Cover page

Official Title:

Multi-center, blinded, randomized, parallel-group, Phase 3 study with aprocitentan in subjects with resistant hypertension (RHT).

ClinicalTrials.gov Identifier:

NCT03541174

Brief Title:

A Research Study to Show the Effect of Aprocitentan in the Treatment of Difficult to Control (Resistant) High Blood Pressure (Hypertension) and Find Out More About Its Safety

(PRECISION)

Date of SAP document:

6 April 2022

APROCITENTAN (ACT-132577)

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

ID-080A301

PRECISION

Multi-center, blinded, randomized, **P**a**R**all**E**l-group, Phase 3 study with apro**CI**tentan in **S**ubjects with Res**I**stant Hypertensi**ON** (RHT).

Document Number: D-22.107

6 April 2022

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LIST OF ABBREVIATIONS AND ACRONYMS

ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
aFAS	Ambulatory blood pressure monitoring Full analysis set
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AOBPM	Automated office blood pressure measurement
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BOCF	Baseline observation carried forward
BP	Blood pressure
CAC	Central Adjudication Committee
CCB	Calcium channel blockers
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CR	Copy Reference
DB	Double-blind
DBP	Diastolic blood pressure
DB-WD	Double-blind Withdrawal
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
EudraCT	European Clinical Trials Database
eTMF	Electronic trial master file
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FU	Follow-up
HBP	Home Blood Pressure
HR	Heart rate
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
IXRS	Interactive Voice/Web Response System
J2R	Jump to Reference
LOCF	Last observation carried forward
LSM	Least Squares Mean
MACE	Major adverse cardiac event(s)
maFAS	Modified ambulatory blood pressure monitoring Full analysis set
MAR	Missing at random
MedDRA	Medical Dictionary for Drug Regulatory Activities
mFAS	Modified Full analysis set
MI	Multiple imputation
MNAR	Missing not at random
mPPS	Modified Per-protocol analysis set
MRA	Mineralocorticoid receptor antagonist
mSAF	Modified Safety analysis set
NT-proBNP	N-terminal pro-brain natriuretic peptide
OR	Odds ratio

PD	Protocol deviation
PK	Pharmacokinetic(s)
PPS	Per-protocol analysis set
PRECISION	PaRallEl-group, Phase 3 study with aproCItentan in Subjects with ResIstant HypertensiON (RHT)
PT	Preferred term
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RHT	Resistant hypertension
RI	Run-in
RIS	Run-in set
RND	All-randomized set
rSAF	Restricted Safety analysis set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SB	Single-blind
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SDTM	Study Data Tabulation Model
SI	Standard International
SiDBP	Sitting diastolic blood pressure
SiSBP	Sitting systolic blood pressure
SMQ	Standardised MedDRA Query
SOC	System organ class
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
WD	Withdrawal

WHO	World Health Organization

1 INTRODUCTION

This SAP is to describe the planned statistical analyses for study ID-080A301 (PRECISION) in detail.

This SAP (Version 3) is based on Version 3 of the ID-080A301 protocol, dated 27 February 2020 [D-20.008], and its addendum, dated 8 April 2020 [D-20.063]. At the time of writing of this SAP Version 3, all subjects had been randomized. This SAP does not address the analysis of biomarkers characterizing the endothelin system activity, which will be addressed in a separate SAP.

Following comments received from regulatory agencies on SAP Version 2, the primary estimand was changed: a treatment policy strategy is now used in the main analysis instead of a hypothetical strategy estimand. The protocol, however, was not amended as the comments were received at a late stage and the change in estimand did not impact the clinical conduct of the study.

Source data for the analyses will be provided as SAS® data sets according to the CDISC SDTM. Analysis data sets will be derived as SAS® data sets according to the CDISC Analysis Data Model, IG version 1.1 or higher. Analyses will be illustrated using code based on SAS® Version 9.4.

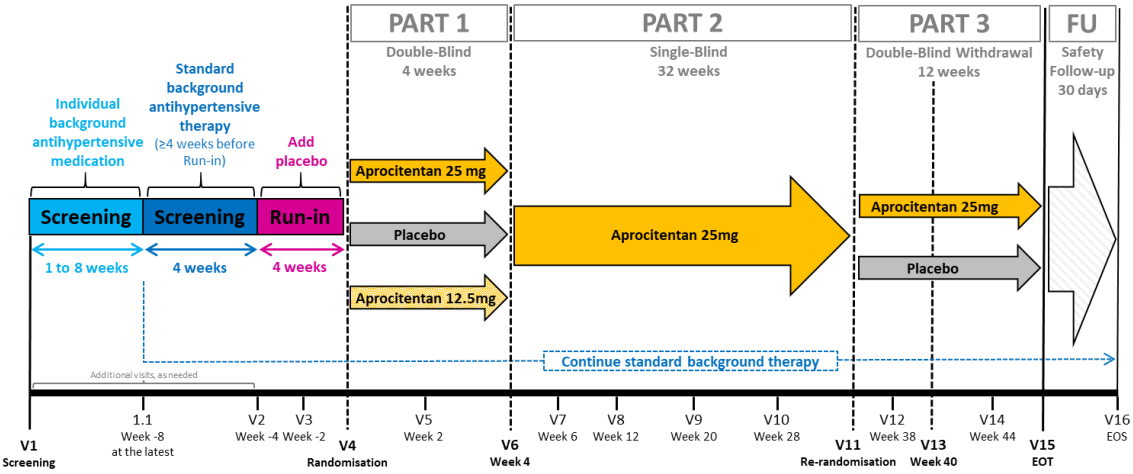
2 STUDY DESIGN AND FLOW

2.1 Study design

ID-080A301 is a study in subjects with RHT who are on a standardized background antihypertensive therapy of a fixed combination of a calcium channel blocker, an angiotensin receptor blocker, and a diuretic (amlodipine, valsartan, and hydrochlorothiazide). The main inclusion criterion at Randomization is a mean SiSBP $\geq$ 140 mmHg, as measured by AOBPM.

The study consists of four periods: a screening period, a placebo RI period, a randomized treatment period and a safety FU period. The study design is displayed in Figure 1.

Figure 1 Study design



EOT = End-of-Treatment; FU = follow-up; V = visit.

The randomized treatment period lasts for 48 weeks [until EOT, as displayed in Figure 1]. The purpose of this period is to evaluate the primary and secondary objectives of the study. This period consists of three sequential parts:

- In the first DB part of 4 weeks, subjects will be randomized to aprocitentan 25 mg, aprocitentan 12.5 mg or placebo in a 1:1:1 ratio.
- In the second SB part of 32 weeks, all subjects will receive aprocitentan 25 mg.
- In the third DB-WD part of 12 weeks, subjects will be re-randomized at Week 36 to aprocitentan 25 mg or placebo in a 1:1 ratio.

The EOT visit will take place at Week 48 (i.e., end of DB-WD part) or earlier in the event of premature discontinuation of study treatment.

Approximately 4000 subjects were expected to be screened in order to enroll approximately 1500 subjects with a diagnosis of RHT into the SB placebo RI period. At least 600 subjects were to be randomized and at least 380 subjects were expected to be re-randomized in the DB-WD part. At least 300 subjects were expected to complete the study (including the 30-day safety FU period). The study was to be conducted at approximately 100 sites in approximately 20 countries.

The sponsor planned to look at the drop-out rate (between Randomization and Re-randomization) nine months after the randomization of the 200th subject.

If the observed drop-out rate was such that the expected number of subjects to be re-randomized in the DB-WD part was less than 380, the number of subjects randomized could have been increased to maintain at least 85% power for the DB-WD part (which is

achieved when 324 subjects are re-randomized). It appeared that the drop-out rate was lower than expected, so no sample size increase was needed to compensate for drop-out.

Ultimately, 730 subjects were randomized. The overrunning was caused by the addition of sites and countries in 2020 meant to compensate for the lower recruitment due to the Covid-19 pandemic. In order to give these new sites a reasonable chance to contribute to the study, the timelines were prolonged, which, combined with a surge in screening when the EOS was announced, lead to an over-recruitment. The study was finally conducted at 193 sites in 22 countries.

2.2 Study visit and assessment schedule

The visit and assessment schedules up to Randomization and from start of DB treatment period up to EOS are given in Table 1 and Table 2, respectively.

Table 1 Visit and assessment schedule up to Randomization

PERIODS	Name / Duration	Screening 4-12 weeks		Run-in 4 weeks			
VISITS[1]	Number	1	1.1[12]	2	3	4	
	Time	Week –16 to Week –8	Week –8 at the latest	Week –4	Week –2	End of Run-in	Randomization
		Additional visits as needed		Day –28 (±4 d)	Day −14 (±2 d)	Day –1	Day 1
Informed consent		X					
Eligibility including confirmation of diagnosis of true RHT		X	X	X[13]	X[13]	X[15]	
Demographics / Medical history		X					
Physical examination		X	X	X	X	X	
Concomitant medications		X	X	X	X	X	X
Body weight, height[2]		X	X	X	X	X[16]	
12-lead ECG[3]		X				X[16]	
Laboratory tests[4]		X				X[16,17]	
Serum pregnancy test		X	X	X		X[16,17]	
Urinalysis[5]						X[16]	
Urine sampling to monitor treatment adherence[6]				X[6]	X	X[16]	
AOBPM (incl. HR)		X	X	X	X	X	
Home BP monitoring[7]			→	→	→	→	→
ABPM						X[16]	X
Blood sampling for biomarkers[8]		X				X	
Accountability of study treatment and standardized background antihypertensive therapy[9]				X	X	X[16]	
Dispensing/return of study treatment and standardized background antihypertensive therapy[10]			X	X[14]		X	X
SAE[11] and AE[11]		X	X	X	X	X	X

[1] Unscheduled visits may be performed at any time during the study.
[2] Body weight is measured at each visit with the same weight scale. Height is only measured at Screening.
[3] ECGs are read centrally.
[4] Hematology and clinical chemistry.
[5] For UACR determination.

[6] Urine sampling at trough (i.e., before intake of study treatment and standardized background antihypertensive therapy). No urine sample to be collected for subjects who do not fulfill Run-in eligibility criteria.
[7] Upon investigator's judgment, a home BP monitoring device will be dispensed, if necessary.
[8] Blood sampling at trough (i.e., before intake of study treatment and standardized background antihypertensive therapy).
[9] Drug accountability (pill counts of study treatment and standardized background antihypertensive therapy).
[10] Study treatment including standardized background antihypertensive therapy should be brought back to each visit.
[11] All AEs and SAEs that occur after signing the informed consent form and up to 30 days after study treatment discontinuation must be reported.
[12] Switch to the standardized background antihypertensive therapy. Visit 1.1 may be at the same day as Visit 1. Additional visits may be performed for further assessments (e.g., to adjust the dose of the standardized background antihypertensive therapy, taking urine samples to monitor adherence).
[13] Run-in eligibility criteria.
[14] From this time point onwards the dose of the standardized background antihypertensive therapy must be kept stable.
[15] Randomization eligibility criteria.
[16] For subjects who permanently discontinue prior to Randomization due to any reason or do not fulfill the randomization eligibility criteria, these tests are not mandatory.
[17] Two samples will be drawn: one sample for the central laboratory and one sample for the local laboratory to measure hemoglobin, creatinine (to determine eGFR), AST/ALT, and a pregnancy test to confirm eligibility of subjects for randomization.

ABPM = ambulatory blood pressure monitoring; AE = adverse event; ALT = alanine aminotransferase; AOBPM = automated office blood pressure measurement; AST = aspartate aminotransferase; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HR = heart rate;; RHT = resistant hypertension; SAE = serious adverse event; UACR = urine albumin-to-creatinine ratio.

Table 2 Visit and assessment schedule from start of DB treatment period up to EOS

PERIODS	Name / Duration	DB Treatment 4 weeks			SB Treatment 32 weeks						DB-WD Treatment 12 weeks					FU[12] 30 days
VISITS[1]	Number	5	6		7	8	9	10	11		12	13		14	15	16
	Time	Week 2	Week 4		Week 6	Week 12	Week 20	Week 28	Week 36		Week 38	Week 40		Week 44	EOT[11] Week 48	EOS (EOT+30 d)
		Day 14 (±2 d)	Day 28 (±2 d)	Day 29	Day 42 (±2 d)	Day 84 (±10 d)	Day 140 (±10 d)	Day 196 (±10 d)	Day 252 (±12 d)	Day 253	Day 266 (±4 d)	Day 280 (±4 d)	Day 281	Day 308 (±4 d)	Day 336 (±4 d)	Day 366 (+3 d)
Physical examination		X	X		X	X	X	X	X		X	X		X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]
Body weight[2]		X	X		X	X	X	X	X		X	X		X	X	X
12-lead ECG[3]			X		X		X		X						X	X
Laboratory tests[4]			X		X	X	X	X	X			X		X	X	X
Urinalysis[5]			X			X	X	X	X			X		X	X	X
Urine sampling to monitor treatment adherence[6]		X	X		X	X	X	X	X		X	X		X	X	
AOBPM (incl. HR)		X	X		X	X	X	X	X		X	X		X	X	X
Home BP monitoring[7]		→														
ABPM			X	X					X	X		X	X			
Blood sampling for PK[8]			X													
Blood sampling for biomarkers[8]			X				X		X			X				
Accountability of study treatment and standardized background antihypertensive therapy[9]		X	X		X	X	X	X	X		X	X		X	X	X
Dispensing/return of study treatment and standardized background antihypertensive therapy			X	X		X	X	X	X	X		X	X	X	X	X
SAE[10] and AE[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]

[1] Unscheduled visits may be performed at any time during the study.
[2] Body weight is measured at each visit with the same weight scale.

[3] ECGs are read centrally.
[4] Hematology and clinical chemistry including NT-proBNP and serum pregnancy test. During SB aprocitentan part, urine pregnancy tests will be performed monthly (i.e., between scheduled visits) at home with kits that are provided to the subject.
[5] For UACR determination.
[6] Urine sampling at trough (i.e., before intake of study treatment and standardized background antihypertensive therapy).
[7] Upon investigator's judgment, a home BP monitoring device will be dispensed, if necessary.
[8] Blood sampling at trough (i.e., before intake of study treatment and standardized background antihypertensive therapy).
[9] Study treatment including standardized background antihypertensive therapy should be brought back at each visit for drug accountability (pill counts).
[10] All AEs and SAEs that occur after signing the informed consent form and up to 30 days after study treatment discontinuation must be reported.
[11] Randomized subjects who prematurely discontinue prior to Week 48/Visit 15 should have an EOT visit scheduled no later than 7 days after the last dose of randomized study treatment.
[12] For subjects who discontinued during the RI period, this will be a phone call to collect adverse events and concomitant medications only.

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AOBPM = automated office blood pressure measurement; BP = blood pressure; DB = double-blind; ECG = electrocardiogram; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; HR = heart rate; NT-proBNP = N-terminal pro-brain natriuretic peptide; PK = pharmacokinetic(s); RI = run-in; SAE = serious adverse event; SB = single-blind; UACR = urine albumin-to-creatinine ratio; WD = withdrawal.

2.3 Overview of analysis periods

The RI period starts at the date of the first dose of RI treatment and ends at the date of the last dose of RI treatment.

The randomized treatment period is divided into three parts: DB, SB aprocitentan and DB-WD. The DB (SB, DB-WD, respectively) part starts at the DB (SB, DB-WD, respectively) treatment start date and ends at the DB (SB, DB-WD, respectively) treatment end date (collected on the Study Treatment Log).

In some analyses the DB and SB aprocitentan parts are combined, indicated as 'DB+SB part'. For details see Section 10.1.1.

2.4 Impact of the COVID-19 pandemic

Idorsia provided instructions and guidance in line with Health Authority guidelines (FDA, EMA and individual national health authorities) released in March 2020. These recommendations and instructions are summarized in an addendum of the protocol [D-20.063]. The impact on the statistical analysis is addressed in Sections 2.4, 5.1.2, 5.1.3, 5.2, 6.2.7, 6.3.7, 6.5.1 and 6.5.2 of this SAP.

3 OBJECTIVES

3.1 Primary objective

The primary objective of the study is to demonstrate the BP lowering effect of aprocitentan when added to standard-of-care in subjects with true RHT.

3.2 Secondary objectives

The secondary objectives of the study are:

- To demonstrate that the effect of aprocitentan on BP is durable when added to standard-of-care in subjects with true RHT.
- To evaluate the long-term safety and tolerability of aprocitentan in subjects with true RHT during 48 weeks of treatment.

3.3 Other objectives

- Evaluate steady-state trough plasma concentrations of aprocitentan after 4 weeks of treatment.
- Evaluate the endothelin system activity and the effect of aprocitentan on micro- and macro-vascular complications based on specific biomarkers.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

4.1.1 Screened set

The SCR includes all subjects who have given informed consent to participate in the study and have a subject number.

4.1.2 Run-in set

The RIS includes all subjects from the SCR who received at least one dose of placebo in the RI period.

4.1.3 All-randomized set

The RND includes all subjects who were randomized.

4.1.4 Full analysis set

The FAS includes all subjects who were randomized and have a baseline SiSBP, measured by AOBPM at trough. Subjects will be evaluated according to their assigned study treatment in the DB part: aprocitentan 25 mg, aprocitentan 12.5 mg or placebo.

4.1.5 Modified Full analysis set

The mFAS includes all subjects from the FAS who were re-randomized in the DB-WD part of the study and who have a DB-WD baseline SiSBP, measured by AOBPM at trough. Subjects will be evaluated according to their assigned study treatment in the DB-WD part: aprocitentan 25 mg or placebo.

4.1.6 Per-protocol analysis set

The PPS includes all subjects from the FAS without protocol deviations that potentially affect the primary endpoint. Reasons for exclusion from the PPS are:

- DB treatment duration less than 21 days.
- Use of at least one medication as per protocol deviation list code 04A04 and 04A07 or use of additional diuretic or rescue medication in DB part.
- Compliance with DB treatment < 80% or > 120% [as calculated in Section 5.5.2].
- Compliance with standardized background antihypertensive therapy in DB part < 80% or > 120% [as calculated in Section 5.5.2].

The purpose of the PPS is to enable a supportive analysis of the DB part.

4.1.7 Modified Per-protocol analysis set

The mPPS includes all subjects from the mFAS without protocol deviations that potentially affect the key secondary endpoint. Reasons for exclusion from the mPPS are:

- DB-WD treatment duration less than 21 days.
- Use of at least one medication as per protocol deviation list code 04A05 and 04A08 or use of additional diuretic or rescue medication in DB-WD part 3.
- Compliance with DB-WD treatment < 80% or > 120% [as calculated in Section 5.5.2].
- Compliance with standardized background antihypertensive therapy in DB-WD part < 80% or > 120% [as calculated in Section 5.5.2].

The purpose of the mPPS is to enable a supportive analysis of the DB-WD part.

4.1.8 Ambulatory blood pressure monitoring Full analysis set

The aFAS includes all subjects from the FAS who have a baseline 24 h mean SBP, measured by ABPM with a total duration of at least 21 hours and at least 70% valid readings [Section 6.4.1]. Subjects will be evaluated according to their assigned study treatment in the DB part.

4.1.9 Modified ambulatory blood pressure monitoring Full analysis set

The maFAS includes all subjects from the mFAS who have a DB-WD baseline 24 h mean SBP, measured by ABPM with a total duration of at least 21 hours and at least 70% valid readings [Section 6.4.1]. Subjects will be evaluated according to their assigned study treatment in the DB-WD part.

4.1.10 Safety analysis set

The SAF includes all randomized subjects who received at least one dose of study treatment in the DB part. Subjects will be evaluated according to the study treatment they received in the DB part. In the unlikely event that a subject received different treatments in the DB part, actual treatment will be set to the highest dose of aprocitentan that subject received (12.5 mg or 25 mg).

4.1.11 Restricted Safety analysis set

The subset of subjects from the SAF who received at least one dose of study treatment in the SB aprocitentan part will be referred to as the rSAF.

4.1.12 Modified Safety analysis set

The mSAF includes subjects from the SAF who received at least one dose of study treatment in the DB-WD part. Subjects will be evaluated according to the study treatment they received in the DB-WD part. In the unlikely event that a subject received different treatments in the DB-WD part, actual treatment will be set to be aprocitentan 25 mg.

4.1.13 Pharmacokinetic set

The PK set includes all subjects from the SAF who received at least one dose of aprocitentan, had evaluable plasma concentrations and did not violate the protocol in a way that might affect the evaluation of the PK endpoint.

Reasons for exclusion from the PK set are:

- DB treatment duration less than 21 days.
- Compliance with DB treatment < 80% or > 120% [as calculated in Section 5.5.2].
- AOBPM not done at trough at Week 4 (V6) as per protocol deviation list code 03F20.
- PK samples not collected at Week 4 (V6) as per protocol deviation list code 03F26.

4.2 Usage of the analysis sets

The role of the analysis sets in each of the study parts (DB, SB aprocitentan and DB-WD) is summarized in Table 3.

Table 3 Role of the analysis sets

Study part	DB	SB aprocitentan	DB-WD
Efficacy endpoints based on AOBPM	FAS (PPS)	–	mFAS (mPPS)
Efficacy endpoints based on ABPM	aFAS	–	maFAS
Safety endpoints	SAF	rSAF	mSAF
Pharmacokinetic endpoints	PK	–	–

ABPM = ambulatory blood pressure monitoring; aFAS = ABPM Full analysis set; AOBPM = automated office blood pressure measurement; DB = double-bind; FAS = Full analysis set; maFAS= modified ABPM Full analysis set; mFAS = modified Full analysis set; mPPS = modified Per-protocol set; mSAF = modified Safety analysis set; PK = pharmacokinetic; PPS = Per-protocol set; rSAF = restricted Safety set; SAF = Safety analysis set; SB = single-blind; WD = withdrawal.

Descriptive statistics for selected efficacy and safety endpoints during the RI period will be based on the RIS. The SCR will be used for subject listings.

5 STUDY SUBJECT VARIABLES AND ANALYSES

5.1 Subject disposition

5.1.1 Study disposition

A subject is considered:

- Screened: if the subject has given informed consent to participate in the study and has received a subject number.
  - A screening failure is defined as a screened subject who did not enter the run-in. The reason for screening failure is collected in the **Run-in Enrolment** eCRF. Subjects who failed screening twice will only be counted once (and only the reason for the last screening failure will be tabulated).
- To have entered the RI period: if the subject received at least one dose of RI treatment (placebo) according to the **Study Treatment Log**.
  - A run-in failure is defined as a subject in run-in who was not randomized. The reason for run-in failure is collected in the **Randomization** eCRF.
- Randomized: if the subject was assigned a randomization number by the IRT system at Visit 4.
  - A DB drop-out is defined as a randomized subject who did not enter the SB aprocitentan part.
- To have entered the SB aprocitentan part if the subject received at least one dose of SB aprocitentan according to the **Study Treatment Log**.
  - A SB aprocitentan drop-out is defined as subject in the SB aprocitentan part who was not re-randomized. The reason for not being re-randomized is collected in **Re-Randomization** eCRF.
- Re-randomized: if the subject was assigned a re-randomization number by the IRT at Visit 11.
  - A DB-WD premature treatment discontinuation is defined as a re-randomized subject who did not complete study treatment.
- To have completed study treatment: if on the **Study Treatment Log** Study period is 'Double-blind Withdrawal Treatment (Part 3)' and Reason for treatment stop is 'Completion as per protocol'.
- To have completed the study: when this is indicated on the **End of Study Status** eCRF.

A disposition graph in the clinical study report will display the numbers of subjects in each category defined above. Subjects will be displayed according assigned study treatment,

where applicable. Any difference between assigned and actual treatment will be added in footnotes.

The number (%) of screening failures (i.e., subjects screened but not in RI) will be calculated based on the SCR. Reasons for not being enrolled in the RI period as collected on the **Enrollment** eCRF will be tabulated for the SCR. All eligibility criteria not met during screening and run-in period and eligibility criteria not met grouped by category of inclusions/exclusions criteria and standardized background antihypertensive therapy status will be summarized on the SCR.

The number (%) of RI failures (i.e., subjects in RI but not randomized) will be calculated based on the RIS. Reasons for not being randomized as collected on the **Randomization** eCRF (Part 1) will be tabulated for the RIS.

The numbers of subjects randomized and re-randomized will be tabulated by treatment group for the FAS and mFAS, respectively. Reasons for not being re-randomized as collected on the **Randomization** eCRF (Part 3) will be tabulated for the FAS.

The numbers of subjects screened, in run-in, randomized and re-randomized will also be provided by country and site.

5.1.2 Study completion/discontinuation

A subject is considered to have prematurely discontinued the study when this is indicated on the **End of Study Status** eCRF. Reasons for premature study discontinuation are collected on the same form and include: withdrawal by subject, AE, lost to FU, death, and other. If the reason for premature study discontinuation was related to the COVID-19 pandemic, this was collected.

Reasons for premature study discontinuation in the RI period will be summarized based on the RIS. Reasons for premature study discontinuation in the randomized treatment period will be summarized for the RND. Reasons related to the COVID-19 pandemic will be included in these summaries and will also be listed as such.

5.1.3 Study treatment completion/discontinuation

A subject is considered to have prematurely discontinued treatment in the RI period if on the **Study Treatment Log** the ‘Study period’ is ‘Single-Blind Run-in’ and ‘Reason for treatment stop’ is ‘Discontinued’.

A subject is considered to have prematurely discontinued study treatment in the DB (SB aprocitentan, DB-WD, respectively) part if on the **Study Treatment Log** the ‘Reason for treatment stop’ is ‘Discontinued’ for the corresponding ‘Study period’.

Reasons for premature discontinuation are collected on the same form and include: AE, lack of efficacy, withdrawal by subject, lost to FU, death, pregnancy, and other. If the

reason for premature study treatment discontinuation was related to the COVID-19 pandemic, this was collected.

The numbers of subjects treated in the DB, SB aprocitentan and DB-WD parts will be tabulated by treatment group in the SAF, rSAF and mSAF, respectively.

The number (%) of subjects with and the reasons for premature treatment discontinuation in the RI period will be summarized based on the RIS.

The number (%) of subjects with and the reasons for premature treatment discontinuation in the randomized treatment period will be summarized by study part and treatment group (within study part) in the SAF, rSAF or mSAF, where appropriate. Reasons for premature study treatment discontinuation related to COVID-19 pandemic will also be summarized.

5.2 Protocol deviations

The number (%) of subjects with all PDs and important PDs (as per PD code list) will be summarized by treatment group and by study part DB+SB and DB-WD based on the FAS (for DB+SB) and based on the mFAS (for DB-WD). In addition, the same summaries of all PDs and important PDs will be provided separately for PDs related to the COVID-19 pandemic as per FDA guidance.

5.3 Exclusion from analysis data sets

The number (%) of subjects excluded from the PPS and the reasons for exclusion [Section 4.1.6] will be tabulated by treatment group based on the FAS. The number (%) of subjects excluded from the mPPS the reasons for exclusion [Section 4.1.7] will be tabulated by treatment group based on the mFAS.

The number (%) of subjects excluded from the PK set and reasons for exclusion will be tabulated by treatment group based on the SAF.

5.4 Subject characteristics

Subject characteristics are obtained at Screening (i.e., Visit 1). If a subject was re-screened and a value changed between Screening and Re-screening, the value at Re-screening should be used.

5.4.1 Demographics

Demographic variables include age, sex, race and ethnicity as collected at Screening on the **Demographics** eCRF form as well as country and region.

Age will also be categorized as 18–< 65, 65–< 75 and ≥ 75 years.

Country will be derived from site number.

Region is provisionally defined as:

- Asia/Australia (Australia, China, South Korea),
- Europe (Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Hungary, Lithuania, Netherlands, Poland, Russia, Spain, Ukraine, United Kingdom, Israel and Greece), and
- North America (Canada, US).

Each of these three regions has at least 50 subjects [section 2.2.5 of ICH 2017a].

Other demographic variables include:

- Height and body weight (converted into cm and kg, respectively, if applicable)
- Body weight at baseline will also be categorized as ≤ 100 kg, >100 kg
- BMI at screening where BMI = weight[kg]/(height[cm]/100)^2
- BMI at screening will also be categorized as < 25, 25– <30, 30– <40 and ≥40 kg/m^2

Demographic variables will be summarized by treatment group as well as overall in the DB and DB-WD periods for the FAS and mFAS, respectively. For European Clinical Trials Database (EudraCT) purposes, the number of subjects treated in each age category (< 18, 18– <65, 65–<85 and ≥ 85 years at Screening) will be summarized for the FAS and mFAS.

5.4.2 Disease characteristics

Disease characteristics include:

- Time from first diagnosis of hypertension [years] = (date of Visit 1 – date of diagnosis)/365.25 (from the **Hypertension History** eCRF) at Screening.
- Number of antihypertensive therapies present at screening [as defined in Section 5.4.4]; <3, 3, 4 and ≥5
- SiSBP and sitting diastolic BP (SiDBP) as measured by AOBPM at screening
- UACR; < 30 mg/g, 30–300 mg/g, > 300 mg/g at Baseline.
- (eGFR; < 30, 30–< 45, 45–< 60, ≥ 60 mL/min/1.73 m^2) according to the CKD-EPI equation [Levey 2009] at Baseline.

Disease characteristics will be summarized by treatment group as well as overall in the DB and DB-WD periods for the FAS and mFAS, respectively.

5.4.3 Medical history

Medical history collected at Screening will be coded using MedDRA. Previous diseases/procedures are medical history where 'Ongoing at informed consent signed' is 'No' on the **Medical History eCRF**. Ongoing diseases/procedures are medical history

where 'Ongoing at informed consent signed' is 'Yes'. If the response to 'Ongoing at Informed consent' is missing, then the disease/procedure is considered as ongoing.

Medical history will be summarized by SOC, PT and treatment group as well as overall in the FAS. This will be done separately for previous and ongoing diseases/ procedures.

5.4.4 Previous and concomitant therapies

Therapies are collected in the **Previous/Concomitant Medications** eCRF, and terms are coded using the WHO Drug code dictionary and the ATC class code using the versions available at database lock.

Previous therapy is medication for which the end date is prior to the date of first randomization. If the end date is (partially) missing, the imputation rules from Section 10.2.2 will be applied.

Concomitant therapy is any medication that is ongoing at Randomization or initiated during the randomized treatment period. In particular:

- DB study treatment concomitant therapies are treatments that are either ongoing at the start of DB study treatment or initiated during the DB treatment part.

SB study treatment concomitant therapies and DB-WD study treatment concomitant therapies are defined similarly. Rules for handling (partially) missing dates are detailed in Section 10.2.2.

A study-concomitant therapy is medication that is ongoing at or initiated after signing of informed consent or initiated up to 30 days after EOT.

The number (%) of subjects having taken at least one concomitant medication will be summarized by ATC classification level 4 and individual preferred name within each ATC classification by study part. Concomitant therapy will be sorted by ATC class and preferred name within each ATC class by descending frequency based on all treatment groups combined.

All study-concomitant medication will be listed, where 'treatment'-concomitant medication will be flagged.

Individual antihypertensive therapies stopped or ongoing during screening period by ATC classifications will be summarized based on the FAS. The following categories will be shown in the table:

- Renin-angiotensin system blockers divided in 2 categories:
  - Angiotensin-converting enzyme inhibitor (ACEi).
  - Angiotensin receptor blockers (ARB).

- Calcium channel blockers (CCB).
- Diuretics
  - Mineralocorticoid receptor antagonist (MRA).
- Beta-blockers.
- Centrally acting antihypertensives.
- Others in combination [as defined in Appendix 14.4].
- Others.

5.5 Study treatment duration and compliance

5.5.1 Treatment duration

Randomized treatment duration (in days) is defined separately for the DB, SB aprocitentan and DB-WD parts as the date of the last dose of treatment in the DB (SB aprocitentan, DB-WD, respectively) part minus the date of the first dose in the DB (SB aprocitentan, DB-WD, respectively) part plus one day, ignoring treatment interruptions. The detailed derivations based on the **Study Treatment Log** are given in Section 10.1.1. Randomized treatment duration will also be expressed in weeks.

RI treatment duration is defined as the date of the last dose of SB placebo minus the date of the first dose of SB placebo plus one day [see Section 10.1.1].

Standardized background antihypertensive therapy duration in the RI period as well as in the DB, SB aprocitentan, and DB-WD parts is defined similarly based on the **Standardized Background Antihypertensive Therapy Log.**

Treatment duration (in days as well as weeks) will be summarized by study part and treatment group (within study part) in the SAF, rSAF and mSAF, respectively. Total exposure (in subject-years, where a year equals 365.25 days) will also be summarized by study part and treatment group.

Time from first dose of DB treatment to (premature) treatment discontinuation in the DB or SB aprocitentan part will be summarized by treatment group using Kaplan-Meier plots (supplemented with a table displaying the numbers of subjects at risk, with an event, and censored by treatment group, using weekly intervals) in the SAF. For subjects who completed the treatment, time to discontinuation will be censored at the last dose of SB treatment (or at the last dose of DB treatment if the subject did not enter the SB part). Additionally, a ‘two-step’ Cox model with a factor for treatment in the DB part will be fitted. This model allows for different treatment effects in the DB and SB aprocitentan parts. The treatment effect in the latter part (if any) is expected to be smaller than in the former part [for details, see Section 8.2].

Time from first dose of DB-WD treatment to (premature) treatment discontinuation in the DB-WD part will be summarized similarly in the mSAF, except that the Cox model is the conventional one.

RI treatment duration will be summarized based on the RIS. Standardized background antihypertensive therapy duration will be summarized by study part and treatment group (within study part) in the SAF, rSAF and mSAF, respectively.

5.5.2 Compliance with study treatment

Randomized treatment compliance is defined separately for the DB, SB aprocitentan and DB-WD parts as:

Compliance = [(number of tablets dispensed – number of tablets returned*) / treatment duration [days].

* If a subject did not return his/her bottle (e.g., the bottle is lost), the compliance will not be calculated and the compliance for the parts will be set to missing. The bottle is allocated to the study part in which it was dispensed.

Here the number of tablets is calculated separately for the DB (SB aprocitentan, DB-WD, respectively) part based on the **Study Treatment Dispensing & Accountability** eCRF and the DB (SB aprocitentan, DB-WD, respectively) treatment duration is defined as in Section 5.5.1.

RI treatment compliance is defined as the number of tablets taken during the RI period according to the **Study Treatment Dispensing & Accountability** eCRF, divided by the RI treatment duration (in days) defined in Section 5.5.1.

Standardized background antihypertensive therapy compliance is defined similarly based on the **Standardized Background Antihypertensive Therapy Dispensing & Accountability** eCRF.

Randomized treatment compliance will be summarized by study part and treatment group (within study part) in the SAF, rSAF and mSAF, respectively. RI treatment compliance will summarized be based on the RIS.

Compliance to the standardized antihypertensive background therapy will be summarized by study part and treatment group (within study part) in the SAF, rSAF and mSAF, respectively.

Adherence (Y/N) to the standardized background antihypertensive therapy (as measured by urinalysis for valsartan) will be summarized by study part, visit and treatment group (both within study part) in the SAF, rSAF and mSAF, respectively.

A subject is considered to have interrupted study treatment or standardized background antihypertensive therapy if on the **Study Treatment Log or Background Therapy Log** the 'Reason for treatment stop' is 'Interruption due to an AE' or 'Interruption not due to an AE'.

Reasons for study treatment interruption will be summarized by study part and treatment group (within study part) in the SAF, rSAF or mSAF, where appropriate.

6 EFFICACY VARIABLES AND ANALYSES

6.1 Overall testing strategy

Three null hypotheses will be tested in this study. The first two null hypotheses (H_{10} and H_{20}) will be tested in parallel using the Bonferroni correction. The third null hypothesis (H_{30}) will only be tested if H_{10} or H_{20} is rejected.

The first null hypothesis H_{10} is that there is no difference between aprocitentan 25 mg and placebo in the DB part in the mean change from baseline to Week 4 in mean trough SiSBP. The alternative hypothesis H_{1a} is that there is a difference between these groups:

$H_{10}: \mu_1 = \mu_0$ vs $H_{1a}: \mu_1 \neq \mu_0$.

Here μ_0 and μ_1 denote the mean change from baseline to Week 4 in mean trough SiSBP in the placebo and aprocitentan 25 mg groups, respectively. This hypothesis will be tested at a two-sided significance level of 0.025.

The second null hypothesis H_{20} is that there is no difference between aprocitentan 12.5 mg and placebo in the DB part in the mean change from baseline to Week 4 in mean trough SiSBP. The alternative hypothesis H_{2a} is that there is a difference between these groups:

$H_{20}: \mu_2 = \mu_0$ vs $H_{2a}: \mu_2 \neq \mu_0$.

Here μ_0 and μ_2 denote the mean change from baseline to Week 4 in mean trough SiSBP in the placebo and aprocitentan 12.5 mg groups, respectively. This hypothesis will be tested at a two-sided significance level of 0.025.

The third null hypothesis H_{30} is that there is no difference between aprocitentan 25 mg and placebo in the DB-WD part in the mean change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP. The alternative hypothesis H_{3a} is that there is a difference between these groups:

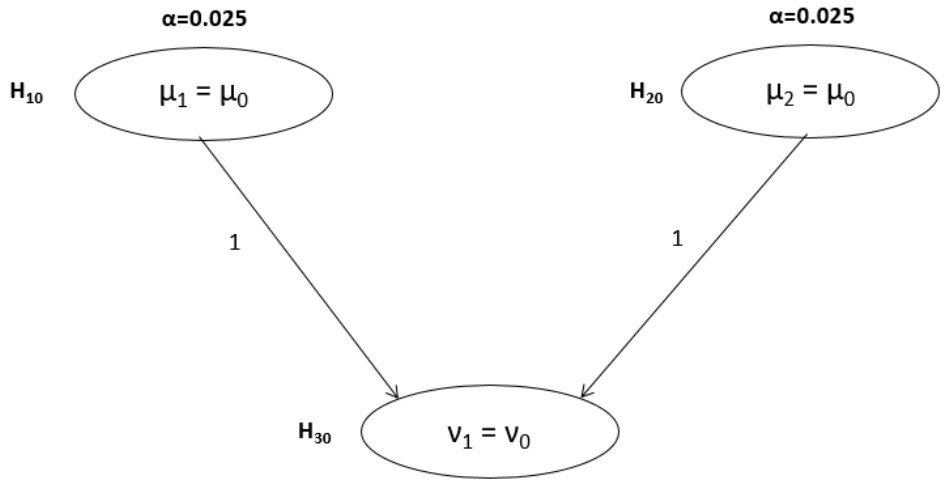
$H_{30}: \nu_1 = \nu_0$ vs $H_{3a}: \nu_1 \neq \nu_0$.

Here ν_0 and ν_1 denote the mean change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP in the placebo and aprocitentan 25 mg groups, respectively. This hypothesis will only be tested if H_{10} or H_{20} is rejected: at a two-sided significance level of

0.05 if both H_{10} and H_{20} have been rejected and at a two-sided significance level of 0.025 if only one of H_{10} and H_{20} has been rejected. The overall type I error is protected at 0.05 [Bretz 2009].

The testing strategy is summarized in Figure 2.

Figure 2 Testing strategy



The '1' next to the arrows indicates that if H_{10} (H_{20}) is rejected the associated alpha of 0.025 will be propagated to test H_{30}.

6.2 Primary endpoint analysis

6.2.1 Variable

The primary efficacy endpoint is the change from baseline to Week 4 of DB treatment in mean trough SiSBP measured by AOBPM.

Here 'mean trough' denotes the average of four AOBPM readings (from a Microlife® WatchBP Office device performing five readings; the first is excluded from the average which will be in the vendor's data transfer) taken at trough (i.e., before the morning intake of study treatment and standardized background antihypertensive therapy).

6.2.2 Intercurrent events and choice of estimand

There are two types of intercurrent events that may interfere with the analysis of the primary endpoint: premature discontinuation of DB treatment or the addition / dose increase of a diuretic. Use of rescue medication, although not allowed during the DB part, will be also considered as an intercurrent event.

All AOBPM measurements, irrespective of any intercurrent event(s), will be included in the main analysis, leading to a treatment policy strategy estimand in ICH terminology [ICH 2017b].

Based on the Phase 2 study in essential hypertension, AC-080A201, it is expected that 5% of subjects in the FAS will have a missing Week 4 AOBPM, mainly due to premature treatment discontinuation. In the main analysis [Section 6.2.3] missing data will not be imputed but will be handled by a mixed model assuming that the data are MAR. Sensitivity analyses will be performed, investigating the impact of deviations from MAR as well as considering a different estimand [Section 6.2.4].

6.2.3 Main analysis for the primary endpoint

The main analysis of the change from baseline to Week 4 (i.e., in the DB part) in mean trough SiSBP measured by AOBPM will be conducted on the FAS. The treatment groups in this analysis are aprocitentan 25 mg, aprocitentan 12.5 mg, and placebo. The first and second null hypotheses (H_{10} and H_{20}) will be tested as described in Section 6.1.

Changes from baseline to post-baseline visits up to Week 4 in mean trough SiSBP will be analyzed using a mixed model with factors for treatment group, visit and treatment by visit interaction, and covariates for baseline SiSBP and the interaction between baseline SiSBP and visit. An unstructured covariance matrix will be used to account for the correlation between repeated BP measurements from the same subject.

LSM differences vs placebo at Week 4 and their 97.5% CIs will be obtained from the model. The associated p-values will be used to test the first and second null hypotheses.

6.2.4 Sensitivity analyses for the primary endpoint

The impact of deviations from the MAR assumption underlying the mixed model will be investigated in sensitivity analyses assuming that in the aprocitentan groups the data are MNAR [Mallinckrodt 2013].

Two control-based MI procedures will be performed under MNAR: a CR and a J2R approach [Carpenter 2013]. In addition, a tipping point approach will be used to assess how severe departures from the MAR assumption must be to overturn the conclusions of the main analysis. For details, see Section 8.2.

In another sensitivity analysis on the FAS, AOBPM measurements obtained *more than one day*[1] after premature discontinuation of DB treatment will be excluded from the main analysis (i.e., considered as missing), leading to a hypothetical strategy estimand in ICH terminology [ICH 2017b]. This approach reflects the anticipation that the effect of a treatment on BP will be lost quickly after the treatment has been discontinued. In this setting, it is not the usual practice to assess effectiveness after (premature) treatment discontinuation [O'Neill 2012]. In addition, AOBPM measurements taken after the

[1] If the last dose of DB treatment is taken at study Day x then an AOBPM measurement taken at Day x + 1 will be included in the analysis, but a measurement taken at Day x + 2 will not.

addition of a diuretic or use of rescue medication that also has an impact on BP will be excluded from the analysis.

Finally, the primary analysis will be performed excluding site 4204 from which the data are considered not trustworthy (as per internal audit report).

6.2.5 Supportive analyses for the primary endpoint

As a supportive analysis, the mixed model (as specified for the main analysis) will be performed on the PPS. An ANCOVA will be performed on the FAS for the change from baseline to Week 4 imputing missing data using LOCF and, separately, using BOCF.

In LOCF a missing post-baseline value will be replaced by the preceding value (except the baseline value; so, the analysis will be restricted to subjects with a post-baseline value). In BOCF, a missing post-baseline value will be replaced by the baseline (so, the change will be zero).

6.2.6 Subgroup analyses for the primary endpoint

The following subgroups will be considered.

- Age at screening (18–< 65, 65–< 75 and ≥ 75 years).
- Sex (male/female).
- Weight at baseline (≤ 100 kg, > 100 kg).
- BMI at screening < 30, 30–< 40 and ≥ 40 kg/$m^{2.}$
- Race (Black or African American, White, Asian, Other*).
- Region (Asia/Australia, Europe, North America, as defined in Section 5.4.1).
- UACR at Baseline (< 30 mg/g, 30–300 mg/g, > 300 mg/g.,
- CKD stage at baseline (1–2 defined as eGFR ≥ 60 mL/min1.73 m^2, 3–4 defined as eGFR 15 to < 60 mL/min/1.73 m^2).
- Diabetes as per medical history (Y/N) (defined as Hyperglycaemia/new onset diabetes mellitus [SMQ]).
- Protocol Version 1/2 vs protocol Version 3 at randomization. Note: in protocol Version 3, beta-blockers were counted as antihypertensive medications at Screening, which was not the case in Version 1/2.

* The 'Other' category will not be considered for subgroup analyses due to the mix of races and small number of subjects limiting the ability (i.e., low power) to detect differences between treatment groups. 'Other' includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and Other.

If the size of a subgroup is lower than 25 subjects, subgroup categories might be pooled.

The aim of the subgroup analyses is to explore the consistency of treatment effect in relevant subgroups. Results of the subgroup analyses will be displayed in a forest plot and will include:

- An estimate of the treatment effect for each aprocitentan dose vs placebo with its 95% CI for each level of the subgroup. It will be calculated as the LSM difference vs placebo at Week 4 obtained separately for each subgroup level as described for the main analysis [Section 6.2.3] but using 95% rather than 97.5% CIs.
- A p-value for the interaction test obtained from the mixed model for the main analysis extended with factors for the subgroup, treatment by subgroup interaction and treatment by subgroup by visit interaction, with appropriate contrasts.
- A vertical reference line displayed at the level of the overall treatment effect.

The study is not designed or powered to detect interactions but an arbitrary two-sided significance level of 0.10 will be used for the interpretation of the interaction test. No multiplicity adjustment is applied as these subgroup analyses are exploratory in nature.

The analyses of the primary endpoint are summarized in Table 4.

6.2.7 Impact of the COVID-19 pandemic on the analysis of primary endpoint

The analysis of the primary endpoint is based on AOBPM data collected at randomization (Visit 4) and Week 4 (Visit 6). Missing data because of missed on-site Visit 4 and Visit 6 due to the COVID-19 pandemic will not be imputed but will be handled by the mixed model specified for the primary endpoint analysis.

If Visit 4 and/or Visit 6 was performed off-site and AOBPM could not be performed, HBP was to be measured instead. These values will be summarized using descriptive statistics [D-20.063] and will not be used for the analysis of primary endpoint.

6.3 Key secondary endpoint analysis

6.3.1 Variable

The key secondary efficacy endpoint is the change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP measured by AOBPM.

6.3.2 Intercurrent events and choice of estimand

There are three types of intercurrent events that may interfere with the analysis of the key secondary endpoint: premature discontinuation of DB-WD treatment, initiation of antihypertensive rescue medication (in the DB-WD part) or the addition / dose increase of a diuretic (in the DB-WD part).

All AOBPM measurements, irrespective of any intercurrent event(s), will be included in the analysis, leading to a treatment policy strategy estimand in ICH terminology [ICH 2017b].

It is expected that 10% of subjects in the mFAS will have a missing Week 40 AOBPM. In the main analysis [Section 6.3.3] missing data will not be imputed but will be handled by a mixed model assuming that the missing data are MAR. Sensitivity analyses will be performed, investigating the impact of deviations from MAR as well as considering a different estimand [Section 6.3.4].

6.3.3 Main analysis for the key secondary endpoint

The main analysis for the change from DB-WD baseline (Week 36) to Week 40 (i.e., in the DB-WD part) in mean trough SiSBP measured by AOBPM will be conducted on the mFAS. The treatment groups in this analysis are aprocitentan 25 mg and placebo. The analyses will be adjusted for the stratum at Re-randomization (i.e., randomized treatment in the DB part). The third null hypothesis (H_{30}) will be tested as described in Section 6.1.

Changes from DB-WD baseline (Week 36) to visits up to Week 40 in mean trough SiSBP will be analyzed using a mixed model with factors for stratum (i.e., randomized treatment in the DB part), treatment group, visit, and treatment by visit interaction and covariates for DB-WD baseline (Week 36) SiSBP and the interaction between DB-WD baseline (Week 36) SiSBP and visit and an unstructured covariance matrix.

LSM differences vs placebo for the change from DB-WD baseline (Week 36) to Week 40 and their 95% CIs will be obtained from the model. The associated p-values will be used to test the third null hypothesis.

6.3.4 Sensitivity analyses for the key secondary endpoint

The impact of deviations from the MAR assumption underlying the mixed model will be investigated in sensitivity analyses under MNAR as described in Section 6.2.4 and detailed in Section 8.2.

In another sensitivity analysis on the mFAS, all AOBPM measurements obtained *more than one day* after premature discontinuation of DB-WD treatment will be excluded from the main analysis. In addition, the initiation of antihypertensive rescue medication could influence the BP of a subject [O'Neill 2012]. For this reason, AOBPM measurements obtained after initiation of antihypertensive rescue medication in the DB-WD part will also be excluded from this analysis (i.e., considered as missing), leading to a hypothetical strategy estimand in ICH terminology [ICH 2017b]. Finally, AOBPM measurements taken after the addition of a diuretic (but also having an impact on BP) will be excluded from the analysis. (Note: antihypertensive rescue medication or a diuretic initiated in the SB aprocitentan part that is continued unchanged in the DB-WD part will *not* lead to exclusion from analysis).

Finally, the main analysis for the key secondary endpoint will be performed excluding site 4204 from which the data are considered not trustworthy (as per internal audit report).

6.3.5 Supportive analyses for the key secondary endpoint

As supportive analyses, the mixed model (as specified for the main analysis) will be performed in the mPPS and ANCOVAs will be performed on the mFAS for the change from DB-WD baseline (Week 36) to Week 40 imputing missing data using LOCF and BOCF, respectively.

6.3.6 Subgroup analyses for the key secondary endpoint

Subgroup analyses in the DB-WD part will be performed as described for the DB part but only for age, sex, race and region [as defined in Section 6.2.6]. In addition, a subgroup analysis based on the SiSBP at DB-WD baseline (< 135 mmHg vs ≥ 135 mmHg) will be performed. Subjects without antihypertensive rescue medication are considered an enriched sub-population of the mFAS.

The analyses of the key secondary endpoint are summarized in Table 4.

6.3.7 Impact of the COVID-19 pandemic on the analysis of key secondary endpoint

The analysis of the key secondary endpoint is based on AOBPM data collected at re-randomization (Visit 11) and Week 40 (Visit 13). Missing data because of missed on-site Visit 11 and Visit 13 due to the COVID-19 pandemic will be handled by the mixed model specified for the key secondary endpoint analysis.

If Visit 11 and/or Visit 13 was performed off-site and AOBPM could not be performed, HBP was to be measured instead. These values will be summarized using descriptive statistics and will not be used for the analysis of the key secondary endpoint [D-20.063].

6.4 Other secondary efficacy endpoints analyses

6.4.1 Variables

The other secondary efficacy endpoints are:

- Change from baseline to Week 4 of DB treatment in mean trough SiDBP measured by AOBPM.
- Changes from baseline to Week 4 of DB treatment in 24 h mean systolic BP (SBP) and diastolic BP (DBP) measured by 24 h ABPM.
  - At each visit the 24 h mean SBP (or DBP) is derived from the area under the SBP-time (or DBP-time) curve, divided by the time span. The area under the curve is calculated by the trapezoidal rule. Time points later than 24 hours after the first time point will be excluded from the calculation. The change from baseline to Week 4 will be obtained by subtraction.
- Change from DB-WD baseline (Week 36) to Week 40 of DB-WD treatment in mean trough SiDBP measured by AOBPM.

- Changes from DB-WD baseline (Week 36) to Week 40 of DB-WD treatment in 24 h mean SBP and DBP measured by 24 h ABPM.
  - These are derived similarly to changes from baseline to Week 4 of DB treatment in 24 h mean SBP and DBP, with baseline and Week 4 replaced by DB-WD baseline (Week 36) and Week 40, respectively.

Each 24 h ABPM reading is supplemented by six quality criteria (provided by the vendor):

1. Start time must be between 06:00 and 12:00
2. Minimum duration of 24 hours after beginning of test
3. Minimum of 70% valid readings in the period
4. Total Required Hours is at least 21
5. Total Exception Hours is at most 3
6. Total Consecutive Exception Hours is 0

The main evaluation of ABPM data will be performed based on ABPMs with at least 70% valid readings and a total duration of at least 21 hours. In the calculation of the percentage, ABPM measurements performed during the first ten minutes will be counted as a single measurement to account for the manual measurements performed by the subject in testing the device. A supportive evaluation will be based on ABPM readings that satisfy all six criteria mentioned above.

6.4.2 Analyses

All other secondary efficacy variables will be tested at the two-sided significance level of 0.05. No correction for multiplicity will be applied.

- *Change from baseline to Week 4 of DB treatment in mean trough SiDBP measured by AOBPM* will be analyzed in the FAS using the same mixed model as specified for SiSBP (main analysis) in the DB part.
- *Changes from baseline to Week 4 of DB treatment in 24 h mean SBP and DBP measured by ABPM* will be analyzed in the aFAS using an ANCOVA with a factor for treatment group and a covariate for baseline 24 h mean SBP (or DBP).
- *Change from DB-WD baseline (Week 36) to Week 40 of DB-WD treatment in mean trough SiDBP as measured by AOBPM* will be analyzed in the mFAS using the same mixed model as specified for SiSBP (main analysis) in the DB-WD part.
- *Changes from DB-WD baseline (Week* 36) *to Week 40 of DB-WD treatment in 24 h mean SBP and DBP as measured by ABPM* will be analyzed in the maFAS using the same ANCOVA as described for changes from baseline to Week 4 of DB treatment in 24 h mean SBP and DBP, but with baseline replaced by DB-WD baseline (Week 36).

The analyses of the other secondary endpoints are summarized in Table 4.

6.5 Other efficacy endpoints

6.5.1 Variables

- Changes from baseline to Week 2 of DB treatment in mean trough SiSBP and SiDBP measured by AOBPM.
- Changes from baseline to Week 4 in daytime and nighttime mean SBP and DBP measured by 24 h ABPM:
  - Daytime is defined as between 09:00 and 21:00.
  - Nighttime is defined as between 01:00 and 06:00 [O'Brien 2013].
- Changes from DB-WD baseline (Week 36) to Week 38, Week 44 and Week 48 of DB-WD treatment in mean trough SiSBP and SiDBP measured by AOBPM.
- Changes from DB-WD baseline (Week 36) to Week 40 in daytime and nighttime mean SBP and DBP measured by 24 h ABPM.
- Ratios to baseline for all assessed time points in the DB and SB aprocitentan parts and to DB-WD baseline (Week 36) for all assessed time points in the DB-WD part in UACR.
- Discontinuation of randomized study treatment due to lack of efficacy (as collected on the **Study Treatment Log**) by study part (DB, SB aprocitentan and DB-WD).
- Initiation of antihypertensive rescue medication (as indicated on the **Previous/Concomitant Medication** eCRF) in the SB aprocitentan part or DB-WD part. (Rescue medication is not allowed in the DB part).
- Observed values of home SBP/DBP by visit collected due to the COVID-19 pandemic in the DB, SB aprocitentan, and DB-WD parts.

The following endpoints related to BP control and response were added as compared to the protocol [refer to Section 11]:

- Binary control variables will be created at each visit for SiSBP and SiDBP measured by AOBPM:
  - SBP Control = 'Yes' if patient achieved a mean trough SiSBP of < 135 mmHg or < 140 mmHg at the visit. SBP Control= 'No' otherwise.
  - DBP Control = 'Yes' if patient achieved a mean trough SiDBP of < 85 mmHg or < 90 mmHg at the visit. DBP Control= 'No' otherwise.
  - SBP/DBP control = 'Yes' if patient achieved a mean trough SiSBP of < 135 mmHg and SiDBP of < 85 mmHg or SiSBP of < 140 and SiDBP of < 90 mmHg at the visit. SBP/DBP control = 'No' otherwise.

- Binary response variable will be created at each visit in the DB and SB parts of the study for SiSBP and SiDBP measured by AOBPM:
  - SBP Response = 'Yes' if patient achieved a reduction in SiSBP from baseline of ≥ 10 mmHg or ≥ 15 mmHg in the DB and SB aprocitentan parts. SBP Response = 'No' otherwise.
  - DBP Response = 'Yes' if patient achieved a reduction in SiDBP from baseline of ≥ 5 mmHg or ≥ 10 mmHg in the DB and SB aprocitentan parts. DBP Response = 'No' otherwise.
  - SBP/DBP Response = 'Yes' if patient achieved a reduction in SiSBP from baseline of ≥ 10 mmHg and SiDBP of ≥ 5 mmHg or achieved a reduction in SiSBP from baseline ≥ 15 mmHg and SiDBP of ≥ 10 mmHg at the visit. SBP/DBP response = 'No' otherwise.
- A binary response variable will also be created for each visit in the DB-WD part (in which a blood pressure increase may occur)
  - SBP Withdrawal Response = 'Yes' if patient achieved an increase in SiSBP from DB-WD baseline of ≥ 5 mmHg or ≥ 10 mmHg in the DB-WD part. SBP Withdrawal Response = 'No' otherwise.
  - DBP Withdrawal Response = 'Yes' if patient achieved an increase in SiDBP from DB-WD baseline of ≥ 3 mmHg or ≥ 6 mmHg in the DB-WD part. DBP Withdrawal Response = 'No' otherwise.
  - SBP/DBP Withdrawal Response = 'Yes' if patient achieved an increase in SiSBP from DB-WD baseline of ≥ 5 mmHg and SiDBP of ≥ 3 mmHg or an increase in SiSBP from DB-WD baseline of ≥ 10 mmHg and SiDBP of ≥ 6 mmHg. SBP/DBP Withdrawal response = 'No' otherwise.

6.5.2 Analyses

All other efficacy variables will be tested at the two-sided significance level of 0.05. No correction for multiplicity will be applied.

- *Changes from baseline to Week 2 of DB treatment in mean trough SiSBP and SiDBP measured by AOBPM* will be analyzed using the mixed model described for changes from baseline to Week 4 in mean trough SiSBP and SiDBP, respectively.
- *Changes from baseline to Week 4 in daytime and nighttime mean SBP and DBP measured by ABPM* will be analyzed in the aFAS using the same ANCOVA as described for 24 h mean SBP and DBP.
- *Changes from DB-WD baseline (Week 36) to Week 38 of DB-WD treatment in mean trough SiSBP and SiDBP measured by AOBPM* will be analyzed in the mFAS using the mixed model described for changes from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP and SiDBP, respectively.

  - *Changes from DB-WD baseline (Week 36) to Weeks 40 and 48 of DB-WD treatment in mean trough SiSBP/SiDBP measured by AOBPM* will be analyzed in the mFAS using the same mixed model, extended with Week 44 and Week 48.

- *Changes from DB-WD baseline (Week 36) to Week 40 in daytime and nighttime mean SBP and DBP measured by ABPM* will be analyzed in the maFAS using the same ANCOVA as described for 24 h mean.
- *Ratios to baseline (and DB-WD baseline [Week 36] as applicable) for all assessed time points of DB+SB and DB-WD parts in UACR* will be log transformed and analyzed using a mixed model with a factor for treatment group, visit, treatment by visit interaction, covariates for baseline (DB-WD baseline [Week 36]) log UACR and visit by baseline (DB-WD baseline [Week 36]) interaction and an unstructured covariance matrix. This will be done separately for the DB+SB part on the FAS and for the DB-WD part on the mFAS.
- *The number (%) of subjects who discontinued study treatment due to lack of efficacy* will be tabulated by study part (DB, SB aprocitentan and DB-WD) and treatment group (within study part) in the FAS (2×) and mFAS, respectively. If there are *at least 12* subjects discontinued due to lack of efficacy, time from Randomization to treatment discontinuation due to lack of efficacy in the DB or SB aprocitentan part will be summarized by treatment group using Kaplan-Meier plots in the FAS. For subjects who did not discontinue treatment or discontinued treatment for reasons other than lack of efficacy, time to discontinuation will be censored at the last dose of DB or SB treatment (whichever comes last). Additionally, a 'two-step' Cox model with a factor for treatment will be fitted [see Section 8.2 for details]. Time from Re-randomization to treatment discontinuation due to lack of efficacy in the DB-WD part will be summarized similarly in the mSAF, except that the Cox model is the conventional one. For subjects who did not discontinue treatment or discontinued treatment for reasons other than lack of efficacy in the DB-WD part, time to discontinuation will be censored at the last DB-WD treatment + 30 days (or EOS date, whichever comes first).
- *The number (%) of subjects who initiated antihypertensive rescue medication* will be summarized by study part (SB and DB-WD; rescue medication is not allowed in the DB part) and treatment group (within study part).
- Home SBP/DBP collected due to the COVID-19 pandemic will be summarized by visit in DB, SB and DB-WD parts using descriptive statistics.
- *The number (%) of subjects with SBP/DBP Control* will be tabulated for the DB+SB and DB-WD parts at each visit by treatment group in the FAS and mFAS, respectively. Subjects with a missing value at a given visit will be excluded from the analysis at that visit. The Cochran-Mantel-Haenszel (CMH) test will be used to test for a difference in the Control proportions at Week 4 between treatment groups in DB part on the FAS and at Week 40 between treatment groups in DB-WD part (stratified by randomized

treatment in the DB part) on the mFAS. The treatment effect will be expressed in terms of the aprocitentan to placebo OR and corresponding 95% CI. An OR > 1 will indicate a benefit of aprocitentan as compared to placebo.

- *The number (%) of subjects with SBP/DBP Response* will be tabulated for the DB+SB and DB-WD parts at each visit by treatment group in the FAS and mFAS, respectively. Similar analyses as for control will be done at Week 4 and Week 40.

The analyses of the other endpoints are summarized in Table 4.

6.6 Overview of efficacy analyses

The efficacy analyses are summarized in Table 4.

Each analysis will be accompanied by a summary table with the descriptive statistics.

Table 4 Summary of efficacy analyses

Endpoint	Measured by	Analysis	Model	Analysis set	Visits	Data after intercurrent event*
Primary efficacy						
Change from baseline to Week 4 in SiSBP	AOBPM	Main	Mixed model	FAS	Weeks 2,4	Included
		Sensitivity	Multiple imputation (J2R)	FAS	Weeks 2,4	Included
			Multiple imputation (CR)	FAS	Weeks 2,4	Included
			Multiple imputation (tipping point)	FAS	Weeks 2,4	Included
			Mixed model	FAS	Weeks 2,4	Excluded
		Supportive	Mixed model	PPS	Weeks 2,4	NA
			LOCF-ANCOVA	FAS	Weeks 2,4	Included
			BOCF-ANCOVA	FAS	Weeks 2,4	Included
		Subgroup	Mixed model by subgroup	FAS	Weeks 2,4	Included
Key secondary efficacy						
Change from DB-WD baseline (Week 36) to Week 40 in SiSBP	AOBPM	Main	Mixed model	mFAS	Weeks 38,40	Included
		Sensitivity	Multiple imputation (J2R)	mFAS	Weeks 38,40	Included
			Multiple imputation (CR)	mFAS	Weeks 38,40	Included
			Multiple imputation (tipping point)	mFAS	Weeks 38,40	Included
			Mixed model	mFAS	Weeks 38,40	Excluded
		Supportive	Mixed model	mPPS	Weeks 38,40	NA
			LOCF-ANCOVA	mFAS	Weeks 38,40	Included
			BOCF-ANCOVA	mFAS	Weeks 38,40	Included
		Subgroup	Mixed model by subgroup	mFAS	Weeks 38,40	Included

Endpoint	Measured by	Analysis	Model	Analysis set	Visits	Data after intercurrent event*
Other secondary efficacy						
Change from baseline to Week 4 in SiDBP	AOBPM		Mixed model	FAS	Weeks 2,4	Included
Change from baseline to Week 4 in SiDBP	AOBPM		Mixed model	FAS	Weeks 2,4	Excluded
Change from baseline to Week 4 in SiDBP	AOBPM		Mixed model	PPS	Weeks 2,4	NA
Change from baseline to Week 4 in 24 h mean SBP	ABPM		ANCOVA	aFAS	Week 4	Included
Change from baseline to Week 4 in 24 h mean DBP	ABPM		ANCOVA	aFAS	Week 4	Included
Change from DB-WD baseline (Week 36) to Week 40 in SiDBP	AOBPM		Mixed model	mFAS	Weeks 38,40	Included
Change from DB-WD baseline to Week 40 in SiDBP	AOBPM		Mixed model	mFAS	Weeks 38,40	Excluded
Change from DB-WD baseline to Week 40 in SiDBP	AOBPM		Mixed model	mFAS	Weeks 38,40	Included
Change from DB-WD baseline (Week 36) to Week 40 in 24 h mean SBP	ABPM		ANCOVA	maFAS	Week 40	Included
Change from DB-WD baseline (Week 36) to Week 40 in 24 h mean DBP	ABPM		ANCOVA	maFAS	Week 40	Included
Other efficacy						
Change from baseline to Week 4 in mean daytime SBP	ABPM		ANCOVA	aFAS	Week 4	Included
Change from baseline to Week 4 in mean nighttime SBP	ABPM		ANCOVA	aFAS	Week 4	Included
Change from baseline to Week 4 in mean daytime DBP	ABPM		ANCOVA	aFAS	Week 4	Included
Change from baseline to Week 4 in mean nighttime DBP	ABPM		ANCOVA	aFAS	Week 4	Included
Change from DB-WD baseline (Week 36) to Week 38 in SiSBP	AOBPM		Mixed model (key secondary)	mFAS	Weeks 38,40	Included
Changes from DB-WD baseline (Week 36) to Weeks 44 and 48 in SiSBP	AOBPM		Mixed model	mFAS	Weeks 38,40, 44, 48	Included
Changes from DB-WD baseline (Week 36) to Week 38 in SiDBP	AOBPM		Mixed model	mFAS	Weeks 38,40	Included

Endpoint	Measured by	Analysis	Model	Analysis set	Visits	Data after intercurrent event*
Changes from DB-WD baseline (Week 36) to Weeks 44 and 48 in SiDBP	AOBPM		Mixed model	mFAS	Weeks 38,40, 44, 48	Included
Change from DB-WD baseline (Week 36) to Week 40 in mean daytime SBP	ABPM		ANCOVA	maFAS	Week 40	Included
Change from DB-WD baseline (Week 36) to Week 40 in mean nighttime SBP	ABPM		ANCOVA	maFAS	Week 40	Included
Change from DB-WD baseline (Week 36) to Week 40 in mean daytime DBP	ABPM		ANCOVA	maFAS	Week 40	Included
Change from DB-WD baseline (Week 36) to Week 40 in mean nighttime DBP	ABPM		ANCOVA	maFAS	Week 40	Included
Ratio to baseline of UACR			Mixed model	FAS	Week 2 up to Week 36	Included
Ratio to DB-WD baseline (Week 36) of UACR			Mixed model	mFAS	Week 38 up to Week 48	Included
Time from Randomization to discontinuation of study treatment due to lack of efficacy			Cox model (two-step)	FAS	NA	NA
Time from Re-randomization to discontinuation of study treatment due to lack of efficacy			Cox model	mFAS	NA	NA

* In the DB part: Premature DB treatment discontinuation or addition / dose increase of diuretic (whichever comes first); in the DB-WD part: Premature DB-WD treatment discontinuation, initiation of antihypertensive rescue medication or addition / dose increase of diuretic (whichever comes first).

ABPM = ambulatory blood pressure monitoring; aFAS = ABPM Full analysis set; ANCOVA = analysis of covariance; AOBPM = automated office blood pressure measurement; CR = Copy Reference; DB = double-blind; DBP = diastolic blood pressure; FAS = Full analysis set; J2R = Jump to Reference; LOCF = last observation carried forward; maFAS = modified ABPM Full analysis set; mFAS = modified Full analysis set; mPPS = modified Per-Protocol set; NA = not applicable; PPS = Per-Protocol Set; SiDBP = (mean trough) sitting diastolic blood pressure; SiSBP = (mean trough) sitting systolic blood pressure; UACR = urine albumin-to-creatinine ratio; WD = withdrawal.

6.7 Analysis of pharmacokinetic variables

Trough plasma concentrations of aprocitentan are measured at steady state at Week 4. Trough is defined as a sample taken in the morning of the Visit 6 prior to study treatment administration of Visit 6.

Aprocitentan plasma concentrations obtained at Week 4 (Visit 6) will be summarized for the aprocitentan 12.5 mg and 25 mg groups only. Summary statistics include arithmetic mean, SD of the mean, minimum, maximum, median, coefficient of variation (CV%), and number of observations. In these calculations, all values below the limit of quantification will be set to zero. Additionally, summaries will be created by age category, sex, and race.

PK data will be listed for all subjects in the aprocitentan 12.5 mg and 25 mg groups as well as for those subjects in the placebo group that were included as controls.

7 SAFETY VARIABLES AND ANALYSES

Safety analyses in the DB and SB aprocitentan parts will be performed on the SAF and rSAF, respectively. Safety analyses in the DB-WD part will be performed on the mSAF.

All safety data will be listed. In the unlikely event that a subject receives DB treatment (or SB aprocitentan treatment, respectively) without being randomized, this subject will not be included in the SAF (or rSAF, respectively), but their safety data will be listed. Similarly, in the unlikely event that a subject received DB-WD treatment without being re-randomized, this subject will not be included in the mSAF, but their safety data will be listed.

7.1 Adverse events

7.1.1 Variables

7.1.1.1 Treatment-emergent adverse events

The original terms used by the investigators to describe AEs in the **Adverse Events** eCRF are assigned a PT and a SOC for classification and tabulation using MedDRA (last available version).

Subjects who experienced the same AE more than once within a specified time period (as qualified by the same PT) are counted only once.

An event/assessment is treatment-emergent if the onset/assessment date is between the start date of the randomized treatment period up to EOT+30 days (begin and end dates included). More in particular:

- An event/assessment is DB treatment emergent if the onset/assessment date is between the start date of the DB part up to the day before the start date of the SB treatment part (or EOT + 30 days if the subject did not enter the SB part);

- An event/assessment is SB treatment emergent if the onset/assessment date is between the start date of the SB aprocitentan part up to the day before the start date of the DB-WD treatment part (or EOT + 30 days if the subject did not enter the DB-WD part);
- An event/assessment is DB-WD treatment emergent if the onset/assessment date is between the start date of the DB-WD part up to EOT + 30 days.

An event/assessment with an onset/assessment date between the start date of the run-in period up to the start of randomized treatment period (if the subject is randomized; EOT if the subject is not randomized) will be designated as run-in-emergent.

7.1.1.2 Relationship of treatment-emergent adverse events

Relationship to study treatment, standardized background antihypertensive therapy and study design or protocol-mandated procedures is determined by the investigator as 'Unrelated' or 'Related' **Adverse Events eCRF**. If (even after repeated querying) the relationship is missing, the event is considered 'Related'.

7.1.1.3 Intensity of treatment-emergent adverse events

The intensity of an AE is determined by the investigator as 'mild', 'moderate' or 'severe' on the **Adverse Events eCRF**. If an AE increases in severity this will be collected in a separate record with a new onset date (including a link to the record with the lower intensity; both AEs are considered treatment-emergent and will be analyzed as such). Subjects who experienced the same AE more than once within a specified period/part (as qualified by the same PT) but with different intensities are counted only once, using the worst reported intensity. If (even after repeated querying) the intensity is missing, the event is considered severe.

7.1.1.4 Serious adverse events

An SAE is defined as an AE where 'Serious' is 'Yes' the **Adverse Events** eCRF.

7.1.1.5 Adverse events leading to discontinuation of study treatment

These are AEs where 'Action taken with study treatment (aprocitentan or placebo)' is 'Permanently discontinued' on the **Adverse Events** eCRF.

Notes: AEs starting in the RI period, but leading to discontinuation of study treatment in the randomized treatment period will be counted in the latter period; AEs leading to discontinuation of standardized background antihypertensive therapy are not counted.

7.1.1.6 Adverse events of special interest (AESIs)

AESIs include anaemia (or haemodilution), hepatic disorders, oedema / fluid retention and decompensation/aggravation of heart failure. These are defined using MedDRA version 24.0 in Appendix 14.3.

7.1.2 Analysis

An overview table will be provided displaying by study part (DB, SB aprocitentan or DB-WD) and treatment group (within each study part) the number (%) of subjects with at least one treatment-emergent: AE, SAE, AE leading to premature discontinuation of study treatment, AESI, MACE and MACE-plus (the latter two as confirmed by adjudication).

A similar overview table (but without study part and treatment group) will also be provided for run-in-emergent AEs based on the RIS.

Treatment-emergent AEs will be tabulated by study part (DB, SB aprocitentan or DB-WD), and treatment group (within each study part), SOC and PTs within each SOC: the number and percentage of subjects who experienced at least one AE, at least one AE within each SOC and at least one AE within each PT will be displayed. AEs will also be summarized by decreasing frequency of PT in the aprocitentan 25 mg group.

A similar table (but without study part and treatment group) will also be provided for run-in-emergent AEs based on the RIS.

AEs will also be tabulated by maximum intensity and relationship to aprocitentan or placebo. Relationship to standardized background antihypertensive therapy will only be listed.

If an AE starts in one study part and ends in the next part without increasing intensity, it is counted only in the first part.

Treatment-emergent SAEs will be summarized in a similar manner as AEs.

For EudraCT purposes, non-serious and total death / serious AEs will be summarized separately by study part.

AEs leading to premature discontinuation of study treatment will be summarized in a similar manner as AEs. AESI (except hepatic disorders) will be summarized by CKD stage at Baseline.

The time from Randomization to (first) oedema / fluid retention AESI in the DB or SB aprocitentan part will be summarized by treatment group using Kaplan-Meier plots (supplemented by a table displaying the numbers of subjects at risk, those with an event, and those censored by treatment group, using weekly intervals). For subjects without oedema / fluid retention, the time will be censored at the last dose of DB or SB treatment, whichever comes last. Additionally, a ‘two-step’ Cox model with a factor for treatment will be fitted [see Section 8.2 for details].

The time from Re-randomization to (first) oedema / fluid retention in the DB-WD part will be summarized similarly. For subjects without oedema / fluid retention, the time will be censored at the last DB-WD treatment + 30 days (or EOS date, whichever comes first)

The time from Randomization or Re-randomization to (first) oedema / fluid retention AESI in the DB or DB-WD will be summarized by CKD stage at Baseline.

7.2 Death

Death information is taken from the **Death** eCRF. The primary cause of death is reported on the same form.

The number (%) of deaths will be tabulated by study part (DB, SB aprocitentan and DB-WD) and treatment group (within study part).

All deaths will be listed, along with the original terms used by the investigator to describe the primary death cause and associated MedDRA PTs.

7.3 Laboratory tests

7.3.1 Variables

Laboratory assessments are performed according to the schedule of assessments [Table 1 and Table 2]. Laboratory data are evaluated in SI units as provided by the central laboratory. The following tests are considered:

- Hematology: hemoglobin, hematocrit, erythrocyte count, reticulocyte count, leukocyte count with differential counts, platelet count, mean corpuscular volume.
- Clinical Chemistry: aminotransferases (aspartate aminotransferase [AST] / alanine aminotransferase [ALT]), alkaline phosphatase, bilirubin and direct bilirubin, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, creatinine, eGFR (estimated using the CKD-EPI creatinine equation), urate, albumin, protein, glucose, sodium, potassium.
- Urinalysis: UACR.

For women of childbearing potential, urine as well as serum pregnancy tests are performed, but these results will not be summarized as part of the laboratory data. Positive pregnancy tests (if any) will be reported.

Results of local laboratory tests (collected on the **Local Laboratory Hematology** and **Local Laboratory Clinical Chemistry** eCRF) will not be used in summaries but will be listed.

Laboratory marked abnormalities are defined in Section 14.2. When determining double-blind treatment-emergent marked laboratory abnormalities, all assessments (including the unscheduled ones) are considered.

All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the rules described in Section 10.1.2.

7.3.2 Analysis

Changes from baseline for laboratory tests to visits in the DB+SB part will be summarized using descriptive statistics by visit and treatment group (in the DB part). Changes from DB-WD baseline (Week 36) to visits in the DB-WD part and up to EOS will be summarized by visit and treatment group (in the DB-WD part). Data will be displayed in SI units whenever possible and graphical approaches will be applied for certain variables.

Percentage changes from baseline in plasma volume to visits in the DB+SB part will be estimated based on baseline (V4) as well as post-baseline (Vx) in hemoglobin and hematocrit (as a fraction between 0 and 1) using the following formula [Strauss 1951]:

$$estimated\ change = 100 \times \frac{hemoglobin\ (V4)}{hemoglobin(Vx)} \times \frac{1 - hematocrit\ (Vx)}{1 - hematocrit(V4)} - 100$$

Percentage changes from Week 36 (V11) in plasma volume to visits in the DB-WD part will be estimated similarly but with V4 replaced by V11. Estimated changes in plasma volume will be summarized by visit and treatment group (in the DB+SB part or DB-WD part, where appropriate).

The number (%) of subjects with laboratory marked abnormalities will be tabulated by study part (DB, SB, and DB-WD) and treatment group (within study part). In addition, the number (%) of subjects with AST or ALT > 3 × the ULN combined with bilirubin > 2 × ULN will be tabulated. In addition, AST or ALT > 5 or 10 × ULN will also be tabulated.

7.4 Electrocardiography

7.4.1 Variables

A standard 12-lead ECG is performed as defined in the schedule of assessments [Table 1 and Table 2]. ECG data will be electronically transferred from the ECG laboratory database to Idorsia and will not be (re-)calculated.

The following variables will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), and QTcF (ms). Note that HR will be evaluated only in the context of the ECG. For vital signs, pulse rate will be used based on assessment done during AOBPM.

ECG abnormalities are defined as follows:

- QTcF (Fridericia's formula) maximum value > 450 ms, > 480 ms, or > 500 ms;
- Maximum increase from baseline in QTcF (Fridericia's formula) > 30 ms, > 60 ms.

All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the visit windows described in Section 10.1.2.

7.4.2 Analysis

Descriptive statistics by study part (DB+SB and DB-WD), visit and treatment group (within study part) will be provided for observed values and absolute changes from baseline (or DB-WD baseline (Week 36), where appropriate) in numeric 12-lead ECG values (HR, PR, QRS, QT, QTcB, QTcF).

The number (%) of subjects with treatment-emergent ECG abnormalities will be summarized by study part (DB, SB, and DB-WD), visit and treatment group (within study part). These are presented cumulatively, e.g., a QTc value of 501 ms is reported in the > 450 ms (H), > 480 ms (HH) and > 500 ms (HHH) categories; the same applies to abnormalities related to changes from baseline (or Week 36, where appropriate).

ECG findings will be summarized by study part (DB, SB, and DB-WD) and treatment group (within study part).

7.5 Vital signs and body weight

7.5.1 Variables

Body weight and pulse rate (this term is used to distinguish it from heart rate measured by ECG) are assessed according to the schedule of assessments [Table 1 and Table 2]. Pulse rate is measured simultaneously with AOBPM and the average of four readings (calculated by the vendor) will be used in the analysis. All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the visit windows described in Section 10.1.2.

7.5.2 Analysis

Descriptive statistics by study part (DB+SB and DB-WD), visit and treatment group (within study part) will be provided for observed values as well as absolute changes from baseline to each visit in the DB and SB parts and from DB-WD baseline (Week 36) to each visit in the DB-WD part and up to EOS for body weight and pulse rate.

7.6 Other safety variables and analyses

7.6.1 Treatment-emergent MACE and MACE-plus

MACE is defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. MACE-plus includes, in addition, hospitalization for heart failure. The analyses will focus on MACE-plus.

Treatment-emergent MACE-plus events confirmed by the CAC are reported on the **Consensus Event Adjudication Form.** The number (%) of subjects with confirmed MACE-plus and sub-categories (i.e., death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) will be tabulated by study part (DB, SB aprocitentan, or DB-WD) and treatment group (within study part). MACE-plus will be summarized by CKD stage at Baseline.

If there are *at least 12* subjects with an adjudication confirmed MACE-plus, the time from Randomization to (first) MACE-plus in the DB or SB aprocitentan part will be summarized by treatment group using Kaplan-Meier plots (supplemented by a table displaying the numbers of subjects at risk, with an event and censored by treatment group, using weekly intervals). For subjects without MACE-plus, the time will be censored at the last dose of DB or SB treatment (whichever comes last). Additionally, a 'two-step' Cox model with a factor for treatment will be fitted [see Section 8.2 for details].

If there are *at least 12* subjects with an adjudication confirmed MACE -plus, the time from Re-randomization to (first) MACE-plus in the DB-WD part will be summarized similarly, except that the Cox model is the conventional one. For subjects without MACE-plus, the time will be censored at the last dose of DB-WD treatment + 30 days (or EOS date, whichever comes first).

For each treatment group, exposure-adjusted MACE-plus incidence rates will be provided per 100 subject-years. The exposure-adjusted incidence rate is calculated as the total number of subjects who experienced the MACE-plus event, divided by the total subject-time at risk during each study part. For subjects who had the MACE-plus event while on study treatment, subject-time at risk is the time from start date of study treatment to date of first event in the respective study part. For subjects who did not experience the MACE-plus event, subject-time at risk is the duration of study treatment in the respective study part. The total subject-time at risk is the sum of all the subject-times at risk. These tables will include the total number of subjects, the total subject-years on study, the total subject-years at risk per event, and the incidence rate (number of subjects with the event / total subject-years at risk for the event × 100). An exact 95% CI will be constructed based on the Poisson distribution.

7.6.2 Increase in dose of existing diuretic or addition of new diuretic due to fluid retention

A 'diuretic due to fluid retention' is any medication on the **Previous/Concomitant Medications** eCRF as defined in Appendix 14.4 with the indication 'Adverse Event' where the 'Main Event' is fluid retention as defined in Appendix 14.3. The existing diuretic is 25 mg hydrochlorothiazide as part of the standardized background antihypertensive therapy.

This endpoint will be analyzed similarly to MACE-plus.

7.6.3 Analysis of biomarker variables

Ratios to baseline of NT-proBNP will be log transformed (base e). Observed values at Baseline, visits in DB and SB part, and changes from baseline (including the geometric mean [and SD] ratio of post-baseline to baseline) will be summarized using descriptive statistics. Ratios to DB-WD baseline of NT-proBNP in the DB-WD part and up to EOS will be analyzed similarly, but with baseline replaced by DB-WD baseline.

Ratios to baseline of Mid-regional pro-atrial natriuretic peptide and Troponin will be analyzed similarly to NT-proBNP.

The analysis of biomarkers characterizing the endothelin system and renin angiotensin system activity will be addressed in a separate SAP.

7.7 Overview of safety analyses

The safety analyses are summarized here:

Table 5 Summary of safety analyses

Endpoint	Part	Analysis set	Visits	Statistical analysis (if applicable)
Adverse events	DB	SAF	NA	
	SB	rSAF	NA	
	DB-WD	mSAF	NA	
Serious adverse events	DB	SAF	NA	
	SB	rSAF	NA	
	DB-WD	mSAF	NA	
Adverse events leading to treatment discontinuation	DB	SAF	NA	
	SB	rSAF	NA	
	DB-WD	mSAF	NA	
Adverse event of special interest	DB	SAF	NA	
	SB	rSAF	NA	
	DB-WD	mSAF	NA	
Laboratory values and changes from baseline	DB+SB	SAF	Week 4, 6, 12, 20, 28 and 36	
Laboratory values and changes from DB-WD baseline (Week 36)	DB-WD	mSAF	Week 40, 44 and 48	
Number (%) of subjects with marked abnormalities laboratory values	DB,	SAF	NA	
	SB	rSAF		
	DB-WD	mSAF	NA	
Vital signs values and changes from baseline over time	DB+SB	SAF	Week 2 up to Week 36	
Vital signs values and changes from DB-WD baseline (Week 36) over time	DB-WD	mSAF	Week 38 up to Week 48	
ECG values over time and changes from baseline over time	DB+SB	SAF	Week 2 up to Week 36	

Endpoint	Part	Analysis set	Visits	Statistical analysis (if applicable)
ECG values over time and changes from DB-WD baseline (Week 36) over time	DB-WD	mSAF	Week 48	
Number (%) of subjects with marked abnormalities ECG values	DB	SAF	NA	
	SB	rSAF		
	DB-WD	mSAF	NA	
MACE-plus	DB+SB	SAF	NA	Cox model
	DB-WD	mSAF	NA	Cox model
MACE-plus	All	SAF	NA	Incidence rate
Increase or addition of diuretic	DB+SB	SAF	NA	Cox model
	DB-WD	mSAF	NA	Cox model

DB = double-blind; DB-WD = double-blind withdrawal; ECG = electrocardiogram; MACE = major adverse cardiac event; mSAF = modified Safety analysis set; NA = Not applicable as not by visit; NT-proBNP = N-Terminal pro-brain natriuretic peptide; rSAF = restricted Safety analysis set; SAF = Safety analysis set; SB = single-blind.

8 GENERAL STATISTICAL METHODOLOGY

8.1 General rules for data presentations

When data are summarized by study part and treatment group one of the following presentations will be used.

For the DB part:

Aprocitentan 12.5 mg *N = xxx*	*Aprocitentan 25 mg* *N = xxx*	*Placebo* *N = xxx*

For the SB aprocitentan part:

Aprocitentan *25 mg* *N = xxx*

For the combined DB+SB part:

	Aprocitentan 12.5 mg N = xxx	*Aprocitentan 25 mg N = xxx*	*Placebo N = xxx*
DB part	*xx*	*xx*	*xx*
SB part *By randomized treatment group*	*xx*	*xx*	*xx*
SB part *Combined treatment group*		*xx*	

For the DB-WD part:

Aprocitentan 25 mg N = xxx	*Placebo N = xxx*

Here N indicates the number of subjects in a treatment group in the analysis set.

Listings for other than safety variables will be sorted by randomized treatment (A = aprocitentan 12.5 mg, B = aprocitentan 25 mg, C = placebo), re-randomized treatment (D = aprocitentan 25 mg, E = placebo), country, subject number (ascending) and, when appropriate, by visit / date of assessment (ascending). Subjects who are not re-randomized will be listed after those who are re-randomized. Run-in failures (i.e., subjects in run-in who were not randomized) will be listed next and labeled 'RI failure' and screening failures (i.e., screened subjects who did not enter the run-in) will be listed last and labeled 'SCR failure'.

In listings for safety variables, randomized and re-randomized treatment will be replaced by actual treatment in the DB and DB-WD parts, respectively.

Unless noted otherwise, the following descriptive statistics will be used:

- Number (%) of subjects for categorical variables (missing will not be included in the calculation of %).
- Number of non-missing values, mean, SD, median, Q1, Q3, minimum, maximum for continuous variables.
- The category missing will be displayed only if there are missing values.

8.2 Analysis details

8.2.1 Mixed model for repeated measurements

This model is used, for example, for the main analyses of the primary and the key secondary endpoints.

Assuming the data are in 'long' format (i.e., one row for each subject/visit) example SAS® statements for the primary endpoint analysis are:

```
proc mixed data=db;
  class subjid trt01pn avisitn;
  model chg=trt01pn avisitn trt01pn*avisitn base base*avisitn/ ddfm=kr;
  repeated avisitn/ subject=subjid type=un;
  lsmeans trt01pn*avisitn/ diff=control ('3' '6') alpha=0.025;
run;
```

The data set *db* includes baseline SiSBP (*base*) as well as changes (*chg*) from baseline to Weeks 2 and 4. Furthermore, *trt01pn* equals 1, 2 and 3 for aprocitentan 12.5 mg, aprocitentan 25 mg and placebo in the DB part, respectively, and *avisitn* is 5 and 6 for Weeks 2 and 4, respectively. The Bonferroni correction [Section 6.1] will be applied by comparing the two-sided p-values vs 0.025 (rather than adding *adjust=bonf* to the *lsmeans* statement).

Again, assuming the data are in 'long' format example SAS® statements for the secondary endpoint analysis are:

```
proc mixed data=dbwd;
  class trt01pn subjid trt03pn avisitn;
  model chg=trt01pn trt03pn avisitn trt03pn*avisitn wk36 wk36*avisitn/
ddfm=kr;
  repeated avisitn/ subject=subjid type=un;
  lsmeans trt03pn*avisitn/ diff=control ('5' '13') alpha =0.05(1);
run;
```

The data set *dbwd* includes DB-WD baseline (Week 36) SiSBP (*wk36*) as well as changes (*chg*) from DB-WD baseline (Week 36) to Weeks 38 and 40. Furthermore, *trt03pn* equals 4 and 5 for aprocitentan 25 mg and placebo in the DB-WD part, respectively, and *avisitn* is 12 and 13 for Weeks 38 and 40, respectively. Note that *trt01pn* (treatment in the DB part) is now used as a stratum.

(1) The alpha level needs to be adjusted to 0.025 in case one of H_{10} and H_{20} has been rejected.

8.2.2 Controlled imputation assuming missing not at random

Sensitivity analyses assuming the data are MNAR in the aprocitentan groups (and MAR in the placebo group) will be performed using MI. These will be performed assuming a monotone missing data pattern (i.e., if data are missing at a given visit, they are also missing at subsequent visits). Any non-monotone missing data will first be imputed under MAR, which is considered reasonable because the proportion of non-monotone missing data (i.e., AOBPM missing at Week 2, but observed at Week 4) is expected to be low.

Assuming the data are in 'wide' format (i.e., one row for each subject and a variable for each visit) example SAS® statements for the primary endpoint are:

```
proc mi data=db nimpute=250 seed=63496 out=mono;
  var base chg2 chg4;
  mcmc impute=monotone;
run;
```

Here *chg2* and *chg4* are the changes from baseline to Weeks 2 and 4 in SiSBP, respectively. Note that treatment is not included in the imputation model.

Two control-based MI analyses will be performed under MNAR, a CR and a J2R approach [Carpenter 2013]. In these approaches, MI of missing values will be performed based on the assumption that subjects with missing data in the aprocitentan arms follow the trajectory of the placebo arm, conditional on subjects' data available prior to discontinuation (baseline as well as available post-baseline SiSBP for the CR approach; baseline SiSBP only for the J2R approach). Imputation is performed sequentially, one visit at a time [Ratitch 2013]. At each visit a regression model is fitted using data from the placebo arm only, so missing data in the aprocitentan arms are imputed based on the predicted outcome in the placebo arm.

The SAS® statements for the CR approach are:

```
proc mi data=mono nimpute=1 seed=133055 out=CR1;
  by _Imputation_;
  class trt01pn;
  var base chg2;
  monotone regression;
  mnar model (chg2/ modelobs=(trt01pn='3'));
run;


proc mi data=CR1 nimpute=1 seed=130871 out=CR2;
  by _Imputation_;
  class trt01pn;
  var base chg2 chg4;
```

```
  monotone regression;
  mnar model (chg4/ modelobs=(trt01pn='3'));
run;
```

The variable *_Imputation_* is created by the PROC MI statement that generated the monotone missing data. Note that the second PROC MI statement for the CR approach includes change from baseline to Week 2 as a predictor for change from baseline to Week 4, meaning that subjects from the aprocitentan groups who discontinue DB treatment between Week 2 and Week 4 are regarded as subjects from the placebo group with a similar change from baseline to Week 2 in SiSBP.

The SAS® statements for the J2R approach are:

```
proc mi data=mono nimpute=1 seed=130340 out=J2R1;
  by _Imputation_;
  class trt01pn;
  var base chg2;
  monotone regression;
  mnar model (chg2/ modelobs=(trt01pn='3'));
run;

proc mi data=J2R1 nimpute=1 seed=125892 out=J2R2;
  by _Imputation_;
  class trt01pn;
  var base chg4;
  monotone regression;
  mnar model (chg4/ modelobs=(trt01pn='3'));
run;
```

Note that the second PROC MI statement for the J2R approach does *not* include change from baseline to Week 2 as a predictor for change from baseline to Week 4, meaning that subjects from the aprocitentan groups who discontinue DB treatment between Week 2 and Week 4 are 'immediately' regarded as subjects from the placebo group.

The resulting multiple data sets are subsequently analyzed using the same mixed model as for the main analysis. For this purpose, the data set from PROC MI (CR2 or J2R2 in the example), should be transposed to a 'long' format.

Results from these analyses are combined using Rubin's methodology [Rubin 1987] implemented in SAS® PROC MIANALYZE:

```
proc mianalyze parms=diffs;
  class trt01pn avisitn;
  modeleffects trt01pn* avisitn;
```

```
run;
```

The control-based MI models described above are pattern-mixture models, where the patterns are defined based on the subject's last visit. If the number of subjects with missing Week 4 data is greater than expected (i.e., > 5% of the FAS), the reason for premature discontinuation (lack of efficacy, AE, other) may also be considered in defining the patterns.

The SAS® statements for the key secondary endpoint are similar, only with DB-WD baseline (Week 36), Week 38 and Week 40 instead of baseline, Week 2 and Week 4, respectively.

8.2.3 Tipping point analysis assuming missing not at random

The tipping point analysis will be performed using MI assuming a monotone missing data pattern. Any non-monotone missing data will first be imputed under MAR, as described in Section 8.2.2. Missing data will initially be imputed under MAR, but the aprocitentan groups will be 'penalized' by adding a shift of *s* mmHg to each imputed value. This will be done for a series of *s* values (henceforth, shift parameters). Only positive shift parameters will be considered since these correspond to a smaller reduction or larger increase in BP. For each shift parameter the multiple data sets are analyzed using an ANCOVA for the last time point (for the primary endpoint this is *chg4*, the change from baseline to Week 4 in SiSBP) and the results are combined using PROC MIANALYZE. This is implemented in the following SAS® macro:

```
%macro tippoint (dset=, smin=, smax=, step=, seed=, out=);
* data set &dset should be in wide format;

* obtain monotone missing data pattern;
proc mi data=&dset nimpute=250 seed=&seed out=mono;
  var base chg2 chg4;
  mcmc impute=monotone;
run;

proc sort;
  by _Imputation_;
run;

data &out;
  set _null_;
run;

ods select none;
%do s=smin %to &smax %by &step;
proc mi data=mono nimpute=1 seed=&seed out=tip;
```

```
  by _Imputation_;
  class trt01pn;
  var trt01pn base chg2 chg4;
  monotone regression;
  mnar adjust(chg4/ shift=&s adjustobs=(trt01pn='1'));
  mnar adjust(chg4/ shift=&s adjustobs=(trt01pn='2'));
run;

ods output diffs=diffs;
proc mixed data=tip;
  by _Imputation_;
  class trt01pn;
  model chg4=trt01pn base;
  lsmeans trt01pn/ diff=control('3');
run;
ods output close;

ods output parameterestimates=parmest;
proc mianalyze parms=diffs;
  class trt01pn;
  modeleffects trt01pn;
run;
ods output close;

data parmest;
  shift=&s;
  set parmest;
run;

data &out;
  set &out parmest;
run;
%end;
ods select all;
%mend tippoint;
```

An example of the associated macro call is:

```
%tippoint (dset=mono, smin=0, smax=50, step=1, seed=125160, out=tipout);
```

The p-value in data set *tipout* can be plotted vs the shift parameter. The shift parameter at which statistical significance is lost (in the DB part when the two-sided P > 0.025) indicates

how severe departures from the MAR assumption must be to overturn the conclusions of the main analysis.

The tipping point analyses for the DB-WD part are similar to those for the DB part, except that baseline, Week 2 and Week 4 are replaced by DB-WD baseline (Week 36), Week 38 and Week 40, respectively, and the shift applies to the aprocitentan 25 mg group only.

8.2.4 Two-step Cox model

The two-step Cox model [Anderson 1982] is an extension of the conventional Cox model allowing for different treatment effects in different time intervals. The conventional Cox model comparing two treatments vs placebo can be fitted using the SAS® statements like:

```
proc phreg data=<data>;
  model t*e(0)=treat1 treat2/ risklimits ties=breslow;
run;
```

Here *treat1 and treat2* are treatment indicators (treat1 = 1 for treatment 1, 0 otherwise; treat2 = 1 for treatment 2, 0 otherwise; placebo will have treat1 = treat2 = 0), t is the time to event and e is an event indicator (1 = event; 0 = no event). The treatment effects are exponentiated to become hazard ratios vs placebo and by using *risklimits* their 95% CIs are obtained.

In the two-step Cox model the time axis is divided in two time intervals $0 < t \leq C$ and $t > C$ where the value of C is pre-specified. It can be fitted using SAS® statements like:

```
proc phreg data=<data>;
  model t*e(0)=treat11 treat12 treat21 treat22/ risklimits
ties=breslow;
  treat11=treat1*(t<=C);
  treat12=treat1*(t>C);
  treat21=treat2*(t<=C);
  treat22=treat2*(T>C);
run;
```

Here *treat11 and treat12* are time-dependent covariates indicating the effect of treatment 1 in the first ($t \leq C$) and second ($t > C$) interval, respectively. Similarly, *treat21 and treat22* indicate the effect of treatment 2 in the first and second interval, respectively.

In this study the two intervals are the SB and the DB aprocitentan part, respectively, so C = 28 days. (C may be fine-tuned on a subject level using the DB treatment end day [see Section 10.1.1]). The two-step Cox model gives hazard ratios for aprocitentan 12.5 mg vs placebo and aprocitentan 25 mg vs placebo for the DB part as well as the SB aprocitentan part in a single analysis. Note that in the latter part all subjects receive aprocitentan 25 mg, so an analysis based on treatment in the preceding DB part is somewhat artificial. However,

the two-step Cox model ensures that all events are included in the analysis and enables the assessment of 'prolonged' treatment effects (if any).

8.2.5 Control/response analysis

This analysis will be implemented by the following SAS® statement:

```
proc freq;
   tables treatment*response / nocol nopercent cmh1 commonriskdiff;
run;
```

For DB-WD the analysis should be stratified by DB treatment, so treatment in DB (trt01pn) needs to be added in the tables statement.

9 INTERIM ANALYSES

No interim analysis will be performed.

10 GENERAL DEFINITIONS AND DERIVATIONS

Baseline is defined as the last available measurement before or on the day of randomization. The date and time of randomization are taken from the **IXRS Subject** eCRF.

DB-WD baseline (Week 36) is defined as the last available measurement before or on the day of Re-randomization. The date and time of re-randomization are taken from the **IXRS Subject** eCRF.

If both date and time of the measurement are collected, baseline is the last measurement up to the date and time of randomization. If only the date is collected, baseline is the last measurement before the date of randomization.

10.1 Analysis periods and visit windows

10.1.1 Analysis periods

The **screening period** is defined as the time from the informed consent date until one day before the run-in period start date (or EOS if the subject does not enter the run-in).

The **RI period** begins at the date of the first dose of RI treatment and ends at the date of the last dose of RI treatment, collected on the **Study Treatment Log** where 'Study Period' is 'Single Blind Run-in'.

The **randomized treatment period** begins at the DB treatment start date and ends at the *last* of the treatment stop dates collected on the **Study Treatment Log** where 'Study Period' is not 'Single Blind Run-in' and the reason for treatment end is not 'Interruption due to an AE' or 'Interruption not due to an AE'.

The randomized treatment period is divided into three parts: DB, SB aprocitentan and DB-WD.

- The DB part begins at the DB treatment start date and ends at the DB treatment stop date collected on the **Study Treatment Log** where 'Study Period' is 'Double-Blind Treatment (Part 1)' and the reason for treatment end is not 'Interruption due to an AE' or 'Interruption not due to an AE'.
- The SB aprocitentan part begins at the SB treatment start date and ends at the SB treatment stop date collected on the **Study Treatment Log** where 'Study Period' is 'Single-Blind Treatment (Part 2)' and the reason for treatment end is not 'Interruption due to an AE' or 'Interruption not due to an AE'.
- The DB-WD part begins at the DB-WD treatment start date and ends at the DB-WD treatment stop date collected on the **Study Treatment Log** where 'Study Period' is 'Double-Blind Withdrawal Treatment (Part 3)' and the reason for treatment end is not 'Interruption due to an AE' or 'Interruption not due to an AE'.

Should there be any 'gap' between the end of one period and the start of the next, then the gap days are allocated to the former period. In the unlikely case that the gap is more than 30 days, gap days 31, 32, etc. will not be allocated to a study part.

The **safety FU period** begins one day after the end of the randomized treatment period and ends at the date of the EOS visit. Safety data obtained during the safety FU period or at the EOS visit will be allocated to the last part of the subject's randomized treatment period. This is restricted to data collected up to EOT+30 days. Safety data collected beyond that time point will not be allocated to a study part.

10.1.2 Visit windows

For visit-based variables (for visits see schedule of assessments in Table 1 and Table 2), analysis windows are based on study day numbers defined as follows:

Study day is defined for the entire study as assessment date minus randomization date plus 1 day. Thus, the day of randomization is study Day 1. For dates prior to randomization, study day is the negative number of days between the date under consideration and the date of randomization. Thus, the day before randomization date is study Day −1. Study Day 0 does not exist.

Withdrawal (WD) day is defined for the DB-WD part as assessment date minus re-randomization date plus 1 day. If a subject is not re-randomized, then WD day is not defined.

The analysis windows around the visits are given in Table 6. For efficacy variables (except for ABPM measurements) and safety analyses the windows are based on study or WD days and on the start and stop dates of the study parts defined above.

Table 6 Visit windows

	Target		Efficacy		Safety	
Visit	**Study day**	**WD day**	**Lower[a]**	**Upper[a]**	**Lower[a]**	**Upper[a]**
DB part						
4 (Randomization)	1	-		1		1
5 (Week 2)	14	-	8	20	2	20
6 (Week 4)	28	-	21	36[b]	21	36[b]
SB aprocitentan part						
7 (Week 6)	42	-	37[c]	62	37[c]	62
8 (Week 12)	84	-	63	111	63	111
9 (Week 20)	140	-	112	167	112	167
10 (Week 28)	198	-	168	223	168	223
11.1 (Week 36)	252	-	224	258[d]	224	258[d]
DB-WD part						
11.2 (Re-randomization)	-	1		1		1
12 (Week 38)	266	14	8	20	2	20
13 (Week 40)	280	28	21	41	21	41
14 (Week 44)	308	56	42	69	42	69
15 (Week 48)	336	84	70	97	70	97[e]
EOS (EOT + 30 days)	366	114	NA	NA	98	

[a] vs study day for the DB part and vs WD day for DB-WD part. [b] Or end of DB treatment part + one day (whichever comes first). [c] But not before start of SB aprocitentan part (whichever comes first). [d] Or end of SB aprocitentan part + one day (whichever comes first). [e] Or end of DB-WD treatment part + one day (whichever comes first).
DB = double-blind; NA=Not applicable; WD = withdrawal.

If there is more than one value within the same visit window, the value closest to the planned assessment date will be taken. Where multiple assessments fall on the same day or have the same visit label, then the latest in time is used (or with the highest SDTM sequence number, if time is not collected). In the event of equidistant values from the planned time point, the last assessment will be considered for the analyses. If there are records 'on-treatment' and 'off treatment' within the same visit window, use only those 'on-treatment'.

If measurements involve time, the following target times should be considered:

- Target day/time = Target day and time 12:00
- Lower day/time = Lower day and time 0:00
- Upper day/time = Upper day and time 23:59

AOBPM measurements (efficacy) will also have indicator whether the measurement was 'on-treatment'. A measurement is considered on-treatment if it was taken before or within one day[2] of the end of the randomized treatment period (defined above).

10.2 Handling of incomplete dates

In the following, 'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. The 'lower limit' and 'upper limit' refer to the earliest and latest possible dates, respectively. As an example: if start date is 'MAR2017' (i.e., day missing), the lower limit is 01MAR2017 and the upper limit is 31MAR2017; if start date is '2017' (i.e., day and month missing), the lower limit is 01JAN2017 and the upper limit is 31DEC2017. For time from first diagnosis of hypertension, take the lower limit.

10.2.1 Adverse events

The purpose of imputing AE dates is only to assign an AE to a specific treatment phase for the summary tables. No imputed date is considered in the medical evaluation of an AE. The imputation for incomplete AE dates in given in Table 7.

Table 7 Imputation rules for an incomplete or missing AE date

Field	Incomplete date	Missing date
AE resolution date	The upper limit.	No imputation; the AE is considered as ongoing.
AE onset date	The below rule applies. 1.If the (imputed) resolution date is on or after the start of the <study treatment> and if the start of the <study treatment> falls within the upper and lower limits (inclusive), the <study treatment> start date is used 2. If the resolution date is missing and the <study treatment> start date falls within the upper and lower limits (inclusive) the <study treatment> start date is used In all other cases the lower limit is used.	Whichever is the earlier of the date of resolution and the <study treatment> start date.

Depending on the analysis, <study treatment> is SB placebo, DB, SB aprocitentan or DB-WD treatment.

[2] If the randomized treatment period ends at study Day x then an AOBPM measurement taken at Day x + 1 will be 'on treatment', but a measurement taken at Day x + 2 will be 'off-treatment'.

After applying the rules above, it may be that an AE can be allocated to multiple study parts. In that case, it will be allocated one study part according to the following priority: (1) DB part, (2) DB-WD part, (3) SB aprocitentan part and (4) RI period.

10.2.2 Concomitant therapies

The purpose of imputing concomitant therapy / antihypertensive therapy dates is only to assign a concomitant therapy to a specific treatment phase for the summary tables. No imputed date is considered in the medical evaluation of a concomitant therapy / antihypertensive therapy.

Table 8 Imputation rules for an incomplete or missing concomitant therapy or antihypertensive therapy date

Field	Incomplete date	Missing date
Concomitant therapy / Antihypertensive therapy end date	The upper limit.	No imputation; the therapy is considered as ongoing.
Concomitant therapy / Antihypertensive therapy start date	The rules below apply in the order presented: 1. If the (imputed) end date is on or after the start of the <study treatment> and if the start of the <study treatment> falls within the upper and lower limits (inclusive), the <study treatment> start date is used. 2. If the end date is missing and the <study treatment> start date falls within the upper and lower limits (inclusive) the <study treatment> start date is used. 3. In all other cases the lower limit is used. If the concomitant therapy is flagged as PRIOR TO FIRST DOSE and the start date is completely missing; the <study treatment> start date – 1 day is used.	Whichever is the earlier of the concomitant therapy / Antihypertensive therapy end date or <study treatment> start date.

Depending on the analysis, <study treatment> is SB placebo, DB, SB aprocitentan or DB-WD treatment.

After applying the rules above, it may be that a concomitant medication can be allocated to multiple study parts. In that case, it will be allocated one study part according to the following priority: (1) DB part, (2) DB-WD part, (3) SB aprocitentan part and (4) RI period.

11 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

In other efficacy endpoints [section 6.1.3 of the protocol]:

- Discontinuation of randomized study treatment due to confirmed grade 3 (i.e., mean SiSBP/SiDBP ≥ 180/110 mmHg, respectively) hypertension [see section 6.1.3 of the protocol, version 2, D-18.214]

is replaced by [Section 6.5.1 of this SAP]: Discontinuation of study treatment due to lack of efficacy.

Also, in other efficacy endpoints [section 6.1.3 of the protocol]:

- Ratios to baseline for all assessed time points of DB, SB and DB-WD parts in UACR

is replaced by [Section 6.5.1 of this SAP]:

- Ratios to baseline for all assessed time points in the DB and SB aprocitentan parts and ratios to DB-WD baseline (Week 36) for all assessed time points in the DB-WD part in UACR.

In the supportive analyses for the primary endpoint [section 10.3.2.4 of the protocol] LOCF and BOCF analyses were added [Section 6.2.5 of this SAP]. In the supportive analyses for the key secondary endpoint [section 10.3.3.4 of the protocol] a BOCF analysis was added [Section 6.3.5 of this SAP].

In the SAP Version 1 and protocol, the baseline for the DB-WD part was referred to as 'Week 36'. It has now been renamed to 'DB-WD baseline (Week 36)' and defined as the last assessment before or on the day of re-randomization which may be *before* Week 36.

Analysis of AESIs was added to the SAP.

Specifications and analyses related to the COVID-19 pandemic were added to the SAP [D-20.063].

The estimand strategy was changed from that laid out in the protocol [version 3, D-20.008], following comments from regulatory agencies. In brief, the treatment policy strategy is now used for the main estimands, whereas the hypothetical strategy is now used for supplementary estimands.

In detail: in the description of statistical analyses [section 10.3 of the protocol, version 3, D-20.008], for the main analyses in the DB and DB-WD parts, it was specified that:

- AOBPM measurements obtained after premature discontinuation of DB or DB-WD treatment will be excluded from this analysis (i.e., considered as missing), leading to a hypothetical strategy estimand in the terminology of [ICH E9 (R1)].

This was replaced by [see Section 6.2.2 and 6.3.2 of this SAP]:

- All AOBPM measurements obtained after premature discontinuation of DB or DB-WD treatment or the addition/dose increase of a diuretic will be included in the main analysis, leading to a treatment policy strategy estimand in ICH terminology [ICH 2017b].

A hypothetical strategy estimand will be used in sensitivity analyses [see Sections 6.5.1 and 6.3.4 of this SAP].

Endpoints related to BP control and response were added as exploratory endpoint [see Sections 6.5.1 and 6.5.2 of this SAP].

12 LIST OF TABLES, LISTINGS AND FIGURES

The list of Tables, Listings and Figures is available in Idorsia's Electronic Document Management System.

13 REFERENCES

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14 APPENDICES

14.1 Revision history

Version Date	Version	Implemented Change(s)
05-JUL-2018	1.0	Draft 1
15-NOV-2018	2.0	Draft 2
04-APR-2019	1	Final Version 1
23-SEP-2021	2	• Section 1: Indicate protocol amendment and addendum related to the COVID-19 pandemic. • Section 2.1: Update added on the recruitment. • Section 2.4: Section added on the impact of the COVID-19 pandemic. • Section 4.1.6 and 4.17: Clarifications added on the PPS and mPSS sets. • Section 4.1.8 and 4.1.9: Clarifications added on the aFAS and maFAS sets. • Section 4.1.10 and 4.1.12: Actual treatment received definitions added for SAF and mSAF sets. • Section 4.1.13: Clarification added on the PK set. • Section 5.1.2 and 5.1.3: Summaries added for discontinuation reasons study/treatment related to the COVID-19 pandemic. • Section 5.2: Summaries added by study part for all PDs and important PDs and specific summaries related to the COVID-19 pandemic. • Section 5.3: Summary added for subjects excluded from the PK set. • Section 5.4.1: Region definition finalized based on final list of participating countries, BMI category added as a demographic variable. • Section 5.4.2: Clarification of the variables included in the disease characteristics. • Section 5.4.4: Clarifications added on the definitions of previous and concomitant therapy. • Section 5.5.1: Clarifications added for treatment duration calculation.

		• Section 5.5.2: Calculation of compliance updated if bottle not returned. • Section 6.2.2: Clarifications added on the intercurrent events. • Section 6.2.4: Sensitivity analysis added for possible exclusion of site data. • Section 6.2.6: Added subgroups analyses for efficacy. • Section 6.2.7: Section added on the impact of COVID-19 pandemic on the analysis of primary endpoint. • Section 6.3.4: Sensitivity analysis added for possible exclusion of site data. • Section 6.3.7: Section added on the impact of COVID-19 pandemic on the analysis of key secondary endpoint. • Section 6.4.1: Clarification added on the ABPM valid reading specifications. • Section 6.5.2 and 6.5.3: Home SBP/DBP added as another efficacy endpoint to analyze. • Section 7.1.1.6: Section added for AESIs. • Section 7.4.2: Summary added for ECG findings. • Section 7.6.1: Clarification added on the definitions and exposure-adjusted MACE/MACE-plus incidence rates added. • Section 7.6.3: Updated analysis for biomarker. Biomarker analysis moved from efficacy (Section 6.8) to safety (Section 7.6.3). • Section 8.1: General rules for data presentation updated. • Section 10.1.2: Adjustment and clarification for time window added. • Section 10.2.2: Clarification added on the imputation rules. • Section 11: Explanation added on the changes from protocol. • Section 14: Definitions added in the appendices.
06-APR-2022	3	• Section 1: Indicate the change of primary estimand following comments from regulatory agencies. • Section 4.1.6 and 4.1.7: Definitions update for PPS and mPPS. • Section 4.1.13: Clarifications added for PK set.

		• Section 5.1.1: Clarifications on eligibility criteria summaries. • Section 5.4.1: Age and BMI categories adapted. Body weight category added. • Sections 5.4.2: Categorization added for number of antihypertensive therapies present at screening. • Section 5.4.4: Deletion of concomitant therapies summary present at baseline and descriptive table of individual antihypertensive therapies stopped or ongoing during screening period added. • Section 5.5.2: Interruptions moved from Section 5.1.3 to 5.5.2 and additional details provided. • Section 6.2.2: Change of estimand strategy. • Section 6.2.4: Hypothetical strategy estimand will be used for sensitivity analysis. • Section 6.2.6: Subgroups updated or added. • Section 6.3.2: Change of estimand strategy. • Section 6.3.4: Hypothetical strategy estimand will be used for sensitivity analysis. • Section 6.3.6: Subgroups updated or added. • Section 6.5.1: BP control and response as exploratory endpoints. • Section 6.5.2: Addition of analysis specification for BP control and response. • Section 6.6: Update of table summary for efficacy analyses due to change of estimand strategy. • Section 7.1.2: Addition of analyses for time to (first) oedema/fluid retention. • Section 7.3.2: Addition of other thresholds for the marked abnormalities tables. • Section 8.2.2: Adjustment of code for multiple imputation. • Section 8.2.5: New code added for control/response endpoints. • Section 10.1.2: Time window changed and clarified. • Section 14.4: Specifications added for antihypertensive medications.

14.2 Thresholds for marked abnormalities

Parameter	LL	LLL	HH	HHH	HHHH
Hematology					
Hemoglobin	< 100 g/L	< 80 g/L	Increase in > 20 g/L above ULN or above baseline if baseline is above ULN	Increase in > 40 g/L above ULN or above baseline if baseline is above ULN	
Hematocrit	< 28% in women < 32% in men	< 20%	> 55% in women > 60% in men	> 65%	
Platelet count	$< 75 \times 10^9$/L	$< 50 \times 10^9$/L	$> 600\times 10^9$/L	$> 999\times 10^9$/L	
Leukocyte count	$< 3.0 \times 10^9$/L	$< 2.0 \times 10^9$/L	$> 20.0 \times 10^9$/L	$> 100.0 \times 10^9$/L	
Neutrophils	$< 1.5 \times 10^9$/L	$< 1.0 \times 10^9$/L	NA	NA	
Eosinophils	NA	NA	$> 5.0 \times 10^9$	NA	
Lymphocytes	$< 0.8 \times 10^9$/L	$< 0.5 \times 10^9$/L	$> 4.0 \times 10^9$/L	$> 20 \times 10^9$/L	
Blood Chemistry					
AST (U/L)	NA	NA	> 3 × ULN	> 5 × ULN	> 8 × ULN
ALT (U/L)	NA	NA	> 3 × ULN	> 5 × ULN	> 8 × ULN
Alkaline Phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN	
Bilirubin Total (µmol/L)	NA	NA	> 2 × ULN	> 5 × ULN	
Creatinine	NA	NA	> 1.5 × ULN or > 1.5 × baseline if baseline > ULN	> 3 × ULN or > 3 × baseline if baseline > ULN	

Parameter	LL	LLL	HH	HHH	HHHH
Glucose	< 3.0 mmol /L	< 2.2 mmol /L	> 8.9 mmol /L	> 13.9 mmol /L	
Sodium		< 130 mmol/L	> 150 mmol/L	> 155 mmol/L	
Potassium	< 3.2 mmol/L	< 3.0 mmol/L	> 5.5 mmol/L	> 6.0 mmol/L	
Urate	NA	NA	> 590 µmol/L	> 720 µmol/L	
Albumin	< 30 g/L	< 20 g/L	NA	NA	
eGFR	< 60 mL/min/1.73m^2	< 30 mL/min/1.73m^2	NA	NA	
Cholesterol	NA	NA	>7.76 mmol/L	>10.34 mmol/L	
Triglyceride	NA	NA	>1.69 mmol/L	>3.39 mmol/L	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; NA = not applicable; ULN = upper limit of normal.
Baseline = last assessment before randomization, also in the analysis of the DB-WD part.

14.3 Definition of adverse events of specific interest

The SMQs are broad scope, unless stated otherwise.

The definitions below are based on MedDRA version 24.1.

Anaemia is defined as any AE within the "Haematopoietic erythropenia" SMQ or the "Haematopoietic cytopenias affecting more than one type of blood cell" SMQ, or it contains an event with any MedDRA Preferred Term containing the text "anaemia" (with the exception of the PT "Melanaemia"), or with the PT "Haemodilution".

Hepatic disorders are defined as any AE within the 'Hepatic disorders' SMQ.

Oedema / fluid retention is defined as any AE within the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" or with the PTs Swelling of eyelid, Swelling face, Eyelid oedema, Face oedema.

Decompensation/aggravation of heart failure is defined as any AE within the SMQ "Cardiac failure (narrow scope only)".

14.4 Definition of diuretic and antihypertensives medications

1. Diuretics = any medication with
Anatomical Therapeutic Chemical class in
('C03A','C03B','C03C','C03D','C03E','C03X') or
('C08GA','C09BA','C09DA','C07CA','C07CB','C07CG','C07DA','C07DB')

An addition/increase of diuretic is defined as increase if the dose of the existing diuretic (HCTZ) was increased after randomization or addition if a new diuretic was added.

2. In order to derive the categories for the individual antihypertensive therapies stopped or ongoing during screening period the ATC names 2 to 4 are searched for the text strings listed below. The table is restricted for ATC1 class code ='C'.

Text string	Class
ACE INHIBITORS=	Angiotensin-converting enzyme inhibitor (ACEi)
ANGIOTENSIN II RECE=	Angiotensin receptor blockers (ARB)
CALCIUM CHANNEL BLOCK=	Calcium channel blockers (CCB)
DIURETICS= - C03DA (ATC 4)	Diuretics - Mineralocorticoid Receptor Antagonist (MRA)
BETA BLOCK=	Beta-blockers
CENTRALLY ACTING=	Centrally acting antihypertensives
'OTHER COMBINATIONS' in ATC4 only	OTHERS IN COMBINATION
If not in one of the above and ATC 2 codes is in ('C02','C03','C07','C08','C09')	OTHERS

Note: if a text string contains multiple hits (e.g., "ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) AND DIURETICS") each of them will be counted.

For each subject, the number of antihypertensive therapies at screening will be derived as the number of distinct classes (e.g., if a subject has 2 different diuretics, this will be counted as only 1 medication). In addition, the class 'OTHERS IN COMBINATION' will count as 2 medications (as this string is only used in ATC codes if there are more than 2 components).