin lowers blood glucose by insulin independent SGLT1 and SGLT2 inhibition, it is possible for DKA to be present with normal or low blood glucose. Therefore, the Investigator must still consider a DKA event even if blood glucose is low or normal. Please refer to Appendix D for further details regarding DKA.

12 HANDLING OF SUBJECT WITHDRAWAL

12.1 LIST OF TREATMENT WITHDRAWAL CRITERIA

Refer to Section 11.3.3 for cases in which AESI lead to treatment discontinuation.

Pregnancy will lead to permanent treatment discontinuation in all cases (Refer to Section 11.3.3).

12.2 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.

12.3 REPLACEMENT OF PATIENTS

According to the study design, a patient who prematurely ends his/her study period after the start of the baseline period and who received treatment may be replaced in order to have 81 patients who have completed a minimum of 12 days treatment with IMP (sotagliflozin or placebo).

In the case of a discontinuation related to an AE, the replacement may be discussed between the Investigator and the Sponsor.

12.4 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 patient who fails to return to the site at the EOT visit, unless the patient withdraws the consent for follow-up, the Investigator should make every effort to contact the patient (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 patient must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients withdrawn from the study must not be re-included in the study. Their inclusion and treatment numbers must not be reused.

13 STUDY PROCEDURES

13.1 VISIT SCHEDULE

The visit schedule and procedures/assessments are listed in the Study Flow Chart (Section 1.2). The aim of this section is to provide details on how some of the procedures/assessments should be performed. All data obtained during the trial visits are reviewed by the Investigator and/or Sub-Investigators who are qualified in the treatment of heart failure patients and are familiar with the study.

13.1.1 Screening procedures

Patients will undergo Screening assessments at Visit 1 (Day -21 to Day -1, and up to randomization on D1, to allow, for example, cases where the patient may be admitted and likely to be discharged on the same day) following signing of the informed consent form. The patient will receive information on the study objectives and procedures from the Investigator. The patient will have to sign the informed consent prior to any action related to the study.

The interactive response technology system (IRT) will be contacted at Visit 1 for notification of Screening Visit and to obtain the patient identification number.

Screening will include the investigations listed in the Study Flow Chart (Section 1.2) and detailed in Section 10.2.

All patients must have a documented echocardiogram, either performed during Visit 1 or within 12 months from current admission or screening.

Rechecking of any parameters at screening is subject to the Investigator's judgment, allowed once.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for randomization.

13.1.2 Inclusion procedures

Inclusion procedures will be carried out during Screening (D-21 to D-1) or D1, as appropriate for each patient. Those will include the investigations listed in the study flow chart (Section 1.2) and detailed in Section 10.2.

Baseline parameters may be rechecked once, at the Investigator's discretion. 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.

Prior to final inclusion and randomization, all patients must have completed the last planned IV administration (bolus or infusion), and *either* have commenced oral diuretic therapy *or* have a clear and documented plan to commence oral diuretic therapy. Patients may be discharged and return for Day 1 procedures within seven (7) days from discontinuation of IV diuretic administration.

Final inclusion and randomization, as appropriate, will be performed just before commencement of procedures on Day 1. Each patient will receive an incremental identification number corresponding to his/her order of enrollment in the study.

[redacted]

13.1.3 Description by type of visit

13.1.3.1 Visit 2 (Day 1) (Inpatients or Outpatients returning for Day 1 procedures)

Eligible patients will be randomized on Day 1.

Day 1 procedures may be carried out in hospital wards or outpatient units. Please refer to the period flow chart in Section 1.3 for the list of safety and baseline laboratory assessments procedures on Day 1.

The procedures for the assessment of the pharmacodynamic endpoints are described in detail in Section 10.1.2.1 and Section 10.1.2.2.

All eligible patients will have hemoconcentration samples obtained and total body water (deuterium oxide) assessment performed as per Section 10.1.2.1. Deuterium is a stable isotope of hydrogen, abundant in nature and does not pose any radiation or health risk. No special facilities are required for the handling, administration and/or disposal of deuterated samples or solutions.

Sites that have the capacity to perform the additional plasma volume assessment by the ^{3} I-albumin indicator dilution method will follow the procedure described in Section 10.1.2.2. Sites using the ^{3} I-albumin indicator dilution method should follow their institutional guidelines for the type of facility required to handle, administer, and dispose of radioactive material. The maximum dose of ^{3} I-albumin used for the indicator dilution method of plasma volume determination is 25 µCi and within US is listed as ‘exempt’ on air regulations. Each blood sample collected during the procedure will contain < 0.1 µCi of radiation.

Patients will be treated with IMP (sotagliflozin or placebo) for 14 days, commencing on Day 1. IMP administration outside of site visits should take place in the morning between 7 AM and 11 AM daily for the duration of the treatment period. Meals should be taken approximately 15 minutes after IMP administration.

For safety and practical reasons, before any of the procedures or IMP administration on Day 1 (and depending on the site and choice of whether to perform direct or indirect plasma volume/hemoconcentration measurements), an indwelling catheter will be inserted in a peripheral vein of the forearm in order to obtain blood samples.

For patients eligible for discharge from hospital or unit: The patient diary is dispensed during day 1 and instructions/training on its use and completion are provided: Adverse events (AE), Concomitant medications, IMP intake (and whether it was taken before breakfast) and BP measurements (and time) are recorded on a daily basis between Day 2 and last follow up.

The automated BP monitors will also be dispensed on Day 1 and patients will be trained in their use. The technique employed should observe the following (described in detail in Appendix C):

1. First time (performed on Day 1 by the Investigator or qualified site staff): Determine the arm with higher BP (based on SBP) and evaluate for inconsistency of BP between arms to exclude major vascular problems
2. Day 2 until last follow up:
    - Measurements should take place, to the extent possible, within the same time window each day and preferably in the morning between 6 AM and 10 AM.
    - BP obtained after 5-10 minutes in the sitting resting position
    - Measurements should be done in triplicate, not less than 1-2 minutes between readings, and all measurements recorded in the Diary.
    - The same arm, as determined on Day 1 (unless it becomes uncomfortable or contraindicated due to a newly developed skin, musculoskeletal or other condition) should be used throughout the study

Entries in the diary (such as AE and IMP intake, and if not recorded in source documents, concomitant medications and BP) will also be recorded for patients that have not been discharged.

If BP monitoring is not standard, recordings using the BP monitor provided by the Sponsor or other appropriate monitor should be used to obtain BP readings. If the patient is discharged, they will be reminded to continue with diary updates as described above.

13.1.3.2 Discharge procedures

Inpatients eligible for discharge or patients returning to the day care unit for the procedures of Day 1 may be discharged the same day (Day 1), after a complete review of the available safety data by the Investigator, and not less than 6 hours have elapsed from administration of IMP.

[3] I-Albumin has a half-life of 7-8 days. It is safe for patients to return home, without any restrictions as far as use of common areas, lavatory facilities or contact with other people is concerned. Sites should discuss the discharge plan and any restrictions with a radiation officer or nuclear medicine department.

13.1.3.3 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.

13.1.3.4 Visit 3 (Between Day 3 and Day 6) and Visit 4 (Between Day 8 and Day 11) in cohort 1 and 2*; in cohort 3 visit 3 (Between Day 6 and Day 8) and visit 4 removed*

Patients in cohort 1 and 2 who are discharged from hospital will return to the clinical site or other appropriate facility on a day convenient to them between Day 3 and Day 6 (Visit 3) and on a day convenient to them between Day 8 and Day 11 (Visit 4). Patients in cohort 3 who are discharged from the hospital will return to the clinical site or other appropriate facility on a day convenient to them between Day 6 and Day 8 (visit 3). Patients in cohort 1 and 2 will have PK samples obtained in those visits and should be instructed **not** to take their morning dose of IMP on those days, as it will be administered by site staff as per the period flow chart in Section 1.3. Inpatients will also have the same assessments in the hospital or other appropriate unit. PK sampling will **not** be collect from patients in cohort 3 at all, as PK studies were removed from this cohort.

For patients discharged home or patients transferred to other units (for example rehabilitation wards or HF units) who may have mobility or other issues that prevent them from attending the site, the PI or delegate may arrange for the Visit and all relevant assessments to take place at a an appropriate facility and as approved by the Institution and Sponsor.

All patients will have safety assessments, including collection of blood samples for measurement of creatinine, as detailed in the study flow chart, Section 1.2.

Patients returning to the site will bring their Diaries. The information recorded in the Diaries will be transcribed to the eCRFs.

The technique for measuring BP will be reviewed and further training provided as appropriate.

The Investigator will assess compliance with IMP.

In some countries, local guidelines and institutional policies might require patients to stay in hospital for prolonged periods. In those cases, administration of IMP, daily diary recording and assessments for Visit 3 (including patients in cohort 3) and/or Visit 4 (in 1 and 2 only) may take place in the hospital setting. Note: cohort 3 will be conducted exclusively in the US.

13.1.3.5 Visit 5 (Day 14±1)/

Discharged Patients will return to the clinical site on day 14 1 (Visit 5;). Exceptions can be made for those patients who may have been transferred to a step down unit, or rehabilitation ward or a different hospital. In those cases, plasma volume will not be assessed by the radiolabeled albumin method, unless the place is authorized for administration and collection of radioactive samples (such as a nuclear medicine facility) and has been discussed and approved by the relevant authority of the Institution(s) and Sponsor.

On days of site visits patients should be instructed not to take their dose of IMP in the morning of that day, as this will be administered by site staff as per the period flow chart in Section 1.3.

The guidelines described above for Day 1 procedures and discharge, should also apply on day 14. Please refer to the study flow chart in Section 1.2 and the period flow chart in Section 1.3.

A patient who had plasma volume assessment performed on Visit 2 (Day 1) by the ^{3} I-albumin method, should also have plasma volume assessment performed on Visit 5 by the ^{3} I-albumin method (Day 14 1).

A patient who *did not* have plasma volume assessment performed on Visit 2 (Day 1) by the ^{3} I-albumin method, need *not* have plasma volume assessment performed on Visit 5(Day 14 1).

Patients should bring their Diaries, and relevant information will be transcribed to the eCRFs. New diaries will be dispensed.

The technique for measuring BP will be reviewed and further training provided as appropriate.

The Investigator will assess compliance with IMP.

IRT will be notified for end of treatment (EOT).

13.1.3.6 Visit 6 (Day 26-30)

All patients enrolled in the study will be followed up with a telephone interview during that period (between day 26 and day 30). Safety, including adverse events and assessment of BP as recorded in the diary since discontinuation of IMP will be reviewed during the telephone interview.

A clinical site visit during that period is reserved only for those patients who, in the opinion of the Investigator, need followed up in clinic. The rationale and justification for the visit, as well as laboratory or other investigations' results performed to address those concerns, should be clearly documented, and relevant records kept for review by the DMC and Sponsor.

Diaries will be retrieved for those patients returning to the site. The patients who did not return to the site will return their diaries by courier, using a pre-paid service.

IRT will be notified for end of study (EOS).

13.1.4 Study restriction(s)

Throughout the treatment period, patients will be asked to take their breakfast within approximately15 minutes after administration of study drug. Meal times will not be collected in the eCRF anymore in cohort 3.

In cohorts 1 and 2 on study days during Visit 2 and Visit 5 a meal will be provided within approximately 15 minutes after administration of study drug. Patients should fast (water allowed) for 6 hours prior to the administration of IMP.

Similarly in cohort 1 and 2 for Visits 3 and 4, patients should also fast for 6 hours (water allowed) prior to IMP administration. A snack or meal should be taken within 15 min of IMP administration. Note: Visit 4 was eliminated from cohort 3.

During the study, patients will be advised by their physicians on water intake, salt intake and other relevant dietary restrictions which might constitute part of their treatment. On treatment day 1 (Visit 2) and day 14 1 (Visit 5), water and salt intake during the study procedures will be adjusted as per treatment plan.

13.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the case report form must be supported by appropriately identified source documentation.

14 STATISTICAL CONSIDERATIONS

14.1 DETERMINATION OF SAMPLE SIZE

Sample size is based on empirical consideration. No formal sample size calculation has been performed.

14.2 PATIENT DESCRIPTION

14.2.1 Disposition of patients

Screened patients are defined as any patient who meets the inclusion criteria and signed the informed consent.

Randomized and treated patients consist of all patients with a treatment kit number assigned and recorded and received at least one administration of IMP. Patients treated without being randomized will not be considered as randomized and will not be included in any analysis population for which being randomized is required.

The safety data of patients treated but not randomized will be reported separately, and these patients will not be in the safety population.

A detailed description of subject accountability including count of patients screened, randomized and treated, patients who did not complete the study along with the main reason for treatment discontinuation will be provided.

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

14.2.2 Protocol deviations

During the blinded review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment or dosing 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 subject and/or described in the body of the clinical study report.

14.3 ANALYSIS POPULATION

14.3.1 Safety population

All randomized patients who are exposed to IMP (regardless of the amount of treatment administered) will be included in the safety population. For safety analyses, patients will be included in the treatment group as actually received. Non-randomized and treated patients will not be part of the safety population, but their safety data will be summarized separately.

14.3.2 Pharmacokinetic population

The PK population will consist of all patients in the safety population from cohort 1 and 2 who have at least one non-missing and eligible plasma concentration data.

Only 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.

Patients will be analyzed according to the treatment actually received. Patients having received only placebo will not be included in the pharmacokinetic population.

14.3.3 Pharmacodynamic (PD) population

For the main PD endpoints of plasma volume and hemoconcentration, the PD population will consist of all randomized and treated patients who have valid values of the main PD parameters both at baseline and at Day 14/EOT.

14.3.4 Pharmacokinetic/Pharmacodynamic population

All patients being included in both the pharmacokinetic and the pharmacodynamic populations will be included in the pharmacokinetic/pharmacodynamic population. In addition, patients being included in the pharmacodynamic population and having received only placebo will also be included in the pharmacokinetic/pharmacodynamic population.

14.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

14.4.1 Subject demographic characteristics, medical history and diagnoses

The response to IMP might be affected by several variables, including continuous variables (e.g., age, height, weight, body mass index (BMI) and qualitative variables (gender, race and/or ethnicity). BMI can be described both quantitatively and qualitatively (Underweight: BMI is less than 18.5; Normal weight: BMI is 18.5 to 24.9; Overweight: BMI is 25 to 29.9; Obese: BMI is 30 or more). The following variables 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 PK population):

1. Age (years)
2. Height (cm)
3. Body mass index (Kg/m²)
4. Race and/or ethnicity
5. Gender

14.4.2 Baseline pharmacodynamic parameters

Baseline values of PD parameters are defined to be those taken or measured approximately one to three (3) hours prior to the first dosing of study treatment on Day 1.

All baseline PD parameters will be summarized and presented by treatment group as with all other baseline patient characteristics. In addition, for the main PD parameters such as plasma volume and hemoconcentration, the mean baseline values of the PD parameters will also be summarized along with the mean Day 14/EOT values and mean change from baseline values.

14.4.3 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 14.8.2 to Section 14.8.4).

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

14.5 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

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

The following listings will be provided:

- Patients receiving IMP from specified batch
- Randomization scheme.

14.6 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 subject.

14.7 ANALYSIS OF PHARMACODYNAMIC VARIABLES

14.7.1 Description of pharmacodynamic variable(s)

See Section 10.1.1.

Primary PD variables

- Change in hemoconcentration from baseline to D14/EOT as assessed by changes in hematocrit, hemoglobin, albumin and total protein.
- Change in plasma volume in milliliters from baseline to D14/EOT as assessed by the indicator dilution method using ^{3} I-labelled human albumin.

Secondary PD variables:

- Change in erythropoietin (mU/ml) from baseline to D14 measured by chemiluminescent enzyme-labelled immunometric assay
- Change in NT-proBNP (pg/mL) from baseline to D14 measured by standard electrochemiluminescence immunoassay

Other Exploratory PD endpoints

- Change in total body water (mL) from baseline to D14 as assessed by the indicator dilution method using deuterium oxide
- Change in uric acid (mg/dL) from baseline to 14 days as measured by standard assay
- Change in beta-hydroxybutyrate (µM) from baseline to 14 days as measured by standard enzymatic colorimetric assay
- Change in red cell mass (mL) from baseline to D14, as derived from measurements of plasma volume (assessed by the indicator dilution method using ^{3} I-labelled human albumin) and hematocrit
- Change in total blood volume (mL) from baseline to 14 days, as assessed by the indicator dilution method using ^{3} I-labelled human albumin
- Percentage of patients within 15% of ideal blood volume on study day 14
- Blood pressure (sitting, SBP and DBP) at day 14, compared to baseline

14.7.2 Primary analysis

Descriptive statistics for the primary pharmacodynamic endpoints, as raw data and change from baseline will be provided by treatment. Similarly time profile plots of mean +- SEM will be provided by treatment for the main pharmacodynamics endpoints.

14.7.3 Secondary analysis/analysis of secondary variables

Descriptive statistics for all secondary and other pharmacodynamic endpoints, as raw data and change from baseline will be provided by treatment. Similarly time profile plots of mean +- SEM will be provided by treatment for all secondary and other pharmacodynamics endpoints.

For exploratory purposes, the main pharmacodynamic variables, change from baseline to Day 14 in hemoconcentration and plasma volume, will be analyzed using an analysis of covariance (ANCOVA) model with fixed terms for treatment and stratification factor of baseline patient status (diabetic, non-diabetic, ejection fraction status (reduced-preserved), and with baseline plasma volume as covariate. An estimate for the between-group difference in treatment mean changes and corresponding 2-sided 90% confidence interval (CI) will be calculated from the model. The main treatment comparison will be between the pooled treatment (200 mg and 400 mg) group and placebo which will be made at 1-sided α 0.05 (or equivalently, 2-sided α 0.10).

Similar ANCOVA models will be fitted for the secondary and other pharmacodynamic variables or endpoints.

14.8 ANALYSIS OF SAFETY DATA

See also Section 10.2. The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before the first dose of IMP.
- Treatment emergent period for safety population is defined as the time from the first administration of study medication to the end of the Post-treatment Period.

The safety analysis will be based on the review of descriptive statistics (summary tables) and individual data for vital signs, renal function, adverse events (AEs) and other clinical laboratory values and ECG parameters.
Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and the number of patients with Treatment-Emergent Adverse Events (TEAEs) will be summarized by treatment group. Potentially clinically significant abnormalities (PCSAs) for clinical laboratory, vital sign, and ECG data and out-of-normal range values for clinical laboratory data will be flagged and summarized in frequency tables. The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review for clinical laboratory tests, vital signs and ECG parameters.

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 (treatment emergent AE) period** is defined as the time from the first IMP administration up to approximately 5 days after the last IMP administration (approximately 5 times the half-life of sotagliflozin);
- the **post-TEAE period** is defined as the time starting after the TEAE period up to the final study follow up telephone check.

14.8.1 Adverse events

14.8.1.1 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 post-treatment event.

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

14.8.1.2 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 serious TEAE, any TEAE leading to death (if any occurred), and any TEAE leading to permanent treatment discontinuation.
- 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.

14.8.1.3 Deaths, serious, and other significant adverse events

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

14.8.1.4 Adverse events leading to treatment discontinuation

Any AEs leading to permanent treatment discontinuation will be listed.

14.8.1.5 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.

14.8.2 Clinical laboratory evaluations

Baseline definition

The values to be used as the baselines will be the Day 1 predose assessment values. If any of the scheduled baseline tests are repeated for any subject, 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 post-baseline 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 and plots

Raw data and changes from baseline will be summarized in descriptive statistics for all endpoint parameters, by treatment and scheduled time of measurement.

Additionally, graphs over time for these parameters will be presented plotting mean +/- SD by treatment.

PCSA Listings

A listing of individual data from patients with post-baseline 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 > 2ULN 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>1.7 ULN, on the same sample post first dose, irrespective of the definition for the TEAE period.

Out-of-normal range definitions will be listed.

14.8.3 Vital signs

Heart rate (HR), systolic and diastolic blood pressures (SBP and DBP) will be analyzed as raw parameter value (for supine/sitting and standing positions), change from baseline (for supine or sitting position only) and as orthostatism parameter (standing-sitting/supine parameter values).

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 1 pre-dose assessment values. If any of the scheduled baseline tests are repeated for any subject, 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 post-baseline 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 and plots

For heart rate and blood pressures, raw data (supine/sitting and standing positions) and changes from baseline (supine/sitting 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.

Additionally, graphs over time will be presented plotting mean +/- SD by treatment.

PCSA Listings

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

14.8.4 Electrocardiogram

ECG parameters (HR in bpm, QTc, QT, QRS and PR in msec) will be derived from the ECG obtained in hospital or during Visit days as per schedule of events. 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 1 predose assessment values. If any of the scheduled baseline tests are repeated for any subject, 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 post-baseline 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 and plots

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

Additionally, graphs over time will be presented plotting mean +/- SD by treatment.

14.9 ANALYSIS OF PHARMACOKINETIC DATA FROM COHORT 1 AND 2

See also Section 10.3.

14.9.1 Pharmacokinetic parameters

No formal analysis of PK parameters will be performed. Single concentration-time-points will be subject to descriptive statistical analysis.

14.10 INTERIM ANALYSIS

Except DMC safety review planned after cohort 1 and cohort 2, there are no planned interim analysis.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996), and the ICH 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 subject/patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

15.2 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 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 subject.

The 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 patient should be revised whenever important new information becomes available that may be relevant to the subject'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 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.

15.3 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 with any addenda, 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.

16 STUDY MONITORING

16.1 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 Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators 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.

16.2 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.

16.3 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 pre-identified 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 maintained confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

16.4 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 eCRF 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 eCRF.

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 eCRF.

16.5 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.

17 ADDITIONAL REQUIREMENTS

17.1 CURRICULUM VITAE

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

17.2 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.

17.3 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 Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators 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.

17.4 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 /Sub-investigator 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 sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

17.5 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.

The data collected in this study will only be used for the purpose(s) of the study. They may be further processed if they have been pseudonymized.

17.6 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.

17.7 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.

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

17.8.1 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 Sub-investigator, 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 number of patients is included earlier than expected.

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

17.8.2 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.

17.9 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.

17.10 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.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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.

18 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.

19 BIBLIOGRAPHIC REFERENCES

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20 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. Pre-menarchal
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 8.2):
  - 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 13 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 13 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 13.

Table 13 - Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation oral injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion

Vasectomized partner

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.

- Sexual abstinence

  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.

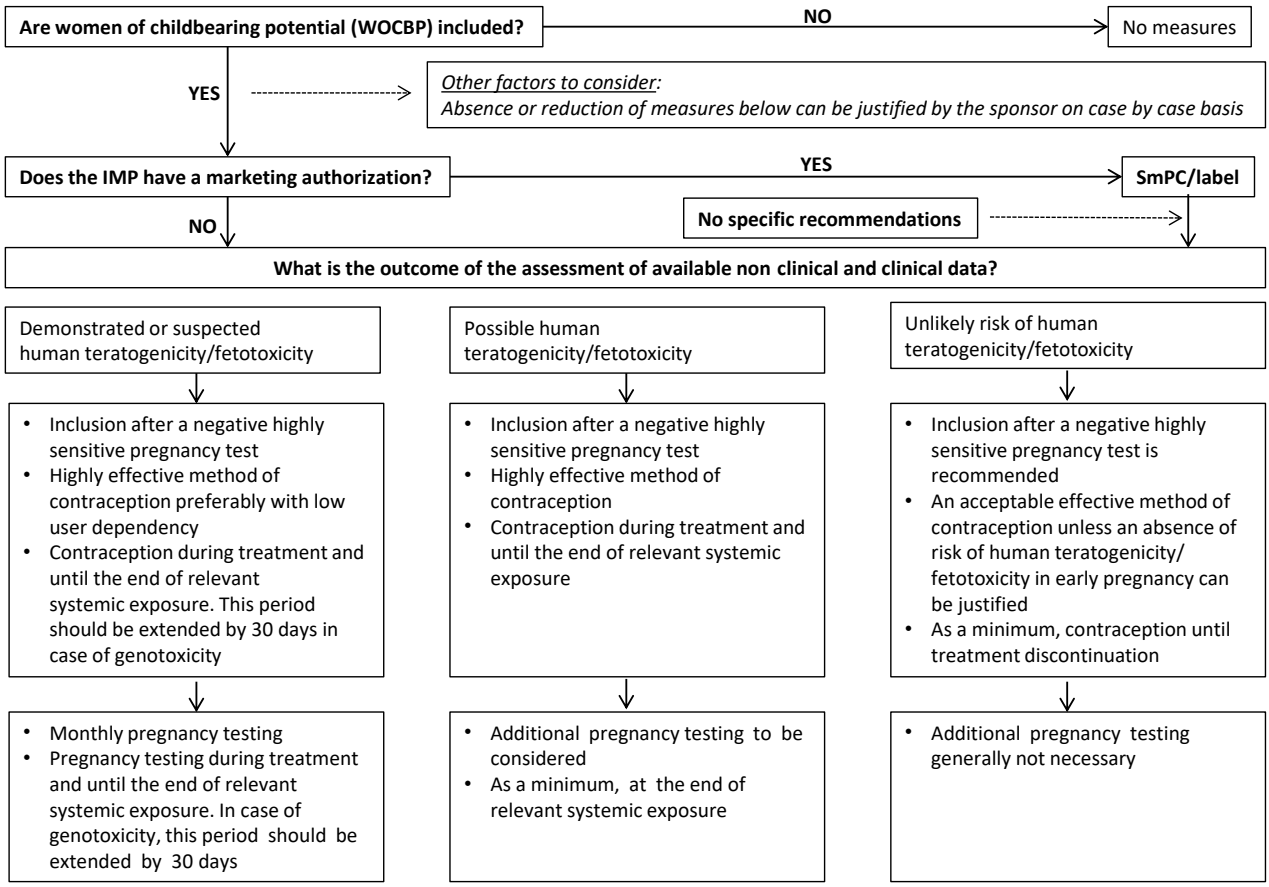
NOTES:

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.

See guidance below

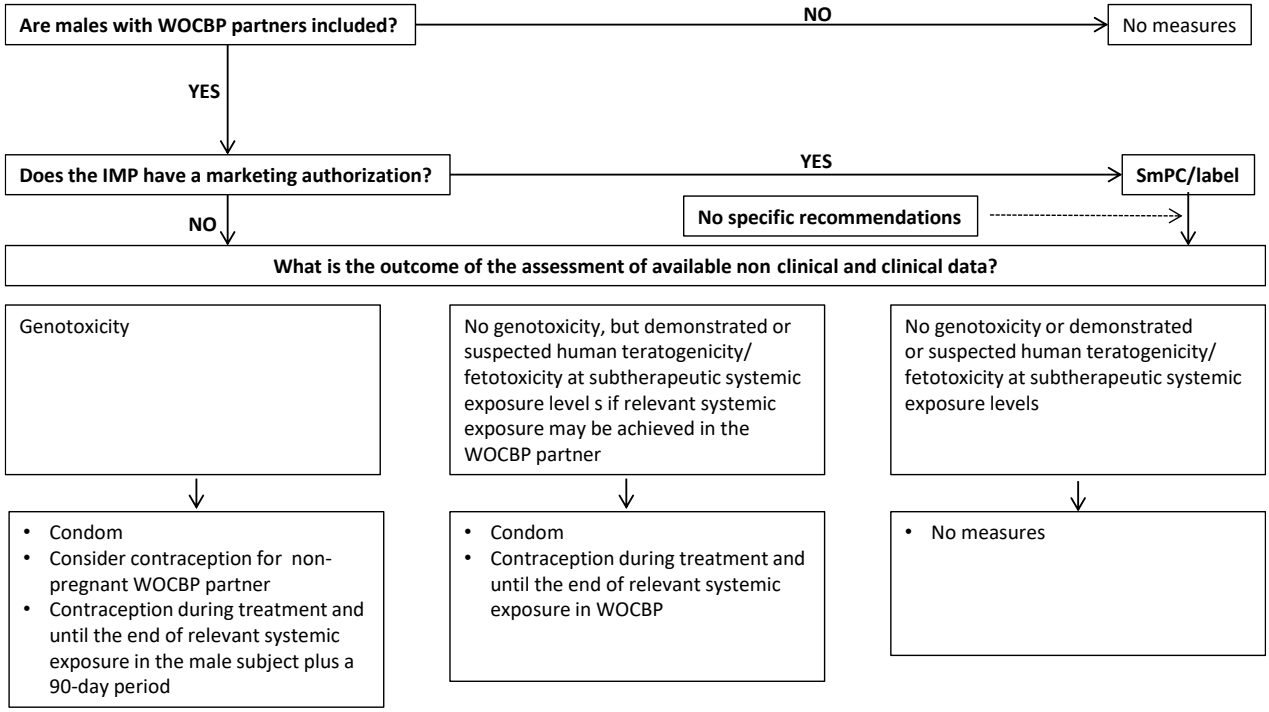
Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Women of Childbearing Potential (WOCBP)



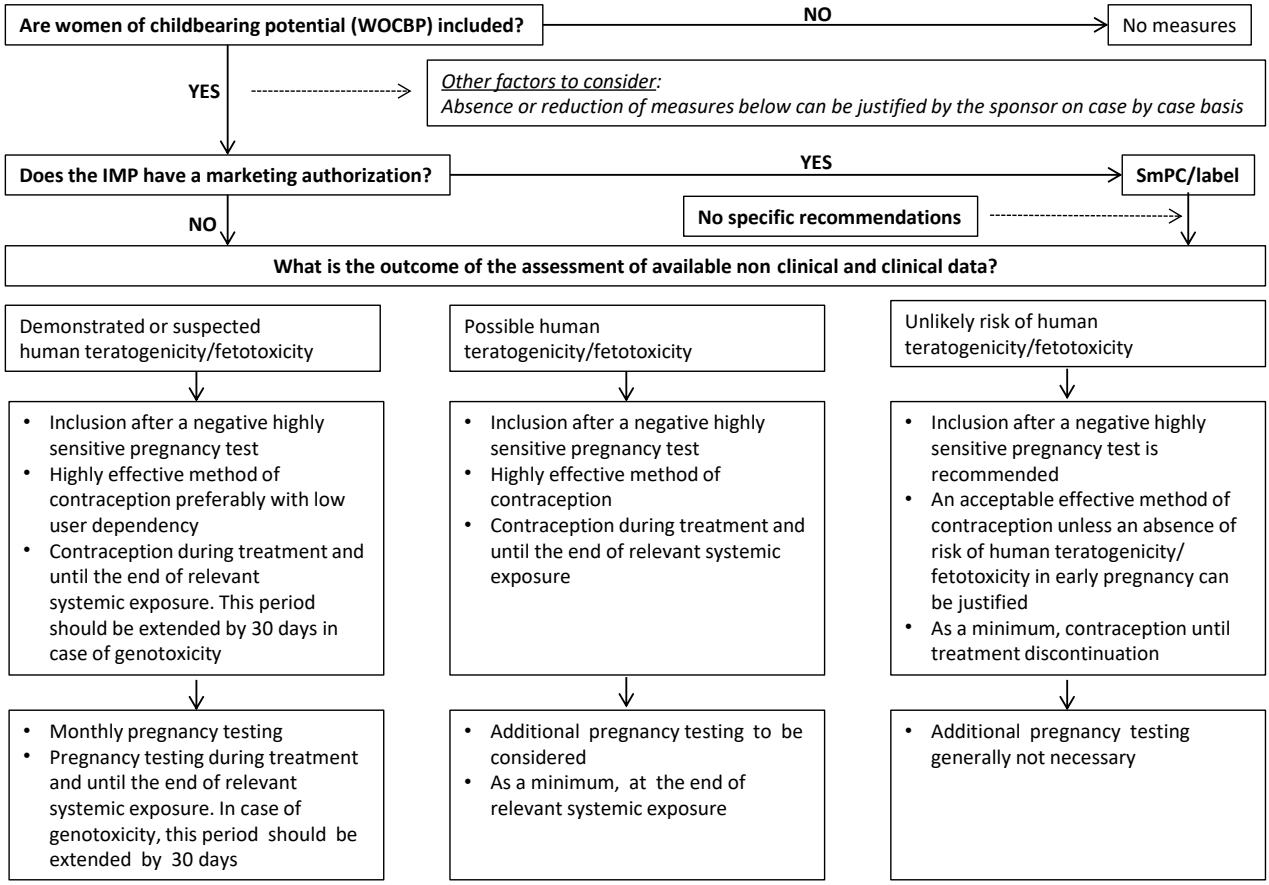
Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Males with WOCBP Partners



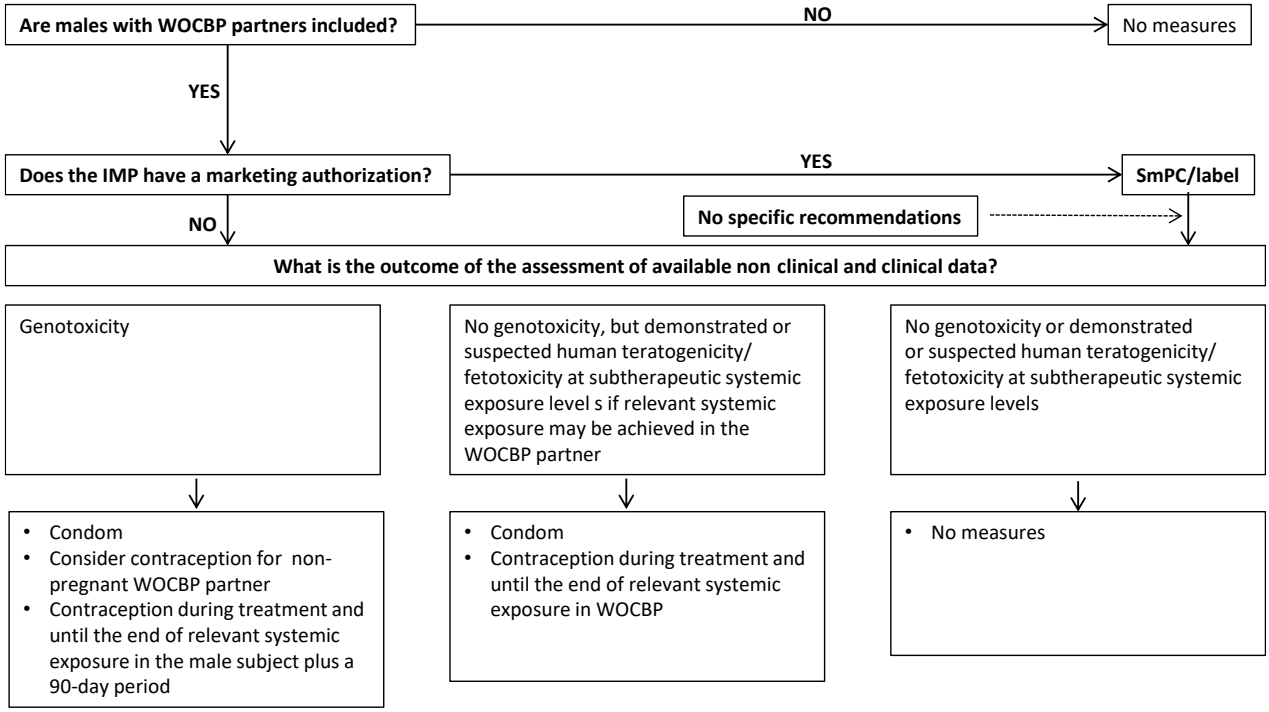
Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

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

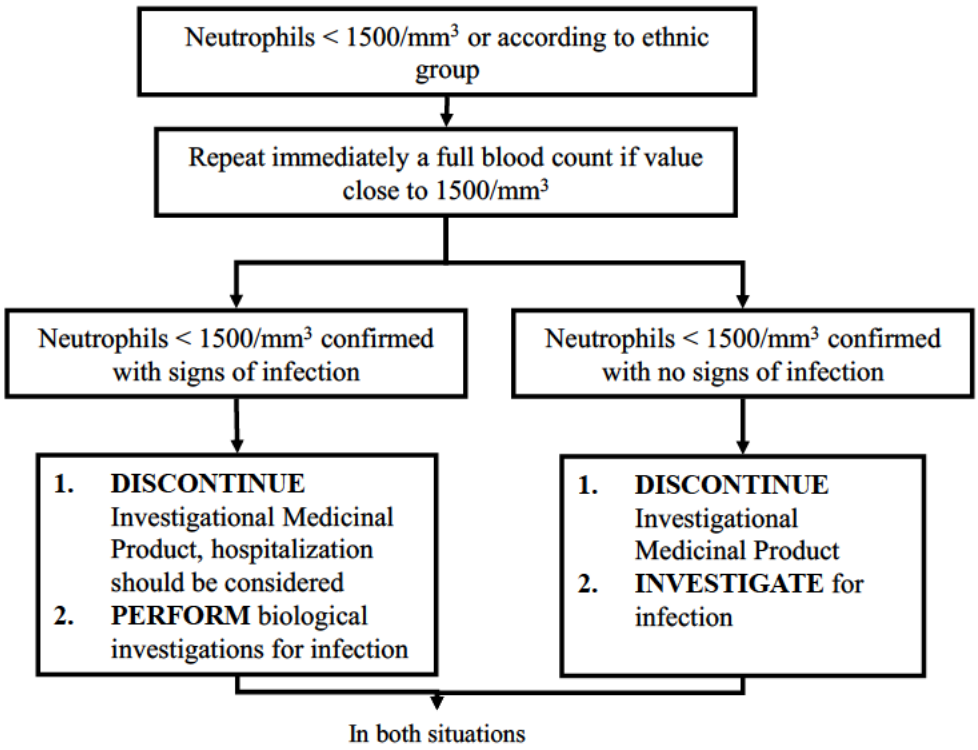
- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from 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 Decision charts

NEUTROPENIA

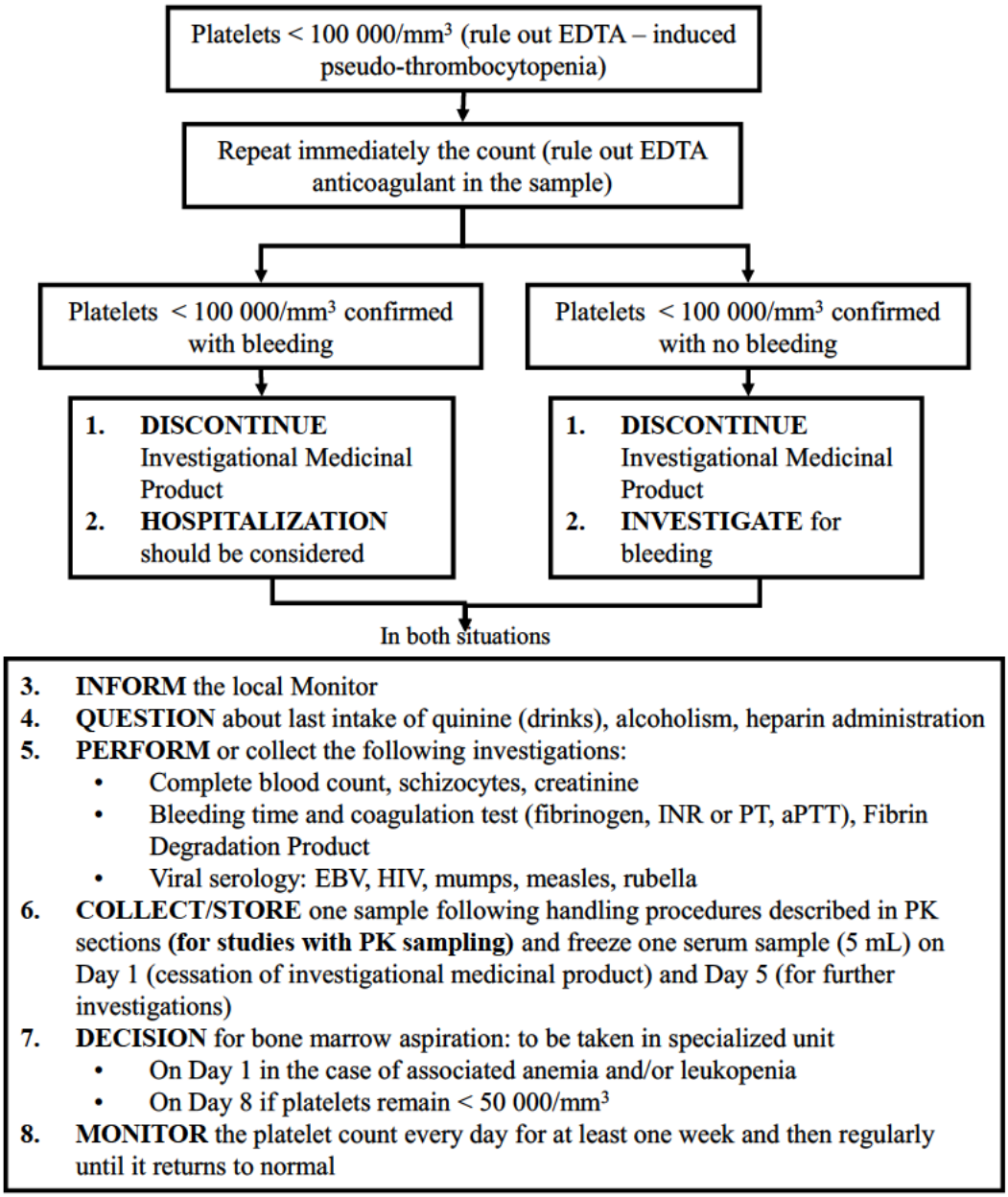


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

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

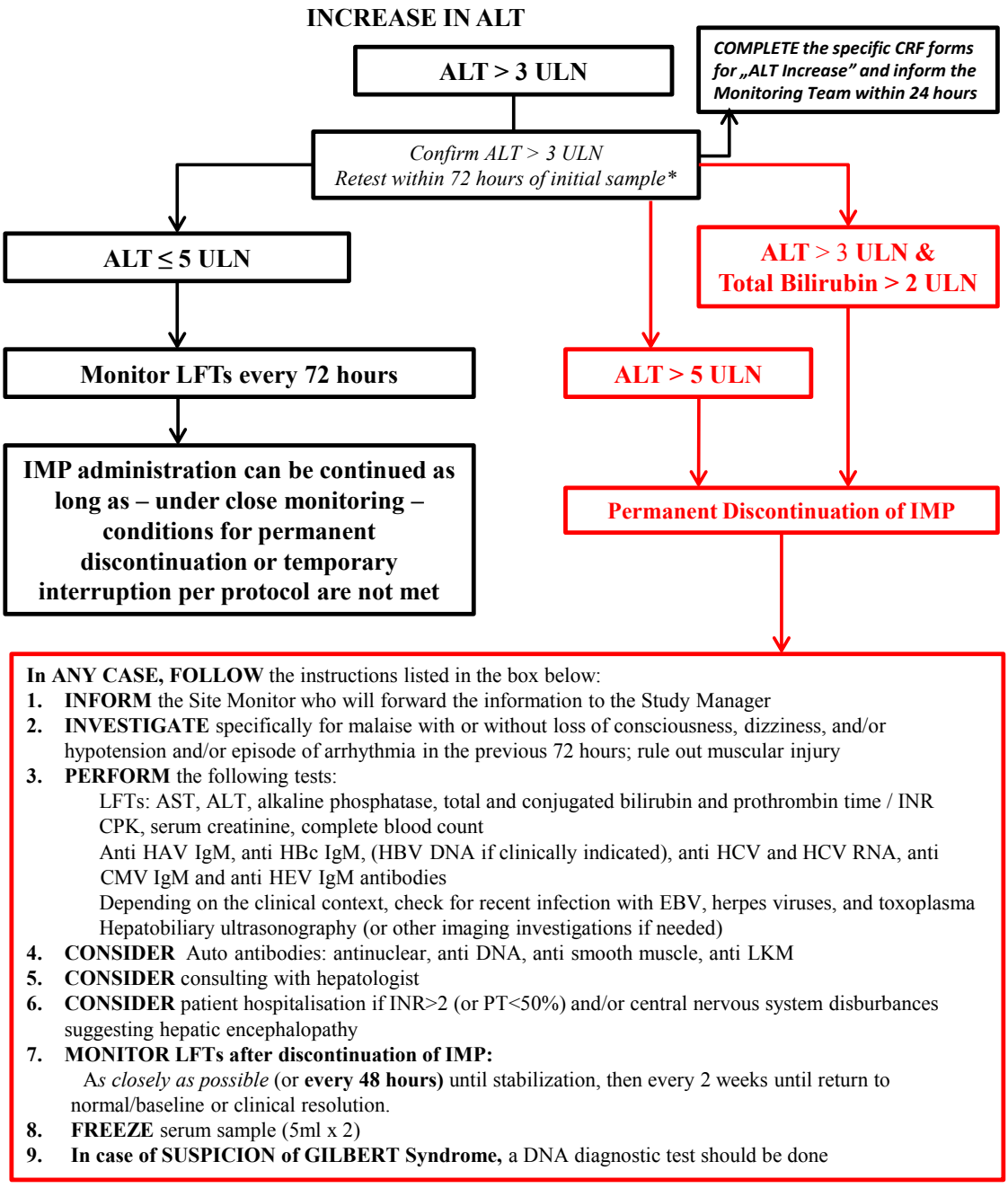
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in Section 11.3.1 is met.

THROMBOCYTOPENIA

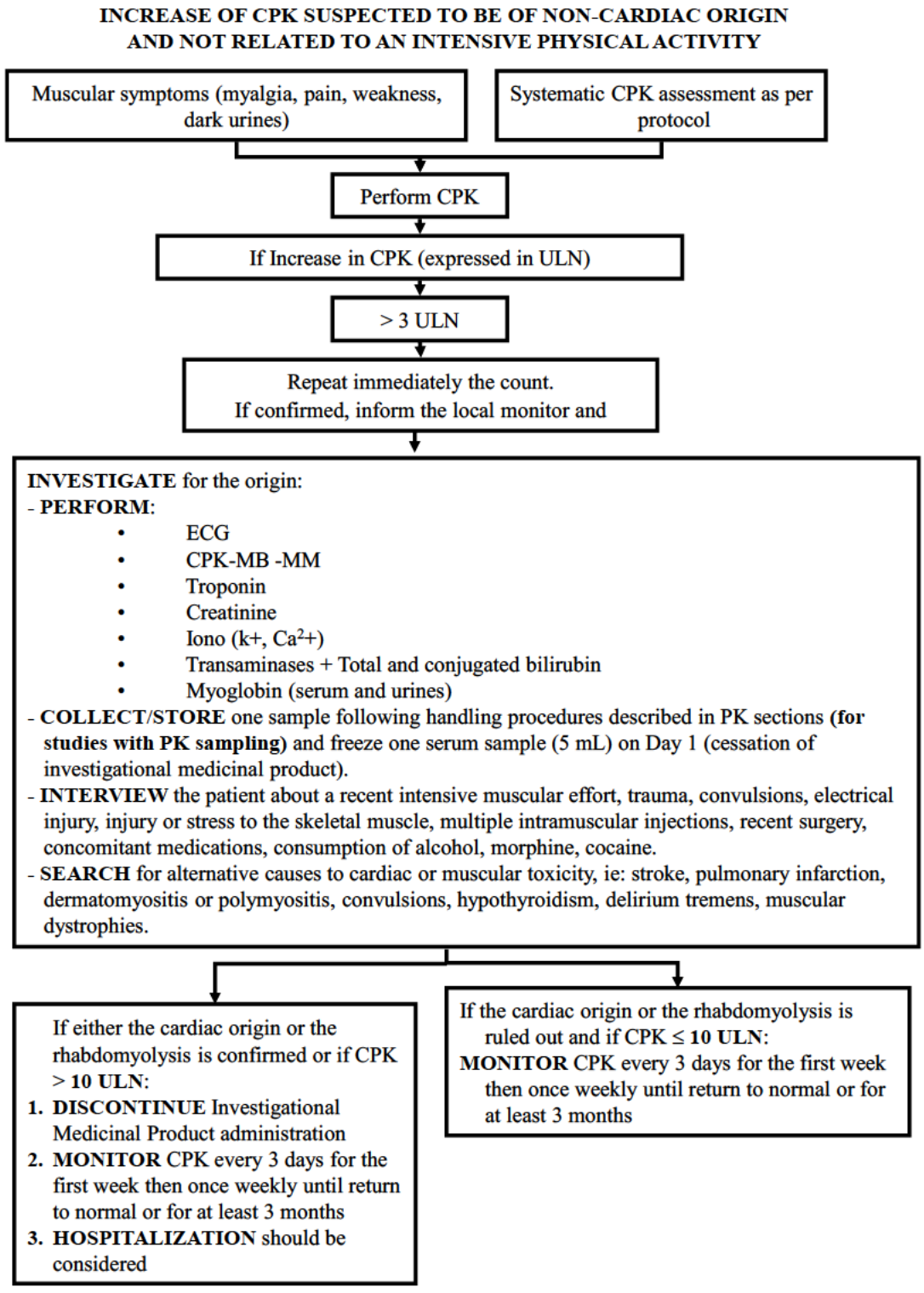


Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in Section 11.3.1 is met.



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 11.3.1 is met.



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 11.3.1 is met.

Appendix C 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 Visit 1 or 2, seated BP should be measured in both arms after a 10 minute rest period, and then again after 1-2 minutes in both arms, in seated position. The arm with the highest DBP will be determined at this visit, and 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

At Visit 1 or 2, immediately following arm selection, with the patient in the same position, an additional seated BP should be measured in the selected arm (at least 1 minute after last measurement).

At all other on-site visits, or when patients monitor their BP at home, following the 5-10-minute rest period, 3 separate seated BPs should be measured in the arm selected at Visits 1 or 2, with at least 2 minute between BP measurements and with the cuff fully deflated between measurements.

All 3 BPs will be recorded in the patient's diary and e-CRF. The mean of the 3 seated BPs will constitute the BP value for that visit.

Three seated pulse rate measurements will also be obtained. The mean of the 3 seated pulse rate measurements will constitute the pulse rate value for that visit.

Appendix D Diabetic ketoacidosis

Recognizing diabetic ketoacidosis

Diabetic ketoacidosis, including atypical (euglycemic) DKA, is the most serious emergency in patients with T1D and T2D. Common precipitating factors include infections, intercurrent illnesses, psychological stress and noncompliance with insulin therapy. Clinical features of DKA at presentation can be nonspecific; however most patients complain of polydipsia and polyuria for several days before onset of DKA. Symptoms of DKA include rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odor to urine or sweat.

It is possible that GI or other AEs occurring with sotagliflozin may mask presenting symptoms of DKA. Because sotagliflozin lowers blood glucose by insulin dependent SGLT1 and SGLT2 inhibition, it is possible for DKA to be present with normal or low blood glucose. Therefore, the Investigator must still consider a DKA event even if blood glucose is low or normal.

More information can be found in the sotagliflozin IB.

If DKA is suspected or confirmed, study treatment should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

Caution should be exercised in patients with risk factors for ketoacidosis and inform patients of the risk factors. These include low reserve of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin due to illness, surgery or alcohol abuse.

In addition, IMP administration should be stopped in patients in hospital for major surgical procedures or due to serious illness.

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

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 adverse event data are collected or the patient reports DKA or intercurrent illness (including infections), generalized weakness, increased weight loss, GI 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, such as assessing blood beta-hydroxybutyrate level (BHB), is appropriate. If BHB or other laboratory testing confirms presence of metabolic acidosis, then the "Possible DKA" e-CRF will be completed.

Appendix E Country Specific Changes

The history of Country specific amendments in Canada) for this amended protocol are irrelevant because the current amendment 3 will be implemented in the US only.

Appendix F Protocol Amendment History

The summary of changes for the current amendment is located above immediately following after the Clinical Trial Summary.

20.1.1 Amended Protocol 1 based on Amendment 1: 09-Jan-2018

REASON FOR AMENDMENT:

- **Change to the duration of the Screening Period from 10 days to 21 days**

  In Section(s): tabulated clinical trial summary, sections 1.1., 1.2 and 1.3, and section 6.2
  Rationale: Increase flexibility for sites and patients.

- **Change to the duration of the interval from discontinuation of intravenous diuretics to randomization from 4 days to 7 days**

  In Section(s): tabulated clinical trial summary, sections 1.1, 1.2 and 1.3, and section 6.2
  Rationale: Increase flexibility for sites and patients.

- **Change to Cohort sample size: Approximately 15 patients in each of Cohorts 1 and 2, and approximately 51 patients in Cohort 3.**

  In Section(s): tabulated clinical trial summary, sections 1.2 and 1.3, section 6.2, section 7.1 and section 13.
  Rationale: Safety for patients is assessed on an ongoing basis by the DMC, which also has the ultimate decision for up-titration from Cohort 1 to Cohort 2, and from Cohort 2 to Cohort 3. The DMC might determine that the absence of any significant adverse events in a sufficient number of patients on sotagliflozin might be sufficient to allow progression to the next Cohort, or similarly to request expansion in the number of patients exposed to IMP.

- **Change to the inclusion/Exclusion criteria**

  In section(s): tabulated clinical trial summary, sections 7.2 & 7.3 of the protocol
  Rationale:
  - **I01.** Clarified to indicate that written consent should be obtained during the screening period.
  - **I03**. Expanded to include subjects admitted to appropriate inpatient and specialized units where heart failure patients are often safely assessed and screened, and to add increase in weight as one of the qualifying criteria for congestion as this is frequently an indicator of worsening heart failure in chronic heart failure patients. Clarified that treatment with intravenous diuretics is a requirement for consideration of patients to randomization whereas it is not important whether they receive bolus or infusion of drug.
  - **I04**. Removed to expand eligibility to patients with new onset heart failure, as treatment with sotagliflozin may also have significant benefits on fluid volume redistribution in eligible congestive and hemodynamically stable patients. New onset

heart failure patients at highest risk will be excluded based on E3-5.
- **I07.** Clarified birth control requirements for male participants.
- **I08**. Simplified for ease of understanding to indicate requirement for intravenous diuretics between screening and randomization, and transition to oral diuretic treatment.
- **I09**. Consolidated criteria for hemodynamic stability at randomization.
- **E03**. Corrected to also account for patients with worsening heart failure that may be admitted to a heart failure unit or infusion center rather than a hospital.
- **E04**. Added and clarified that patients with uncomplicated revascularization following a recent myocardial infarction (index MI, within 1 month) are eligible, as the risk in those patients is significantly less compared to those without revascularization during the index MI or with procedures associated with complications.
- **E05**. Adapted to harmonize with E04 and to indicate that patients who had or scheduled to have a procedure, such as percutaneous coronary intervention or other cardiac intervention, may be eligible if they are stable and congested and in need of diuretic treatment.
- **E12**. Any moderate or severe respiratory disease is an exclusion. Oxygen therapy requirement is redundant in this context.
- **E14**. Corrected previous omission to allow one repeat lab at screening for amylase and/or lipase
- **E15**. Removed, as each case should be individually assessed based on multiple cardiorenal
variables. Added instructions in Section 8.8 (Concomitant Medication).
- **E16**. Modified, as only patients with severe or persistent GU infections at randomization may need to be excluded. GU infections associated with SGLT2-inhibitors are described as mainly mild to moderate in intensity and respond to standard treatment. (European Medicines Agency. Jardiance (empagliflozin) public assessment report. March 2014; European Medicines Agency. Forxiga (dapagliflozin) public assessment report. September 2012; European Medicines Agency. Canagliflozin public assessment report. September 2013.)
- **E18**. Removed, text consolidated with E11.
- **New Exclusions added in response to Health Authority/Ethics Committees' feedback**:
- Exclusion of persons dependent on the sponsor, investigator or study site is added.
- Exclusion for diabetic patients at high risk of lower limb amputations

· **Change to the classification of ^{131}-Iodinated-Albumin and Deuterium Oxide from "Noninvestigational**
medicinal product" to "Non-medicinal product"
In section(s): Tabulated summary and 8.2
Rationale: Correction, as recommended by Health Authority reviews in European Union countries

In addition, other minor changes are listed in the description of changes

20.1.2 Amended Protocol 2 based on Amendment 2: 14-Mar-2018

REASON FOR AMENDMENT:

- **Correction of nomenclature for the non-investigational medicinal products**

  In section(s): tabulated clinical trial summary, sections 9.6, 9.7, 9.11, 11.2.3, 11.3.1, of the protocol
  Rationale:
  Correction (and reversal to the original classification) from 'Non-medicinal product' to 'Noninvestigational medicinal product', to be consistent with generally accepted nomenclature, following clarification of the classification for deuterium oxide and radiolabeled albumin.

- **Change to the inclusion/Exclusion criteria**
  In section(s): tabulated clinical trial summary, section 8.3 of the protocol
  Rationale:
  E02. Added exclusion of persons sectioned due to an official or court order (as per section 1.61 of the ICH/GCP Guideline E6.)
- **Added clarification for patients who may be stable and improving but need to continue their treatment in hospital or transferred to a unit, center or ward, such as rehabilitation ward, during the study**
  In section(s): Sections 1.2, 1.3, 13.1 of the protocol
  Rationale:
  Added guidance on how sites could handle the Visit schedules for those patients who may need to continue part or all of their treatment within a hospital or related setting

- **Added option for exploratory analysis to be performed for safety reasons**
  In section(s): 6.3 Interim analysis, 14.1 Determination of sample size, 14.10 Interim analysis
  Rationale:
  Ad hoc exploratory analysis may be performed for safety reasons and/or if requested by an institutional review board or ethics committee

- **Removed option for a legally-acceptable representative to sign the consent form**
  In section(s): 15.2 Informed Consent
  Rationale:
  Only patients themselves can provide consent to participate in this study

  In addition, other minor changes are listed in the description of changes

Signature Page for VV-CLIN-0463139 v7.0
pdy15079-16-1-1-amended-protocol03

Approve & eSign	[redacted] Clinical 02-Aug-2019 01:16:41 GMT+0000