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 protocol document:

27 February 2020

Aprocitentan / ACT-132577

Resistant Hypertension

Protocol 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)

Study Phase:	3
EudraCT Number:	2017-004393-33
Status and version:	Final Version 3
Date:	27 February 2020
Document type:	Amended global protocol
Idorsia document number (Doc No.):	D-20.008

SPONSOR CONTACT DETAILS

Sponsor	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 CH-4123 Allschwil Switzerland ☎ +41 58 844 00 00
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File.
Medical Emergency Hotline Toll phone number:	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File.

CONTRACT RESEARCH ORGANIZATIONS' INFORMATION

Some study activities will be delegated to Contract Research Organizations (CROs). A list of site-specific contact details can be found in the Investigator Site File.

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia or sponsor

Treatment name / number

Aprocitentan / ACT-132577

Indication

Resistant hypertension

Protocol number, study acronym, study title

ID-080A301, PRECISION

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

I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of aprocitentan, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Title	Name	Date	Signature
PPD	PPD	PPD	PPD

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Aprocitentan / ACT-132577

Indication

Resistant hypertension

Protocol number, study acronym, study title

ID-080A301, PRECISION,

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

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws.

	Country	Site number	Town	Date	Signature
Principal Investigator				_____	_____

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ABPM	Ambulatory blood pressure monitoring
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
aFAS	ABPM Full Analysis Set
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AOBPM	Automated office blood pressure measurement
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
bpm	Beats per minute
CAC	Central Adjudication Committee
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
CR	Copy Reference
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTT	Clinical Trial Team
CYP3A4	Cytochrome P450
DB	Double-blind
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DM	Diabetes mellitus
DOT	Direct observed treatment
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End-of-Study

EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ET	Endothelin
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
HCTZ	Hydrochlorothiazide
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISAC	Independent Statistical Analysis Center
ISF	Investigator Site File
J2R	Jump to Reference
LSM	Least Squares Mean
MACE	Major adverse cardiac event(s)
maFAS	Modified ABPM Full Analysis Set
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MI	Myocardial infarction

MNAR	Missing not at random
MRA	Mineralocorticoid receptor antagonist
MR-proANP	Mid-regional pro-atrial natriuretic peptide
mSAF	Modified Safety Analysis Set
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPS	Per Protocol Set
QS	Quality System
QTc	Corrected QT
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RAS	Renin angiotensin system
RHT	Resistant hypertension
RI	Run-in
RIS	Run-in Set
RSI	Reference safety information
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SB	Single-blind
SBP	Systolic blood pressure
SCR	Screened Set
SiDBP	Sitting diastolic blood pressure
SiSBP	Sitting systolic blood pressure
SIV	Site initiation visit
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction

UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
WD	Withdrawal
WHO	World Health Organization

SUBSTANTIAL GLOBAL AMENDMENT 2

Amendment rationale

This global amendment applies to the global protocol ID-080A301 Version 2 dated 19 September 2018. The resulting amended global protocol is Version 3 dated 27 February 2020.

The main changes to the protocol in this amendment are:

1. The inclusion criteria 4 and 11, section 4.3.
2. The exclusion criteria 5 and 11, section 4.4.
3. The study-specific discontinuation criterion for renal failure, section 5.1.11.2.
4. The forbidden medication, appendix 1.

The changes are as follows:

1. The inclusion criteria 4 and 11 have been modified (strikethrough and/or bold) to:

1a: Inclusion criterion 4:

- Treated with at least 3 antihypertensive therapies of different pharmacological classes ~~including a diuretic~~ for at least 4 weeks before the screening visit (Visit 1). ~~Beta-blockers are not counted as background antihypertensive medication.~~

This criterion was previously selected in line with recent hypertension guidelines (e.g., ESH 2018 [Williams 2018], AHA [Whelton 2017] which recommends a diuretic as one of the 3 background antihypertensive medications, and beta-blockers mainly as the 4th medication or earlier (e.g., as the 2nd or 3rd medication) if it is prescribed for other indications than hypertension (e.g., heart failure, angina, post-myocardial infarction, atrial fibrillation).

Information collected during the screening period in PRECISION show that some subjects are not treated with a diuretic and/or that a beta-blocker is used as an antihypertensive medication. Therefore, to open the recruitment for those patients who have uncontrolled blood pressure (BP) but are treated with a combination of medications that are not strictly aligned to the recent hypertension guidelines, this inclusion criterion was modified.

This modification will not affect the intended patient population in this study which remains true resistant hypertension (RHT). The management of the subjects as per current Version 2 of the protocol beyond screening is not altered as the background antihypertensive medications of all screened subjects will be standardized by switching to a fixed-dose combination of a calcium channel blocker (CCB; amlodipine), an angiotensin

receptor blocker (ARB; valsartan) and a diuretic (hydrochlorothiazide [HCTZ]) for at least 2 months prior to randomization. Subjects who are treated with a beta-blocker at screening will continue to receive the same beta-blocker therapy, in addition to the standardized fixed-dose combination therapy. Subjects will have to have uncontrolled BP (i.e., mean trough sitting systolic blood pressure [SiSBP] ≥ 140 mmHg measured by automated office blood pressure measurement [AOBPM]) despite treatment with 3 antihypertensive medications including a diuretic (in line with the guidelines' recommendation) to continue in the study and enter the run-in period.

1b: Inclusion criterion 11:

- Stable dose of the standardized background antihypertensive therapy ~~since the start~~ **for at least 1 week before Day –1 (end** of the RI period**)**.

This inclusion criterion was previously put in place to ensure a stable dose of the standardized background antihypertensive therapy and consequently a stable blood pressure before randomization.

The standardized background antihypertensive therapy is a triple fixed-dose combination of amlodipine, valsartan and HCTZ. Two dose strengths will be available: 10/160/25 and 5/160/25 mg (amlodipine, valsartan, HCTZ, respectively) to account for potential edema which occurs in a dose-related manner with amlodipine. The protocol recommends use of amlodipine 10 mg (section 5.2.2). Consequently, for subjects having tolerability issues with the higher dose of 10 mg the lower dose of 5 mg can be used.

This modification will not affect the intended patient population and or jeopardize the study results since according to the amlodipine United States Prescribing Information (USPI) patient's response to each dose level of amlodipine is achieved over 7 to 14 days.

2. The screening exclusion criteria 5 and 11 have been extended (bold) to:

2a: Exclusion criterion 5:

- Clinically significant unstable cardiac disease **at screening or in the past** in the opinion of the investigator, e.g., uncontrolled symptomatic arrhythmia, atrial fibrillation, **congestive heart failure** NYHA stage **II with relevant mitral valve insufficiency and/or aortic stenosis, congestive heart failure NYHA stage** III or IV~~, congestive heart failure~~.

This criterion excludes subjects with significant or potential unstable cardiac disease. During the medical review of enrolled subjects, it was noticed that some subjects entered the study with New York Heart Association (NYHA) stage II. However, their medical history suggested possible instability in their cardiac condition due to mitral valve insufficiency and/or aortic stenosis. Therefore, further explanation was added to the

criterion to exclude subjects with clinically significant unstable cardiac conditions to be entered into this study. This modification will not affect the intended patient population in this study. It emphasizes exclusion of subjects with clinically significant unstable cardiac disease.

2b: Exclusion criterion 11:

- Treatment with any medication which may affect BP ~~(e.g., treatment of psychiatric diseases)~~ [see Appendix 1] **and/or treatment with high dose of loop diuretics (i.e., furosemide greater than 80 mg/day, or equivalent dosage of other loop diuretics).**

The third Independent Data Monitoring Committee (IDMC) meeting took place on 3 February 2020. The IDMC recommends continuing the study as planned without modification, however there was one subject with cardiac failure with preserved ejection fraction (NYHA stage II), post procedural pulmonary embolism and diabetes mellitus type 2 who entered the study receiving background antihypertensive medications from different pharmacological classes including the following diuretics: high dose of loop diuretics (i.e., furosemide 80 mg twice a day) and thiazide diuretic (i.e., hydrochlorothiazide 25 mg). These background antihypertensive medications were switched to the standardized background antihypertensive therapy (i.e., triple fixed-dose combination of amlodipine, valsartan and hydrochlorothiazide) according to the protocol. High dose of loop diuretics is normally prescribed for treatment of congestive heart failure (an exclusion criterion for this study, see section 4.4, exclusion criterion 5) and its modification might destabilize clinical conditions of a subject. Therefore, further explanation was added to the criterion to emphasize subjects treated with high dose of loop diuretics are not suitable for this study.

3. The second component of the study-specific discontinuation criterion for renal failure has been modified to:

- Confirmed (within one week) ~~decrease~~ **increase** of ~~≥ 30%~~ **> 2 ×** from baseline in ~~eGFR based on the CKD-EPI equation~~ **serum creatinine**.

This discontinuation criterion was previously based on estimated glomerular filtration rate (eGFR), since eGFR is a biomarker for renal function. However, a decline in eGFR might be related only to hemodynamic modifications as observed with other antihypertensive therapies, such as renin angiotensin blockers [Palmer 2002] and not secondary to structural kidney injury. The BP decrease induces a reduction of the intraglomerular pressure which impacts the eGFR. Endothelin receptor antagonist indeed induces vasodilation on the afferent and efferent intra-glomerular arterioles with presumably a more pronounced effect on the efferent one [Kohan 2011]. Therefore, to avoid discontinuation of subjects due to potentially transient eGFR reduction this criterion was modified. The new criterion is using serum creatinine change. Serum creatinine is less influenced by hemodynamic

modifications and reflects more organ damage of the kidney. This is in line with the Acute Kidney Injury score [Kellum 2013] which is based on serum creatinine level. This ensures appropriate monitoring and discontinuation of subjects at risk of potential kidney injury.

4. Changes of forbidden medication, appendix 1.

- Removal of erythropoiesis-stimulating agents and psychiatric drugs from the list of the forbidden medications and adding them to allowed medications with the provision that they have been initiated and the dose has been stable at least 4 weeks prior to the screening visit, and that the dose is kept stable until the end of treatment.

Information collected during the screening period in PRECISION shows subjects who cannot enter the study because they are treated with these medications. Since it is not expected that stable dose of these medications will impact the BP analysis, these medications were removed from the list of forbidden medications. In addition for completeness, the topical medications allowed are more exhaustively described.

Additional changes have been made to:

- Exclusion criterion 15 in section 4.4: removal of "planned treatment".
- Clarify and provide the definition for overdose, abuse, and misuse in section 9.5.
- Provide more guidance for the documentation of the informed consent process in section 12.3.
- Clarify some inconsistencies and correct some minor errors and typos.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The sections of the protocol affected by this global amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

Section 1.4	Summary of known and potential risks and benefits
Section 3.1	Study design
Section 3.1.1.1	Screening period
Section 3.1.2	Study duration

Section 4.3	Inclusion criteria
Section 4.4	Exclusion criteria
Section 4.5.2	Acceptable methods of contraception
Section 5.1.10	Premature discontinuation of study treatment
Section 5.1.11.2	Renal failure
Section 5.2.2	Mandatory concomitant therapy
Section 5.2.3	Allowed concomitant therapy
Section 7.1.1.2	Re-screening
Section 7.2.1.1	Hypertension history
Section 7.2.3.3	Weight and height
Section 7.2.5	Biomarker assessments
Section 9.5	Reporting of study treatment overdose, misuse, and abuse
Section 11.3	Database management
Section 12.3	Informed consent
Section 13	References
Section 14	Appendices

Summary of previous amendments

Amendment	Date	Main reason(s)
1	19 September 2018	• Merge components of several local amendments which were issued to address the feedback from health authorities to the global protocol ID-080A301 Version 1 to keep consistency in the performance of the study across all countries. • Modify the exclusion criteria 5, 16 and 18. • Removed the NT-proBNP criterion at randomization.

PROTOCOL SYNOPSIS ID-080A301

TITLE	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**
ACRONYM	PRECISION
OBJECTIVES	The primary objective of the study is to demonstrate the blood pressure (BP) lowering effect of aprocitentan when added to standard-of-care in true resistant hypertension (RHT) subjects. 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 true RHT subjects, • to evaluate the long-term safety and tolerability of aprocitentan in true RHT subjects during 48 weeks of treatment.
DESIGN	The study consists of four periods: a screening period, a placebo run-in (RI) period, a randomized treatment period and a safety follow-up (FU) period. **Screening period** This period lasts between 4 and 12 weeks. The purpose of the screening period is to select RHT subjects and confirm the diagnosis of true RHT. During this period the background antihypertensive medication (except beta-blockers) of subjects will be standardized by switching to a fixed combination of a calcium channel blocker (CCB), an angiotensin receptor blocker (ARB) and a diuretic. **Placebo RI period** This single-blind (SB) period lasts for 4 weeks during which placebo will be added to the standardized background antihypertensive therapy in all subjects. The purpose of this period is to confirm that BP remains uncontrolled despite administration of placebo for 4 weeks. **Randomized treatment period** This period lasts for 48 weeks. The purpose of this period is to evaluate the primary and secondary objectives of the study.

	This period consists of 3 sequential parts: • In the first double-blind (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 withdrawal (WD) part of 12 weeks subjects will be re-randomized to aprocitentan 25 mg or placebo in a 1:1 ratio. The End-of-Treatment (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. The EOT visit should preferably take place on the day of the last dose of study treatment but, in any case, no later than 7 days after the last dose of study treatment. **Follow-up (FU) Period** The safety FU period starts on the day after the last dose of study treatment and ends at least 30 days thereafter. For subjects who discontinued during the RI period there will be a safety FU call. For randomized subjects, it will be a safety FU visit. The End-of-Study (EOS) is reached when the subject has completed the safety FU visit/call.
NUMBER OF SUBJECTS	Approximately 4000 subjects are expected to be screened, in order to enroll about 1500 subjects with diagnosis of RHT into the SB placebo RI period and to randomize 600 subjects. A total of 560 subjects are expected to complete the DB treatment part (Week 4) and at least 380 subjects should enter the DB-WD part (Week 36). It is expected that at least 300 subjects will complete the DB-WD part (Week 48).
PLANNED DURATION	Approximately 45 months from First Subject First Visit (i.e., screening visit of first subject) to Last Subject Last Visit (i.e., safety FU visit of last subject).

SITE(S) / COUNTRY(IES)	Approximately 200 sites in approximately 25 countries in Asia, Australia, Europe, and North America (planned).
INCLUSION CRITERIA	The complete list of inclusion criteria is provided in the core text. The main criteria per study period are: **Screening criteria** This study will enroll adult male and female subjects ≥ 18 years old with RHT defined as: Mean sitting systolic BP (SiSBP) ≥ 140 mmHg measured by unattended automated office blood pressure measurement (AOBPM) despite a background antihypertensive medication of at least 3 different pharmacological classes for at least 4 weeks before the screening visit (Visit 1). **RI entry criteria** Subjects with a confirmed diagnosis of RHT who are on standardized background antihypertensive therapy for at least 4 weeks will enter the placebo RI period if their mean trough SiSBP is ≥ 140 mmHg as measured by AOBPM. **Randomization criteria** Subjects who completed the RI period and who have a mean trough SiSBP ≥ 140 mmHg as measured by AOBPM will be randomized.
EXCLUSION CRITERIA	The complete list of exclusion criteria is provided in the core text. The main exclusion criteria are: • Apparent/pseudo RHT due to white coat effect, medical inertia, poor therapeutic adherence, or secondary causes of hypertension (except sleep apnea) • Confirmed severe hypertension (grade 3): mean SiSBP ≥ 180 mmHg and/or sitting diastolic blood pressure (SiDBP) ≥ 110 mmHg, measured by AOBPM at two different time points.
STUDY TREATMENTS	Placebo tablets will be administered during the RI period.

	Investigational treatment During the DB part, aprocitentan 12.5 and 25 mg tablets will be administered. During the SB part, aprocitentan 25 mg tablets will be administered. During the DB-WD part, aprocitentan 25 mg tablets will be administered. **Comparator** Placebo tablets will be administered during the DB and DB-WD parts of the study. Placebo tablets, aprocitentan 12.5 mg tablets and aprocitentan 25 mg tablets will be indistinguishable.
CONCOMITANT THERAPY	**Mandatory therapy** Background antihypertensive medication will be standardized to a fixed combination of a CCB (amlodipine), an ARB (valsartan) and a diuretic (hydrochlorothiazide, HCTZ). The standardized background antihypertensive therapy will be initiated during the screening period, at the latest 4 weeks before the start of the RI period, and will be continued until EOS. Two dose strengths of amlodipine, 5 and 10 mg, will be available in the fixed combination. The standardized background antihypertensive therapy will be 10/160/25 or 5/160/25 mg of amlodipine/valsartan/HCTZ, respectively. The selection of the amlodipine dose strength for an individual subject (either 5 or 10 mg) is at the investigator's discretion and may vary during the screening period. It is required to use the maximal tolerated dose of the background antihypertensive therapy (i.e., 10 mg amlodipine, if there is no tolerability issue) from start of the RI period. The dose strength must be kept stable for at least 1 week before Day –1 (end of the RI period) until the end of the DB part (i.e., Week 4) and during the DB-WD part. The dose strength might be adjusted later on, during the SB aprocitentan part.

	Allowed concomitant therapy Treatments considered necessary for the subject's wellbeing and not categorized as forbidden concomitant medications are allowed during the study. In particular, the following therapies are allowed with the provision that they have been initiated at least 4 weeks prior to the screening visit and that the dose is kept stable until the EOT: • Beta blockers; • Alfuzosin and tamsulosin (alpha-adrenergic receptors blockers) for prostatic symptoms; • Hormonal contraceptives; • Estrogen-replacement treatment; • Sodium-glucose co-transporter 2 inhibitors; • Low dose acetylsalicylic acid for cardiovascular prevention; • Erythropoiesis-stimulating agents; • Psychiatric drugs. In addition, the following therapies are allowed with the provision that they have been initiated at least 4 weeks prior to the screening visit and that the dose is kept stable until the end of the DB part (i.e., Week 4): • Non-steroidal anti-inflammatory drugs; • Selective serotonin reuptake inhibitors and anxiolytics (such as benzodiazepine). During the SB aprocitentan part and DB-WD part, if, in the investigator's opinion, the BP of a subject is not sufficiently controlled, antihypertensive rescue medication can be added as described in Section 5.2.3.1. After Randomization, the dose of the existing diuretic (HCTZ) can be increased or a new diuretic can be added in the event of fluid retention as judged by the investigator as described in Section 5.2.3.2. **Forbidden concomitant therapy** From the screening visit until the EOT visit any drug which may affect BP (other than those mentioned above) is forbidden. A list of medications is provided in Appendix 1.

ENDPOINTS	**Primary efficacy endpoint** The primary efficacy endpoint is the change from baseline to Week 4 of DB treatment in mean trough SiSBP measured by AOBPM. **Secondary efficacy endpoints** The key secondary endpoint is the change from Week 36 (i.e., start of DB-WD) to Week 40 in mean trough SiSBP measured by AOBPM. 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 ambulatory blood pressure monitoring (ABPM); • Change from Week 36 to Week 40 of DB-WD treatment in mean trough SiDBP measured by AOBPM; • Changes from Week 36 to Week 40 of DB-WD treatment in 24 h mean SBP and DBP measured by ABPM. **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Main safety endpoints** • Treatment-emergent[1] adverse events (AEs); • Treatment-emergent[1] serious AEs; • Treatment-emergent[1] AEs leading to premature discontinuation of study treatment; • Treatment-emergent[1] major adverse cardiac events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke; only those events confirmed by Central Adjudication Committee (CAC) will be considered; • Treatment-emergent[1] MACE-plus, defined as cardiovascular death, non-fatal MI, non-fatal stroke and hospitalization for heart failure; only those events confirmed by CAC will be considered; • Increase of the dose of an existing diuretic or addition of a new diuretic due to fluid retention;

	[1]Any AEs/abnormalities temporally associated with the use of study treatment (from RI placebo initiation until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment. **Pharmacokinetic endpoints** • Trough plasma concentration of aprocitentan at Week 4 of the DB part.
ASSESSMENTS	Refer to the schedule of assessments in Table 2 and Table 3.
STATISTICAL METHODOLOGY	**Analysis sets** The Full Analysis Set (FAS) includes all subjects who were randomized and have a baseline SiSBP, measured by AOBPM. This data set will be used for the evaluation of the primary endpoint. The Per Protocol Set (PPS) includes all subjects from the FAS without a major protocol deviation (to be defined in the Statistical Analysis Plan). The modified FAS (mFAS) includes all subjects in the FAS who were re-randomized in the DB-WD part of the study and have a Week 36 SiSBP, measured by AOBPM. This data set will be used for the evaluation of the key secondary endpoint. The ABPM FAS (aFAS) includes all subjects from the FAS who have a baseline 24 h mean SBP, measured by ABPM. The modified aFAS (maFAS) includes all subjects from the aFAS who were re-randomized in the DB-WD part of the study and have a Week 36 24 h mean SBP, measured by ABPM. The Safety Analysis Set (SAF) includes all randomized subjects who received at least one dose of study treatment in the DB part. The modified SAF (mSAF) includes subjects from the SAF who received at least one dose of study treatment in the DB-WD part. **Statistical hypotheses** Three null hypotheses will be tested in this study. The first two hypotheses (H_{10} and H_{20}) will be tested in parallel using the Bonferroni correction. The third 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. 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. 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 Week 36 to Week 40 in mean trough SiSBP. This hypothesis will only be tested if H_{10} or H_{20} has been 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 the H_{10} and H_{20} has been rejected. This way the overall type I error is protected at 0.05. **Type I error and power** The power is set to 90% for the third null hypothesis (H_{30}) which (under the assumptions made in the sample size calculations) implies > 90% power for the first and second null hypothesis. **Analysis of the primary efficacy variable** The main analysis for the DB part will be conducted on the FAS. AOBPM measurements obtained after premature discontinuation of DB treatment will be excluded from this analysis (i.e., considered as missing). 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, time, and treatment by time interaction and covariates for baseline SiSBP and the interaction between baseline and time. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. Least Squares Mean (LSM) differences vs placebo at Week 4 and their 97.5% confidence intervals (CIs) will be obtained from the model. The associated P-values will be used to test the first and second null hypotheses.

	Based on the Phase 2 study, AC-080A201, it is expected that 5% of subjects will have a missing Week 4 AOBPM. Missing data will not be imputed but will be handled by the mixed model assuming that the data are missing at random (MAR). The impact of deviations from the MAR assumption will be investigated in sensitivity analyses using control-based multiple imputation assuming the data in the aprocitentan groups are missing not at random. **Analysis of the key secondary efficacy variable** The main analysis for the DB-WD part will be conducted on the mFAS. AOBPM measurements obtained after premature discontinuation of DB-WD treatment or initiation of antihypertensive rescue medication in the DB-WD part will be excluded from this analysis (i.e., considered as missing). Changes from Week 36 to visits up to Week 48 in mean trough SiSBP will be analyzed using a mixed model with factors for stratum (in the re-randomization), treatment group, time, and treatment by time interaction, covariates for Week 36 SiSBP and the interaction between Week 36 and time and an unstructured covariance matrix. LSM differences vs placebo for the change from 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. It is expected that 10% of subjects in the mFAS will have a missing Week 40 AOBPM. The missing data handling and sensitivity analyses will be similar to those described for the analysis of the primary efficacy endpoint. **Analysis of the other secondary efficacy variables** The other secondary efficacy variables will be analyzed at α=0.05 (two-sided) using 95% CIs. • 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 model as specified for SiSBP 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 Analysis of Covariance (ANCOVA) with a

	factor for treatment group and a covariate for baseline 24 h mean SBP (or DBP). • Change from Week 36 to Week 40 of DB-WD treatment in mean trough SiDBP measured by AOBPM will be analyzed in the mFAS using the same model as specified for SiSBP in the DB-WD part. • Changes from Week 36 to Week 40 of DB-WD treatment in 24 h mean SBP and DBP 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. **Safety analyses** Safety analyses in the DB and SB aprocitentan parts will be performed on the SAF. Safety analyses in the DB-WD part will be performed on the mSAF. Safety endpoints will be summarized by study part (DB, SB and DB-WD; DB+SB combined where appropriate) and treatment group (within study part) using descriptive statistics (e.g., percentages of subjects). Specific safety endpoints will be analyzed using time-to-event methods (Kaplan-Meier plot, Cox model), with time starting at Randomization and accounting for treatment switching (as part of the study design). **Interim analysis** No interim analysis is planned. **Sample Size** The sample size is driven by the power for the key secondary endpoint. The within-group standard deviation for the change from Week 36 to Week 40 in mean trough SiSBP (measured by AOBPM) is expected to be around 15 mmHg based on study AC-080A201. A difference vs placebo ('delta') of at least 5 mmHg in the DB-WD part is considered clinically relevant. With a type I error of 0.05 (two-sided; if both H_{10} and H_{20} have been rejected), the size of the mFAS needed for 90% power to detect a difference of 5 mmHg between aprocitentan 25 mg and placebo

<table>
<tr><td></td><td>would be 380 subjects (190 in each of the two groups in the DB-WD part).

In order to have 380 subjects in the DB-WD part, a total of 600 subjects will be randomized (200 in each of the three groups in the DB part of the study).

For the change from baseline to Week 4 in mean trough SiSBP measured by AOBPM (primary endpoint), the clinically relevant difference vs placebo is around 6 mmHg. The power to detect this difference is well over 90%:

<table><tr><td>Delta (mmHg)</td><td>5.5</td><td>6.0</td><td>6.5</td></tr><tr><td>Power*</td><td>92%</td><td>96%</td><td>98%</td></tr></table>*alpha=0.025 two-sided

In case only one of the two doses in the DB part is statistically significantly better than placebo on the primary endpoint, the secondary endpoint must be tested at alpha=0.025 (two-sided). In that case the power for the DB-WD part is 84%. On average (assuming that testing at 0.025 is less likely than at 0.05), the power for the DB-WD part is approximately 88%.

If the drop-out rate is greater than anticipated the sample size may be increased in order to ensure sufficient power for the DB-WD part. The sample size will not be decreased below 600.</td></tr>
<tr><td>STUDY COMMITTEES</td><td>An independent CAC will review and confirm all reported cases of MACE and MACE-plus in a blinded fashion. The composition and operation of the CAC is described in the CAC charter.

An Independent Data Monitoring Committee (IDMC) has the overall responsibility for safeguarding the interests of subjects by monitoring the benefit-risk ratio and making appropriate recommendations based on all the reported data and thus ensuring that the study is being conducted with the highest scientific and ethical standards. The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter.</td></tr>
</table>

PROTOCOL

1 BACKGROUND

1.1 Hypertension and resistant hypertension

Hypertension (i.e., elevated blood pressure [BP]) is a "silent" killer that rarely causes symptoms. Hypertension is defined in adults by (office) systolic/diastolic BP (SBP/DBP) ≥ 140/90 mmHg and is sub-classified into grade 1 (mild): 140/90 ≤ BP < 160/100, grade 2 (moderate): 160/100 ≤ BP < 180/110, or grade 3 (severe): BP ≥ 180/110 [Williams 2018, Chobanian 2003]. This condition represents a significant global public health concern, as it contributes to vascular and renal morbidity, cardiovascular mortality, and economic burden [Lim 2012, Go 2013].

Despite current knowledge on the management of hypertension and the availability of numerous effective antihypertensive drugs, hypertension remains inadequately controlled in many patients. A number of these uncontrolled patients are considered to have so-called "resistant hypertension" (RHT) or "difficult-to-control hypertension", which is defined as uncontrolled BP (i.e., failure to lower BP to a pre-defined threshold) in patients adhering to lifestyle modifications and to an appropriate regimen of three or more antihypertensive drugs from different pharmacological classes, including a diuretic, in the absence of secondary cause of hypertension [Calhoun 2008, Williams 2018].

"True" RHT should not be confused with "pseudo" or "apparent" RHT, which is far more common than true RHT. White coat effect, improper BP measurement, poor patient adherence, drug-related hypertension, and physician's clinical inertia (i.e., inadequate dose of antihypertensive medications or inappropriate combinations) are frequent causes of pseudo RHT and need to be ruled out before the diagnosis of true RHT is made [White 2014, Sheppard 2017]. Secondary causes of hypertension (e.g., renovascular disease, hyperaldosteronism due to aldosterone-producing adenoma, pheochromocytoma, and thyroid disease) can also cause apparent RHT and require specific targeted therapy. Diagnosis of true RHT requires exclusion of these various medical situations according to local medical practice.

The estimated prevalence of RHT varies from 2 to 30% of the hypertensive population [Sheppard 2017, Williams 2012]. This broad range of the estimate is mainly due to the different sources of information (e.g., insurance healthcare systems, registries, well-controlled therapeutic clinical trials). It is not always clear from these reports whether the prevalence is for "apparent" or "true" RHT.

A critical characteristic of most "true" RHT patients is their complex medical condition. Compared to the hypertensive population, RHT patients are more likely to be older (> 75 years), to be of black race, to have a higher body mass index, albuminuria, reduced renal function, self-reported co-morbidities of diabetes mellitus (DM), coronary heart

disease, and sleep apnea [Myat 2012, White 2014]. Chronic kidney disease (CKD) and DM, in particular, amplify the RHT patients' vulnerability and increase the complexity of RHT treatment [De Nicola 2013, Solini 2014, Rossignol 2015]. In addition, in RHT patients, the risk of cardiovascular events is much higher than in the rest of the hypertensive population. This has been consistently shown in different settings (i.e., clinical trials, observational studies, and international registries) comparing RHT vs non-RHT patients [Daugherty 2012, Kumbhani 2013, Bangalore 2014, Tsioufis 2014]. Consequently, it is important to control BP in the RHT population.

1.1.1 Current treatment of RHT

The RHT population is, by definition, on a background therapy of three or more antihypertensive medications at maximal tolerated doses, which, according to most clinical guidelines, include: an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), a long-acting thiazide diuretic and a calcium channel blocker (CCB), which is the most commonly used type of third background agent in RHT [Poulter 2015]. For some patients, individualization of therapy is needed; e.g., for patients with ischemic heart disease, a beta-blocker is often used in addition to the aforementioned medications.

The choice of the fourth-line therapy prescribed to control BP in RHT patients has not been unequivocally determined. The first therapeutic option recommended by European Society of Cardiology (ESH) / European Society of Cardiology (ESC) guidelines [Williams 2018] is to reinforce the diuretic therapy, by adding one or more diuretic agents with different mechanisms of action to the diuretic already used in the background therapy. Potassium-sparing diuretics, such as a mineralocorticoid receptor antagonists (MRAs), are recommended. The most commonly used MRA in RHT is spironolactone. The effect of this drug as a fourth-line antihypertensive medication in RHT has been brought to the forefront by the positive results of the crossover study PATHWAY-2. This study showed a larger BP decreasing effect of spironolactone (25 mg increased to 50 mg after 6 to 12 weeks) compared to bisoprolol (beta-blocker), and doxazosin (alpha-1 antagonist), in RHT patients [Williams 2015]. However, the insufficient representation of patients with CKD stage 3 which is most frequent comorbidities associated with RHT challenges the external validity of this study [Rossignol 2015]. The use of spironolactone in combination with renin angiotensin system (RAS) blocking medication might potentially increase the risk of hyperkalemia in RHT patients as reported in heart failure [Juurlink 2004] and consequently, might limit the safe use of spironolactone in these patients [Krogager 2017].

Other available antihypertensive therapeutic classes not used in the already prescribed background therapies can also be proposed as fourth-line therapies in RHT patients (e.g., alpha-1 antagonists, centrally active alpha-2 agonists, direct vasodilators). These

therapies have well-known limitations, especially due to their adverse effects, which often lead to discontinuation of therapy [Lancet 1981, Thomopoulos 2016a].

An alternative therapeutic approach in the management of RHT is catheter-based renal denervation. However, there are several limitations in its development program such as small sample sizes, lack of sham-control groups, suboptimal background or comparative antihypertensive therapies, lack of strict ambulatory blood pressure monitoring (ABPM) assessment, and requirement of specialized expertise by the involved radiologists. Due to these limitations, a definitive conclusion cannot be drawn on its efficacy and applicability in RHT [Cai 2017].

1.1.2 Unmet medical need in RHT

As outlined above, even with the current knowledge on the management of hypertension and availability of numerous antihypertensive therapies, hypertension and particularly RHT remains a global public health concern, because:

- Uncontrolled BP despite treatment with 3 or more antihypertensive medications triggers deleterious cardiovascular outcomes;
- Comorbidities such as CKD and DM associated with RHT trigger poor prognosis and induce therapeutic challenges;
- RHT patients are polymedicated; any new therapy proposed in fourth line must be safe on top of existing mandatory background therapies;
- All current therapies that can be proposed as fourth-line therapies in RHT present limitations due to adverse effects, triggering discontinuation and amplifying the well-known poor adherence in this population.

There is a medical need for additional pharmacological therapy acting on pathway(s) different from those currently used [Dhaun 2008, Oparil 2015] in line with the pathophysiology of RHT [see Section 1.2.1].

1.2 Aprocitentan

1.2.1 Mechanism of action and rationale for development in RHT

Aprocitentan is an orally active dual endothelin (ET) receptor antagonist (ERA), selected for clinical development for the treatment of RHT. The peptide ET-1 is a potent vasoconstrictor that can also cause neurohormonal activation, increased aldosterone synthesis and secretion, induce vascular hypertrophy and remodeling, and endothelial dysfunction. ET-1 and its two receptors, ET_A and ET_B, mediate biological processes that may contribute to the pathogenesis of hypertension.

RHT had been frequently associated with volume expansion [Gaddam 2008, Aprocitentan IB], which is a feature of salt-sensitive hypertension. Plasma ET-1

concentrations are increased in hypertensive African-Americans [Ergul 1996], a population with an increased prevalence of salt-sensitive, low-renin hypertension and also RHT [Chrysant 1979, Luft 1979]. ET-1 production is also increased in patients with risk factors to RHT such as obesity, DM, and CKD. RHT may therefore represent an "ET-dependent form" of hypertension. Accordingly, ERAs demonstrate greater efficacy in salt-dependent / low renin than in high/normal renin animal models of hypertension [Schiffrin 1998]. Nonclinical data with aprocitentan have confirmed these expectations and findings [Aprocitentan IB].

The mechanism of action of aprocitentan seems appropriate to the RHT pathophysiological profile [Dhaun 2008] and is distinct from drugs interfering with the RAS or producing sodium depletion [Davenport 2016]. Therefore, it is anticipated that it can be combined with background therapy including RAS blockers and diuretics without increasing their risks while providing additional BP lowering potential [Weber 2009].

1.2.2 Nonclinical summary

Nonclinical studies have been conducted to characterize the pharmacology and pharmacokinetics (PK) of aprocitentan. In rat models of systemic hypertension, single and chronic oral administration of aprocitentan dose-dependently decreased mean arterial BP without increasing heart rate (HR) and showed synergistic BP-lowering effects in two different animal models (spontaneously hypertensive rats, deoxycorticosterone acetate-salt rat model) when combined with an ARB.

More detailed information on the nonclinical data generated on aprocitentan can be found in the Investigator's Brochure (IB) [Aprocitentan IB].

1.2.3 Clinical summary

Phase 1 clinical studies

A total of six Phase 1 studies have been clinically completed; these studies characterized the safety, tolerability, PK, and pharmacodynamics (PD) of aprocitentan in 144 male and female subjects. In these studies, aprocitentan was given as single doses of up to 600 mg and multiple doses up to 100 mg once daily.

Pharmacokinetics

After absorption of aprocitentan, with peak plasma concentrations reached at 3–9 h for the different doses, elimination was slow, with an apparent elimination half-life of approximately 44 h. The PK properties of aprocitentan after single and multiple dosing were similar and support once-daily dosing. Steady-state conditions were reached by Day 8 of dosing with an accumulation of aprocitentan by approximately 3-fold. Based on PK, aprocitentan can be administered with or without food and no dose adjustment is required

for sex, elderly subjects, and subjects with mild, moderate, or severe (i.e., estimated glomerular filtration rate [eGFR] ≥15 mL/min) renal function impairment.

A clinical drug-drug interaction (DDI) study with midazolam showed that aprocitentan did not influence the PK of drugs that are substrates of any cytochrome P450 and, therefore, these drugs can be administered concomitantly without need for dose adaptation. Likewise, a clinical DDI study with rosuvastatin showed that aprocitentan did not influence the PK of drugs that are substrates of the efflux transporter breast cancer resistance protein, therefore these drugs can be administered concomitantly without need for dose adaptation.

The primary results of the human absorption, distribution, metabolism, elimination study showed that urine represented the most important elimination route of aprocitentan and its metabolites. Formation of the two most abundant metabolites of aprocitentan in urine and feces, respectively, is not expected to be dependent on cytochrome P450 (CYP)3A4. Therefore, aprocitentan can be concomitantly administered with drugs that are inhibitors or inducers of CYP3A4.

More detailed information on nonclinical and clinical PK data generated on aprocitentan can be found in the IB [Aprocitentan IB].

Pharmacodynamics

PD were investigated in the mechanistic Phase 1 study AC-080-102 in which healthy male subjects received a twice daily (o.d.) dose of aprocitentan (10, 25 or 50 mg) or placebo for 9 days in a 2-way cross-over design [D-18.046]. An extra sodium load was given from Day −3 to Day 9 to ensure that subjects had a sodium excretion > 170 mmol/day. PK and PD variables were assessed on Day 1 and Day 9 with aprocitentan at steady-state conditions.

The primary endpoint was the change from baseline (Day 1) to Day 9 in body weight (kg). A non-inferiority approach was applied in which at least one aprocitentan dose had to be non-inferior to placebo with respect to change from baseline to Day 9 in body weight, defined as the upper limit of the 90% confidence interval (CI) for the difference excluding 1 kg.

The 10 mg aprocitentan dose was considered non-inferior to placebo, despite a (statistically non-significant) mean increase in body weight of +0.425 kg since the upper limit of the 90% CI did not exceed 1 kg. In contrast, for both the 25 and 50 mg doses, the upper limit of the 90% CI exceeded 1 kg, therefore, for both non-inferiority was not concluded. The mean body weight increases were +0.771 and +0.825 kg with 25 and 50 mg aprocitentan, respectively. The increases in body weight were considered to be modest, with a minimal difference between 25 and 50 mg aprocitentan, and were not associated with peripheral edema in these healthy subjects. In addition, decreases in hemoglobin vs placebo were

observed, for which exploratory modeling suggested a dose-relationship, together with slight, non-dose-dependent decreases in hematocrit. When plasma uric acid mean changes from baseline to Day 9 were corrected for placebo, a decrease was observed with the two higher doses of aprocitentan, but not at 10 mg.

Aprocitentan did not affect sodium excretion in a clear way in the healthy salt-loaded subjects in this study, as was demonstrated by unchanged sodium clearance, fractional excretion of sodium, and sodium excretion rates between baseline and Day 9. Other exploratory renal function parameters assessed in this study did not identify clear signs of sodium retention, even though the observed increases in body weight suggested that some extent of sodium retention should have at least transiently been present.

Plasma hormones were measured in study AC-080-102 to assess any possible development of adaptive mechanisms. Due to the high salt intake, plasma aldosterone and renin activity levels were low, and there were no clear patterns of changes in body fluid regulating hormones between baseline and Day 9.

Tolerability and safety

In the entry-into-human study AC-080-101, aprocitentan was well tolerated at single oral doses of up to and including 600 mg, and multiple oral doses of up to and including 100 mg o.d. for 10 days. No deaths or serious adverse events (SAEs) were reported.

After single-dose administration, under fasted conditions, more subjects reported adverse events (AEs) with increasing dose. The most frequently reported AEs were headache (10/30 subjects on aprocitentan 2/8 subjects on placebo with headache reported by all subjects treated with 600 mg aprocitentan), nausea (3 and 1, respectively), postural orthostatic tachycardia (3 and 1, respectively), and nasal congestion (2 and 1, respectively). There were no relevant differences in safety findings between subjects in fed and fasted conditions.

After multiple-dose administration, whilst at lower doses there were no apparent differences in proportion of subjects reporting AEs compared with placebo (ranging from 57–67% of the subjects on aprocitentan compared to 67% of the subjects on placebo). A larger proportion of healthy subjects (71%) and elderly subjects (83%) treated with 100 mg/day aprocitentan reported AEs when compared to its matching placebo (67% and 50%, respectively). The most frequently reported AE was headache. Reporting of headache increased with dose and was not observed in subjects treated with placebo.

Compared with placebo and lower doses of aprocitentan, 100 mg aprocitentan appeared to increase body weight in both healthy adult and healthy elderly subjects.

The safety profiles of subsequent Phase 1 studies were in line with observations in study AC-080-101.

More detailed information on clinical safety data generated on aprocitentan can be found in the IB [Aprocitentan IB].

Phase 2 dose-finding study AC-080A201

A Phase 2 placebo- and active-controlled, dose-finding study explored four doses of aprocitentan (5, 10, 25, and 50 mg o.d.) on sitting DBP (SiDBP) measured at trough by unattended automated office blood pressure measurement (AOBPM) in subjects with grade 1 or 2 essential hypertension with no background therapy. Additionally, sitting SBP (SiSBP) and 24 hour SBP/DBP measured by ABPM, as well as the safety and tolerability of the four aprocitentan doses were evaluated. The active reference was 20 mg lisinopril o.d. The study consisted of a single-blind (SB) placebo period of 4–6 weeks, followed by a double-blind (DB) treatment period of 8 weeks. A withdrawal (WD) period of 2 weeks with SB placebo started after the end of the DB treatment period. After the last dose of the SB WD study treatment, there was a safety follow-up (FU) period of at least 2 weeks.

A total of 490 subjects were randomized to placebo, aprocitentan 5, 10, 25 or 50 mg, or 20 mg lisinopril in a 1:1:1:1:1:1 ratio. Overall, the key demographic and clinical characteristics of the study population at baseline were representative of the general essential hypertension population and well-balanced across all groups.

At baseline, the average SiSBP/SiDBP was 149.7/97.6 mmHg (Per Protocol Set [PPS]).

The mean changes from baseline to Week 8 in SiSBP/SiDBP in the placebo and aprocitentan 5, 10, 25 and 50 mg groups were –7.7/–4.9, –10.3/–6.3, –15.0/–9.9, –18.5/–12.0, –15.1/–10.0 mmHg, respectively. In the lisinopril 20 mg group the mean change from baseline in SiSBP/SiDBP was –12.8/–8.4.

The differences vs placebo for SiSBP/SiDBP were –2.45/–1.31, –7.05/–4.93, –9.90/–6.99, –7.58/–4.95 mmHg for aprocitentan 5, 10, 25 and 50 mg respectively.

The primary efficacy objective for this study was met in that a dose-response relationship was detected among the placebo and aprocitentan groups for the change from baseline to Week 8 in mean SiDBP (primary endpoint; $P < 0.0001$). A quadratic model fitted the data best. A similar dose-response relationship was detected for the change from baseline to Week 8 in mean SiSBP (secondary endpoint). The results of the analyses for the ABPM endpoints were consistent with those for the primary endpoint.

As observed with other ERAs, a dose-dependent decrease in hemoglobin (as well as hematocrit, protein and albumin) was observed at Week 8 in the aprocitentan groups, as compared to placebo and lisinopril 20 mg groups. Additionally, a dose-dependent increase

in estimated plasma volume (calculated based on changes in hemoglobin and hematocrit [Strauss 1951]) was detected ranging from 3.0% to 9.5% in the aprocitentan groups vs 1.6% in the lisinopril 20 mg group and –0.3% in the placebo group. No change of weight was observed across all doses of aprocitentan.

All four doses of aprocitentan were well tolerated. The proportions of subjects in the aprocitentan dose groups who had at least one AE during the DB study treatment period ranged from 22.0% to 40.2% and showed no apparent dose response. The incidences in the placebo (36.6%) and lisinopril (32.1%) groups were within the same range. The most frequently reported AEs in the 6 treatment groups were: headache, nasopharyngitis, upper respiratory tract infection, arthralgia, dizziness and pain in extremity. Edema AEs were reported for 4 subjects, 2 subjects each in the aprocitentan 25 mg (2.4%) and 50 mg (2.5%) groups.

More detailed information can be found in the IB [Aprocitentan IB].

1.2.4 Aprocitentan dose rationale

The doses of aprocitentan for clinical development in RHT were identified based on the results of the Phase 2 dose-finding study (AC-080A201) and were supported by the results of the AC-080-102 study in healthy subjects on a high sodium diet.

In the Phase 2 dose-finding study placebo-corrected differences in the change from baseline to Week 8 in mean SiSBP/SiDBP were statistically significant for aprocitentan 10 mg ($P < 0.05$ / $P < 0.01$), aprocitentan 25 mg ($P < 0.001$/ $P < 0.0001$) and aprocitentan 50 mg ($P < 0.01$/ $P < 0.01$). Numerically, the 25 mg dose was the best dose (–9.90/–6.99 mmHg). The 10 mg (–7.05/–4.93 mmHg) and 50 mg (–7.58/–4.95 mmHg) doses were similar, indicating that a "plateau" of the dose response curve may have been reached.

In the Phase 1 study AC-080-102, [Section 1.2.3] non-inferiority vs placebo in change from baseline to Day 9 in body weight could not be demonstrated for the doses of 25 and 50 mg aprocitentan. However, the increases in body weight were considered to be modest and were not associated with peripheral edema in these healthy subjects. Aprocitentan did not affect sodium excretion in a clear way in the healthy salt-loaded subjects and there were no clear signs of sodium retention. Statistical comparison of body weight changes from baseline of treatment vs placebo showed only a significant p-value of 0.017 for the 50 mg dose, suggesting that 25 mg could have a more favorable profile than 50 mg.

In summary, aprocitentan in the range of 10 to 25 mg provides the best benefit (reduction of BP) / risk (hemoglobin decrease, weight increase) profile. Therefore, aprocitentan doses of 12.5 mg o.d. and 25 mg o.d. have been selected for further development.

1.3 Rationale of the study

The rationale for this Phase 3 study is based on (i) the mechanism of action of aprocitentan that addresses the RHT pathophysiological mechanism [Dhaun 2008 and Section 1.2.1], and (ii) the recognition of an unmet medical need for these patients [see Section 1.1.2].

1.4 Summary of known and potential risks and benefits

Based on the mechanism of action of aprocitentan, current nonclinical data, and clinical data from the Phase 1 studies and Phase 2 study in adult subjects with essential hypertension on mono-therapy, it is anticipated that aprocitentan will reduce the BP of subjects participating in this study in a durable and safe manner.

During the study subjects will be carefully followed at regular visits for up to 68 weeks in hypertension specialized centers. All visit assessments (e.g., BP measurement, blood sampling, electrocardiogram [ECG]) are part of the routine standard-of-care for subjects with RHT, although their frequency may be higher in the study. The most invasive procedure repeated at each visit will be blood sampling, which requires the use of needles.

All subjects will be treated with aprocitentan 25 mg for 32 weeks in the SB aprocitentan part. In addition, an antihypertensive triple fixed combination will be provided to all subjects at least 4 weeks before entering the run-in (RI) period until the End-of-Study (EOS; i.e., for at least 60 weeks) to standardize their background antihypertensive medication. This fixed combination medication has been approved and commercialized for several years in different countries for treatment of hypertension. For detailed information refer to the package insert provided in the site file.

The potential risks for subjects participating in this study are related to those based on the pre-clinical and clinical findings of aprocitentan [see Sections 1.2.2 and 1.2.3, and section 1.5 of the Aprocitentan IB].

There is a potential risk in both placebo and aprocitentan treatment groups that BP may not be reduced. However, the placebo periods are limited to short periods of time [see Section 3.1.1.2 and 3.1.1.3]. It should be noted that no harm was reported when placebo was used for a similarly short period of time [see Section 3.2]. In addition, based on the Phase 2 data it is anticipated that aprocitentan will decrease BP.

The following measures will contribute to minimize the risks for the subjects participating in the study:

- Exclusion of subjects with confirmed severe hypertension (i.e., grade 3), recent severe cardiovascular disease (heart failure New York Heart Association [NYHA] stage III and IV), N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥ 500 pg/mL, stroke,

severe CKD (i.e., grade 5), low hemoglobin, and high alanine and aspartate aminotransferase (ALT/AST) [see Section 4.4].

- Use of a highly effective method of contraception for women of childbearing potential.
- Laboratory tests performed prior to initiation of study treatment and frequently thereafter [as defined in Table 2 and Table 3] until EOS.
- Close follow-up of the subjects throughout the study with site visits [see Section 7.1].
- Possibility to add antihypertensive rescue medication at the discretion of the investigator during the SB aprocitentan and DB-WD parts of the study in the event that BP is not satisfactorily controlled (confirmed by second measurement), despite confirmed adherence to standardized background antihypertensive therapy [see Section 5.2.3.1].
- Study-specific criteria for interrupting or stopping study treatment [see Section 5.1.11].
- Monitoring of safety and efficacy data by an Independent Data Monitoring Committee (IDMC) [see Section 3.3.2].

It is the investigator's responsibility to monitor the risk-benefit ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual subject, and to discontinue study treatment or the study if, based on medical judgment, he/she believes that continuation would be detrimental to the subjects' well-being.

For further information on the efficacy and safety profile of aprocitentan, please refer to the IB [Aprocitentan IB].

2 STUDY OBJECTIVES

2.1 Primary objective

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

2.2 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 true RHT subjects
- to evaluate the long-term safety and tolerability of aprocitentan in true RHT subjects during 48 weeks of treatment.

2.3 Other objectives

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

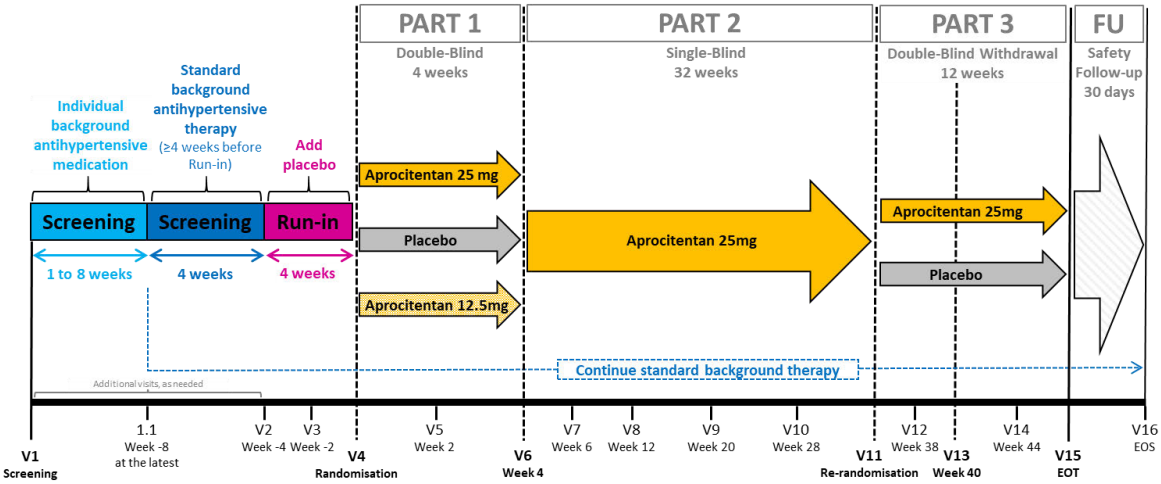
3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multicenter, randomized, parallel-group, blinded Phase 3 study with aprocitentan in subjects with true RHT.

The overall study design is depicted in [Figure 1].

Figure 1 Study design



Approximately 4000 subjects are expected to be screened, in order to enroll about 1500 subjects with diagnosis of RHT into the SB placebo RI period. At least 600 subjects will be randomized and at least 300 subjects are expected to complete the study (i.e., the 30 day safety follow-up period). The study will be conducted in approximately 200 sites in approximately 25 countries.

Once the randomization target has been met, the sponsor might decide to close the recruitment. In such a case, study participants still in the screening period may not enter the run-in period and be randomized.

3.1.1 Study periods

The study comprises the following consecutive periods:

3.1.1.1 Screening period

This period lasts between 4 and 12 weeks. It starts at the screening visit with the signing of the informed consent form (ICF) and ends the day before the subject enters the RI period.

The purpose of the screening period is to select RHT subjects and confirm the diagnosis of true RHT.

At least 4 weeks before the start of the RI period, the background antihypertensive medication (except beta-blockers) of subjects with diagnosis of true RHT and having mean trough SiSBP ≥ 140 mmHg measured by AOBPM will be standardized by switching to a fixed combination of a CCB (amlodipine), an ARB (valsartan) and a diuretic (hydrochlorothiazide [HCTZ]).

In case a beta-blocker is used as one of the background antihypertensive medications or for any other indication (e.g., heart failure, angina, post-myocardial infarction [MI], atrial fibrillation), this can be kept, with the provision that it has been initiated and the dose kept stable for at least 4 weeks prior to the screening visit and that the dose is kept stable until the End-of-Treatment (EOT).

The number of site visits is flexible during this period and depends on tests/assessments needed to be performed.

3.1.1.2 Placebo run-in period

This SB period lasts for 4 weeks, beginning with the first dose of SB placebo and ending at Randomization (after completion of the 24 h ABPM recording on the last dose of SB placebo). It consists of 3 site visits: Visit 2 at the start of the RI (i.e., 4 weeks before Randomization), Visit 3 (i.e., 2 weeks before Randomization) and Visit 4 at the end of the RI (Day –1; i.e., 1 day before Randomization).

The purpose of this period is to confirm that mean trough SiSBP measured by AOPBM remains ≥ 140 mmHg despite administration of placebo for 4 weeks on top of the standardized background antihypertensive therapy. The rationale for administering placebo during the RI is discussed in Section 3.2.

3.1.1.3 Randomized treatment period

This period lasts for 48 weeks. It starts at Randomization (i.e., Day 1 of the DB part) and ends at the EOT visit (i.e., at end of the DB-WD part).

This period consists of 3 sequential parts:

Part 1 is DB, randomized, parallel-group and placebo-controlled and lasts for 4 weeks. Subjects will receive aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo in a 1:1:1 ratio. It starts at Randomization (i.e., Day 1) with the first dose of DB study treatment and ends

after completion of the Week 4 24 h ABPM recording on the last dose of DB study treatment. It consists of 3 site visits: Visit 4 at Randomization (i.e., Day 1), Visit 5 at Week 2 and Visit 6 at Week 4 (i.e., end of the DB part).

The purpose of this period is to demonstrate the BP lowering effect of aprocitentan in true RHT subjects (i.e., the primary objective of the study**).**

Part 2 is SB and single-arm and lasts for 32 weeks. All subjects will receive aprocitentan 25 mg. It starts with the first dose of the SB study treatment (after completion of the Week 4 24 h ABPM) and ends after completion of the Week 36 24 h ABPM recording on the last dose of SB treatment. It consists of 5 site visits: Visit 7 at Week 6, Visit 8 at Week 12, Visit 9 at Week 20, Visit 10 at Week 28 and Visit 11 at Week 36 (i.e., end of the SB aprocitentan part).

Part 3 is DB-WD, randomized, parallel-group and placebo-controlled and lasts for 12 weeks. Subjects will be re-randomized to aprocitentan 25 mg or placebo in a 1:1 ratio. This part starts with the first dose of the DB-WD study treatment (after completion of the Week 36 24 h ABPM recording) and ends after completion of the Week 48 (i.e., DB-WD EOT) assessments. It consists of 4 visits: Visit 12 at Week 38, Visit 13 at Week 40, Visit 14 at Week 44 and Visit 15 at Week 48 (i.e., EOT).

The purpose of parts 2 and 3 is to demonstrate that the BP lowering effect of aprocitentan on BP is sustained over a period of 36 weeks in true RHT subjects (i.e., the key secondary objective).

EOT is at Week 48 (i.e., end of DB-WD part) or earlier in the event of premature discontinuation of study treatment. The EOT visit should preferably take place as soon as possible after the last dose of study treatment but, in any case, no later than 7 days. Premature discontinuation of study treatment is described in Section 5.1.10.

3.1.1.4 Safety follow-up (FU) period

The safety FU period starts on the day after the last dose of study treatment and ends at Visit 16 with a safety FU visit/call:

- For subjects who entered the RI period, but who were not randomized (i.e., who received only SB placebo) it will be a safety FU call.
- For randomized subjects it will be a safety FU visit.

The safety FU visit/call must take place 30 (+3) days after the last dose of study treatment. For an individual subject, EOS corresponds to the safety FU call or safety FU visit.

The visit schedule and protocol-mandated procedures will be performed according to the tables of assessments [Table 2 and Table 3] and as described in Section 7.

3.1.2 Study duration

Subject participation in the study will be up to 68 weeks.

The study starts with the first subject first visit and ends with the last subject last visit. The study is expected to last approximately 45 months.

3.2 Overall study design rationale

This study is designed to show that aprocitentan reduces BP and that this effect is sustained (durable) in subjects with RHT.

This study has a RI period of 4 weeks. During this period, placebo will be administered in order to exclude potential placebo responders and, thus, reduce the placebo effect in the DB part. An RI period of at least 2, sometimes as long as 4, weeks was used for the development of antihypertensive agents. A prolonged RI period of 4 weeks may be necessary to avoid bias due to the regression-toward-the-mean phenomenon. [EMA 2016a].

3.2.1 Rationale for DB part

The 4 weeks DB part is designed to demonstrate the effect of 2 doses of aprocitentan (12.5 and 25 mg) on BP at Week 4, compared to placebo. The analysis after 4 weeks of treatment reduces the likelihood of missing data. In addition, in the dose-finding study AC-080A201, at least 80% of the expected BP reduction was already observed in the first 4 weeks of treatment. Placebo is used as the control group due to high variability of BP, especially on top of background therapies in true RHT subjects.

The use of placebo does not create an unethical situation due to the following reasons:

- Subjects are already on background antihypertensive medications and severe (grade 3) hypertensive subjects will not be allowed to enter into this study.
- Subjects are closely followed during these 4 weeks with visits at Week 2 and Week 4.
- Study-specific discontinuation criteria have been set-up [see Section 5.1.11].
- Subjects who experience (confirmed) essential hypertension grade 3 must permanently stop the study treatment.
- Use of placebo in numerous recent placebo- or sham-controlled studies in similar population (i.e., RHT) on stable triple background antihypertensive medications didn't report safety concern [Václavík 2011, Williams 2015, Bhatt 2014].
- No irreversible harm was reported during this short-term period (4–8 weeks) by an FDA meta-analysis of 590 individual hypertension clinical trials involving 64,438 subjects randomized to experimental drug and 21,699 randomized to placebo [DeFelice 2008].

3.2.2 Rationale for SB aprocitentan part and DB-WD part

These 2 parts are designed to demonstrate the long-term BP lowering effect of aprocitentan. In chronic diseases (e.g., heart failure) or special population (e.g., pediatric) placebo cannot be administered for a long period of time or not at all. For these cases, a randomized WD design is now standard when the objective is to demonstrate that the long-term effect on BP is sustained [O'Neill 2012]. In a randomized WD design, a long-term SB active treatment part is followed by a DB-WD part in which subjects are randomized to investigational drug or placebo.

In this study, all subjects who enter into the SB aprocitentan part will be treated for 32 weeks with aprocitentan 25 mg. This period is followed by DB-WD part where subjects will remain either on aprocitentan 25 mg or switch to placebo in a 1:1 ratio for 12 weeks.

The BP will be analyzed at Week 4 of the DB-WD period (i.e., Week 40) key secondary endpoint). This duration is selected and justified based on the half-life of aprocitentan (i.e., 44 hours). The total duration of the DB-WD part will be 12 weeks to be able to also explore the durability at Week 8 and Week 12.

3.3 Study committees

3.3.1 Independent Central Adjudication Committee

An independent Central Adjudication Committee (CAC) provides ongoing review of all reported cases of major adverse cardiac events (MACE) and MACE-plus in a blinded fashion. To ensure the proper and comprehensive review and adjudication of MACE events, additional subject data may be requested by the CAC.

The composition and operation of the CAC is described in the CAC charter.

3.3.2 Independent Data Monitoring Committee

An IDMC has the overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC are described in the IDMC charter.

Unblinded data will be delivered to the IDMC by an Independent Statistical Analysis Center (ISAC).

4 STUDY POPULATION

4.1 Selection of study population

RHT is defined as BP that is not controlled to a pre-defined threshold [described in Table 1] in patients adhering to lifestyle modifications and to an appropriate regimen of three or more antihypertensive drugs from different pharmacological classes including a diuretic, in the absence of a secondary cause of hypertension [Calhoun 2008, Williams 2018].

The definition of uncontrolled BP varies with the method of measurement, as shown in Table 1.

Table 1 BP thresholds for the definition of uncontrolled BP (i.e., hypertension)

Method of measurement	SBP and/or DBP (mmHg)
Automated office BP measurement*	≥ 135/85*
Ambulatory BP monitoring**	
- Daytime (or awake)	≥ 135/85**
- Night time (or sleep)	≥ 120/70**
- 24 hour	≥ 130/80**
Home BP monitoring**	≥ 135/85**

* The term automated office BP measurement (AOBPM) refers to BP measurement obtained using a fully automated electronic sphygmomanometer that records multiple BP readings with the patient resting undisturbed in a quiet place without medical staff being present [Leung 2017, Myers 2010].
** Extracted from [Williams 2018].
ABPM = ambulatory blood pressure monitoring; AOBPM = automated office blood pressure measurement; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

In order to minimize the rate of screening and RI failures, the investigator is encouraged to have a comprehensive medical history available for patients they intend to screen. Review of subject charts allows the identification of apparent RHT and helps avoid inappropriate subject screening. Subjects with any of the chronic conditions mentioned in the exclusion criteria list [see Section 4.4] should not be considered for screening.

This study will enroll adult male and female subjects with a diagnosis of true RHT [Section 1.1 and Section 4.2] having a mean SiSBP measured by AOBPM ≥ 140 mmHg. This higher threshold (as compared to the table above) was chosen in order to minimize screening failures that are likely to occur following the switch to the standardized background antihypertensive therapy. The BP randomization criterion will also be mean trough SiSBP ≥ 140 mmHg in order to increase the sensitivity of the study to observe treatment effects.

4.2 Rationale for the selection of the study population

Among the hypertensive population, RHT was selected as the targeted study population [see Section 4.1]. No antihypertensive therapy has been specifically developed and approved for the treatment of this population. Furthermore, all existing antihypertensive therapies used as fourth-line therapy in this population have some limitations with respect to adverse drug reactions. This is one of the major causes of treatment discontinuation. This, consequently cause uncontrolled BP which is one of the main reasons for increased cardiovascular outcomes [Thomopoulos 2016a, Thomopoulos 2016b]. Hence, there is an unmet need for this vulnerable and complex patient population who are at high cardiovascular risk.

In this study, subjects with true RHT are included in order to demonstrate the efficacy, durability of the effect, and safety of aprocitentan in a hypertensive population with high medical need. Subjects with "pseudo" or "apparent" (terms are used interchangeably) RHT, which is far more common than "true" RHT will be excluded from the study.

The selection criteria for this patient population follow the recommendation of the ESH and ESC joint guideline [Williams 2018], the American Heart Association Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [Whelton 2017], as well as several other national guidelines [Denolle 2014, McCormack 2013].

Subjects with confirmed severe hypertension (grade 3), recent major cardiovascular, renal, cerebrovascular medical complications, and heart failure NYHA stage III-IV are excluded from the study. This is because these patients could potentially be at greater risk of experiencing side effects, and/or their conditions could interfere with the evaluation of the treatment effect, study assessments and interpretation of study results.

4.3 Inclusion criteria

For inclusion in the study, the subject must fulfill all of the following inclusion criteria at the specified study visits. It is not permitted to waive any of the criteria for any subject:

Screening criteria

1. Signed and dated ICF prior to any study-mandated procedure.
2. Male and female subjects; 18 years (or year of country specific majority) or older.
3. Historical documentation in the subject's medical records of uncontrolled BP despite at least 3 background antihypertensive medications within 1 year before screening visit.
4. Treated with at least 3 antihypertensive therapies of different pharmacological classes for at least 4 weeks before the screening visit (Visit 1).

5. Mean SiSBP ≥ 140 mmHg measured by AOBPM at screening visit.
6. Documentation in the subject's medical records of diagnosis of RHT according to the site's medical practice:
   - Exclusion of secondary causes of hypertension (e.g., serum aldosterone, plasma renin activity, duplex/doppler ultrasonography, computer tomography angiography assessments are performed to exclude the secondary causes of hypertension [Rimoldi 2013]),
   - Adherence to medication (e.g., how the adherence was checked and/or monitored) to eliminate apparent RHT.
7. A woman of childbearing potential [see definition in Section 4.5.1] is eligible only if the following applies:
   - Negative pregnancy test at Screening and at baseline (i.e., end of RI period).
   - Agreement to undertake pregnancy tests during the study and up to 30 days after randomized study treatment discontinuation.
   - Agreement to use methods of birth control as described in Section 4.5 from Screening up to at least 30 days after randomized study treatment discontinuation.
8. Mean trough SiSBP ≥ 140 mmHg measured by AOBPM at the switch from background antihypertensive medications (i.e., at least 3 medications from different pharmacological classes]) to the standardized background antihypertensive therapy.

RI entry criteria

9. Switched to the standardized background antihypertensive therapy at least 4 weeks before the first RI visit.
10. Mean trough SiSBP ≥ 140 mmHg measured by AOBPM.

Randomization criteria (end of RI)

11. Stable dose of the standardized background antihypertensive therapy for at least 1 week before Day –1 (end of the RI period).
12. Mean trough SiSBP ≥ 140 mmHg measured by AOBPM.
13. Subjects demonstrating ≥ 80% compliance (pill counting) to study treatment (i.e., placebo) as well as ≥ 80% compliance (pill counting) to the standardized background antihypertensive therapy during the RI period.

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria at the specified study visits. It is not permitted to waive any of the criteria for any subject:

Screening period criteria

Disease/condition:

1. Pregnant or lactating subjects.
2. Apparent/pseudo RHT due to white coat effect, medical inertia, poor therapeutic adherence, or secondary causes of hypertension (not including obstructive sleep apnea).
3. Confirmed severe hypertension (grade 3) defined as mean SiSBP ≥ 180 mmHg and/or SiDBP ≥ 110 mmHg measured by AOBPM at two different time points.

   The BP re-measurement can be during the screening visit (e.g., after at least 3 h), or at the next planned visit, or at an unscheduled visit. The time of re-measurement is at the investigator's discretion, taking into consideration the subject's medical history.
4. Known and documented transient ischemic attack, stroke, unstable angina or MI within 6 months prior to Screening.
5. Clinically significant unstable cardiac disease at screening or in the past in the opinion of the investigator, e.g., uncontrolled symptomatic arrhythmia, atrial fibrillation, congestive heart failure NYHA stage II with relevant mitral valve insufficiency and/or aortic stenosis, congestive heart failure NYHA stage III or IV.
6. Severe renal insufficiency defined as an eGFR per the CKD Epidemiology (CKD-EPI) collaboration creatinine equation < 15 mL/min/1.73 m^2.
7. Type 1 DM.
8. Subjects working night shifts.

   A maximum of 2 night shifts per week is permitted except within 3 days prior to a study visit. Night shifts are not allowed during visits at which ABPM is recorded.
9. Any known factor, disease or clinically relevant medical or surgical conditions that, in the opinion of the investigator, might put the subject at risk, interfere with treatment compliance, study conduct or interpretation of the results.
10. Known concomitant life-threatening disease with a life expectancy < 18 months of Screening.

Treatments:

11. Treatment with any medication which may affect BP [see Appendix 1] and/or treatment with high dose of loop diuretics (i.e., furosemide greater than 80 mg/day, or equivalent dosage of other loop diuretics).
12. Treatment with any other ERAs.
13. Contraindication and/or known hypersensitivity to any of the three components of the standardized background antihypertensive therapies (fixed combination of CCB

[amlodipine], ARB [valsartan] and diuretic [HCTZ]) according to their labels or drugs of the same class, or to any of the excipients.

14. Known hypersensitivity to aprocitentan or drugs of the same class, or any of the excipients.
15. Treatment with another investigational treatment within 3 months prior to Screening.
16. Laboratory assessments based on central laboratory
    - ALT or AST > 3 times the upper limit of normal range, or severe hepatic impairment.
    - Hemoglobin < 100 g/L.
    - NT-proBNP ≥ 500 pg/mL.

    If one of these criteria is not met based on central laboratory report, a re-test must be performed before Visit 2 (e.g., at the next screening visit, or at an unscheduled visit). If the value is confirmed, the subject must discontinue from screening.

RI period exclusion criteria

17. Confirmed severe hypertension (grade 3) defined as mean SiSBP ≥ 180 mmHg and/or SiDBP ≥ 110 mmHg measured by AOBPM at two different time points.

The BP re-measurement can be during the first RI Visit (e.g., after at least 3 h), or at the next planned visit, or at an unscheduled visit. The time of re-measurement is at the investigator's discretion, taking into consideration the subject's medical history.

Randomization exclusion criteria

18. Laboratory assessments based on local laboratory.
    - ALT or AST > 3 times the upper limit of normal range.
    - Hemoglobin < 100 g/L.
    - eGFR per the CKD-EPI creatinine equation < 15 mL/min/1.73 m^2.

At any time between Screening and Randomization the investigator/delegate must verify that the subject does not fulfill the exclusion criteria checked at the screening visit (as applicable).

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy,

- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]),
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis,

Childbearing potential status will be assessed at each visit and recorded in the electronic case report form (eCRF).

4.5.2 Acceptable methods of contraception

The methods of birth control used (including non-pharmacological methods) must be recorded in the eCRF.

Note: The documentation of method of contraception can be based on the site personnel's review of the subject's medical records, medical examination or medical history interview of the subject.

The use of one of the following options is regarded as a highly effective method of contraception:

Option 1
One method from this list:
Standard intrauterine device (IUD)
(Copper T380A IUD)
Intrauterine system (LNg 20IUS: progesterone IUS)
Progesterone implant
Tubal sterilization

Option 2
One method from this list:
Estrogen and progestogen oral contraceptives ("the Pill")
Estrogen and progestogen transdermal patch
Vaginal ring
Progesterone injection
PLUS one method from this list:
Male condom
Diaphragm with spermicide
Cervical cap spermicide

Option 3
One method from this list:
Partner's vasectomy
PLUS one method from this list:
Male condom
Diaphragm with spermicide
Cervical cap with spermicide
Estrogen and progestogen oral contraceptives ("the Pill")
Estrogen and progestogen transdermal patch
Vaginal ring
Progesterone injection

IUD, Intrauterine Device; IUS, Intrauterine System.

If hormonal contraception is one of the methods used then it must have been initiated at least 4 weeks prior to the screening visit (Visit 1) [see Section 5.2.3].

Option 3: vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

5 TREATMENTS

5.1 Study treatment

This section applies to study treatment (aprocitentan/placebo). The standardized background antihypertensive therapy is described in Section 5.2.2.

5.1.1 Investigational treatment and matching placebo

Aprocitentan is currently available for clinical study use as identical tablets of 12.5 and 25 mg containing aprocitentan and inactive excipients.

Placebo tablets will be identical in appearance to the aprocitentan tablets, and will contain inactive excipients.

5.1.2 Study treatment dosing and rationale

For this confirmatory study in RHT, dosages of 12.5 and 25 mg (o.d.) are selected. The rationale has been provided in Section 1.2.4.

5.1.3 Study treatment administration

Study treatment is supplied in bottles containing 36 tablets to cover a 4-week treatment period accounting for one extra week (if needed).

The subjects must be instructed to take one tablet from the bottle orally o.d. irrespective of food intake every morning and not to take it on the morning of study visit days. On the day of the study visits, study treatment must be administered only after the completion of the visit assessments as indicated in Section 7.2.

The study personnel must remind subjects at each visit of the study treatment intake requirements. The reminders must be documented in the subject's chart.

5.1.4 Treatment assignment

After the informed consent has been signed the investigator/delegate gets a subject number through the Interactive Response Technology (IRT) system at Visit 1 (screening visit).

During the screening period, subjects will be switched to the standardized background antihypertensive therapy [see Section 5.2.2], which will be dispensed via the IRT system.

At the first RI visit the investigator/delegate contacts the IRT system to get a study treatment number (i.e., bottle number) for the 4 weeks of the RI period. In the RI period all subjects will receive placebo in a SB fashion.

At Visit 4 / Randomization (Day 1) the investigator/delegate contacts the IRT system to randomize the subject to aprocitentan 12.5 mg, aprocitentan 25 mg or placebo in a

1:1:1 ratio. The IRT system assigns a randomization number to the subject and a bottle number to match the treatment arm assigned by the randomization list.

At the end of the DB part (Week 4) the investigator/delegate contacts the IRT system to get the treatment number (i.e., bottle number) for the SB aprocitentan part. All subjects in this period will be assigned to 25 mg aprocitentan.

At the end of the SB treatment part (Week 36), the investigator/delegate contacts the IRT system to re-randomize the subject to aprocitentan 25 mg or placebo in a 1:1 ratio. The re-randomization will be stratified by randomized treatment in the DB part, which will not be revealed. The IRT system assigns a (scrambled) re-randomization number to the subject and a bottle number to match the treatment arm assigned by the re-randomization list.

The IRT system is handled by an external independent vendor which will generate two randomization lists, one for the DB part and another for the DB-WD part.

5.1.5 Blinding

This study will have two SB parts: the SB placebo RI period prior to Randomization and the SB aprocitentan part of 32 weeks. Accordingly, study personnel must not inform the subject of the treatment received during these parts.

Parts 1 (DB) and 3 (WD-DB) of the study will be performed in a DB fashion. The investigator and study personnel, the subjects, the Clinical Research Associates (CRAs), sponsor personnel, and vendor/CRO personnel involved in the conduct of the study will remain blinded to the study treatment received by the subjects during the DB treatment periods until study closure. To ensure adequate supply of study treatment, the IRT vendor personnel responsible for clinical study supply distribution and the sponsor individuals contributing to clinical supply distribution will need to be unblinded at subject level and depot level, respectively. These persons will be clearly identified, their unblinding will be documented in the trial master file, and they will not take part in any Clinical Trial Team (CTT) meetings after study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list will be kept strictly confidential, and accessible only to IRT vendor and sponsor authorized persons (i.e., Pharmaceutical Development department, Bioanalytical Laboratory group, ISAC and IDMC), who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment bottles will be packaged in the same way.

To minimize the possibility of systematic unblinding, the PK results will be communicated/transferred by the Bioanalytical Laboratory Group to the sponsor and CRO personnel involved in the conduct of the study only after database lock.

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database lock, in accordance with the sponsor's Quality System (QS) documents.

5.1.6.2 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) [see definition in Section 9.1.3] occurs in a subject participating in the study, the sponsor's Global Drug Safety department will request the unblinding of the treatment assignment to meet regulatory reporting requirements.

The treatment assignment will not be communicated to site personnel or subjects, or to the sponsor CTT or any vendor/CRO personnel involved in the conduct of the study.

Unblinded SUSAR information will be provided to respective health authorities and Independent Ethics Committees / Institutional Review Boards (IECs/IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.3 Emergency procedure for unblinding

The investigator, study personnel, subjects, CRAs, sponsor personnel, and any CRO personnel involved in the conduct of the study must remain blinded to the subject's treatment assignment.

The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded treatment assignment through the IRT system. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible, and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended unblinding with the sponsor personnel.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, the sponsor personnel must be informed as soon as possible before or after the unblinding.

The circumstances leading to unblinding must be documented in the hospital charts, the Investigator Site File (ISF) and in the eCRF.

5.1.7 Study treatment supply

Manufacturing, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice, GCP, and any local or national regulatory requirements.

All study treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

5.1.7.1 Study treatment packaging and labeling

Study treatment is provided as tablets in childproof bottles. Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

5.1.7.2 Study treatment distribution and storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label. The storage conditions must be explained to the subject.

5.1.7.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used, and unused study treatment bottles at each visit. Should the treatment bottle dispensed at a scheduled visit be lost or damaged, a replacement bottle can be requested via the IRT system. The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. In exceptional circumstances (e.g., if the subject lost the study treatment between two visits, or if the subject is unable to return to the site due to a medical emergency/hospitalization at another hospital), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit. An accurate study treatment record of the date and amount of study treatment dispensed to each subject must be available at the site for inspection at any time.

5.1.7.4 Study treatment return and destruction

The protocol-mandated study treatment return procedures may not be altered without prior written approval from the sponsor. On an ongoing basis and/or on termination of the study, the CRA will collect used and unused treatment kits, which will be sent to the warehouse, where the sponsor personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by the sponsor personnel or the deputy, and written permission for destruction has been obtained from the sponsor.

5.1.8 Study treatment adherence

Adherence to medications is one of the key elements in the treatment of chronic diseases such as hypertension/RHT. In this study, study treatment adherence will be assessed throughout the study based on study treatment accountability (tablets count) for study treatment and the standardized background antihypertensive therapy, monitoring of the

intake of the standardized background antihypertensive therapy by urine analysis, and direct observed treatment (DOT) at the four planned ABPM assessments [see Section 7.2.2.2].

5.1.8.1 Study treatment adherence based on accountability

The inventory of study treatment and the standardized background antihypertensive therapy dispensed to and returned by the subject (i.e., study treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. It is to be recorded by site personnel on the study treatment dispensing and accountability log and in the eCRF, and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (i.e., bottle) dispensed to the subject:

- Dispensed bottle (study treatment) / blister or bottle (standardized background antihypertensive therapy) ID number;
- Date dispensed / number of tablets dispensed (pre-populated in eCRF);
- Date returned / number of tablets returned.

All supplies, including partially used or empty bottles/blisters must be retained at the site until they are verified by the CRA.

If the subject omits to bring the remaining study treatment to a study visit, at which new study treatment will be dispensed [see Table 2 and Table 3], he/she must be instructed to not take any tablets from the forgotten study treatment bottle and to return it at the next visit.

For each time interval between two visits (i.e., "period"), the adherence to study treatment and, separately, the standardized background antihypertensive therapy based on study treatment accountability will be calculated by the sponsor using the following formula:

Adherence based on study treatment accountability =

([number of tablets dispensed at visit n – number of tablets returned at Visit n + 1) / number of tablets that should have been taken during the period)] × 100

The period is defined as the number of days between Visit n (or date of first study treatment intake if randomization visit) and Visit n + 1 (or date of last study treatment intake if EOT visit).

Between visits, adherence based on study treatment and the standardized background antihypertensive therapy accountability is expected to be at least 80%.

Adherence at the end of the RI period is one of the randomization criterion. Subjects with adherence values below 80% for study treatment and/or the standardized background antihypertensive therapy will be considered as RI failure and cannot be randomized. In order to minimize misuse of study medication by the subject (e.g., throwing out tablets from the returned bottles) and to properly evaluate this randomization criterion, the study staff must not inform the subject about this criterion.

Adherence values below 80% for the study treatment and/or the standardized background antihypertensive therapy without a medical justification (e.g., AE) after the randomization visit is considered a protocol deviation, which will be reported as such to the sponsor by the CRA. In such cases, the investigator/delegates must discuss and clarify the reasons for non-compliance with the subject and take appropriate actions to avoid re-occurrence. This discussion must take place prior to providing the next study treatment to the subject. The outcome of the discussion must be documented in the source documents.

5.1.8.2 Standardized background antihypertensive therapy adherence based on urine analysis

Urine samples will be collected throughout the study from initiation of the standardized background antihypertensive therapy. The samples must be collected at trough, i.e., before taking the study treatment and the standardized background antihypertensive therapy. The urine will be analyzed for the presence of valsartan (one of the components of the standardized triple combination). The results of urine analysis from each visit will be used to discuss the importance of study treatment intake with poorly adherent subjects.

In such cases, the investigator/delegates must call the subject within 1 week of receiving the data to clarify the reasons for non-adherence, and take appropriate actions to avoid re-occurrence. The subject must be re-trained on the intake of study treatment and the standardized background therapy, and risks associated with uncontrolled BP caused potentially by not taking the study treatment as instructed. The date of phone call and main points discussed with the subject must be documented in the subject's chart.

5.1.9 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted. Study treatment may be temporarily interrupted in response to an AE, or other reasons (e.g., diagnostic or therapeutic procedure, a laboratory abnormality, study treatment forgotten).

If study treatment is interrupted by the subject for any reason, he/she must immediately inform the investigator. Interruptions of study treatment should be no longer than 7 consecutive days during DB part and DB-WD part. During the SB aprocitentan part the interruptions of study treatment could be 14 consecutive days. Otherwise, permanent study treatment discontinuation should be considered.

All study treatment interruptions must be recorded in the eCRF.

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or sponsor personnel. The main reason (e.g., AE, hypertension grade 3) must be documented in the eCRF.

A subject has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawing from study treatment only or by withdrawing from any further participation in the study (i.e., premature WD from the study [see Section 8.2]). Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject.

Study-specific criteria for discontinuation of study treatment (aprocitentan/placebo) are described in Section 5.1.11.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study, provided that the subject's consent for this limited participation in the study has not been withdrawn.

- If a subject discontinues study treatment during the RI period the subject will be asked to perform the end of RI visit and a safety FU call 30 (+3) days thereafter. The standardized background antihypertensive therapy will only be provided until the end of RI visit. Thereafter, antihypertensive medication(s) should be administered according to local standard-of-care at the investigator's discretion.
- If a randomized subject discontinues study treatment the subject will be asked to perform the EOT visit (i.e., Visit 15) as soon as possible after the last dose of study treatment but, in any case, no later than 7 days and a safety FU visit 30 (+3) days thereafter. Antihypertensive medication(s) should be administered according to local standard-of-care at the investigator's discretion. The standardized background antihypertensive therapy may be continued until the completion of the safety FU visit.

  The following visits must be performed for subjects who prematurely discontinued during the DB part and DB-WD part:

  – If a randomized subject discontinues study treatment during the DB part the subject will be asked to perform the scheduled Week 4 visit. If the scheduled Week 4 visit is within 7 days of the EOT or safety FU visit, the Week 4 visit can be skipped.

– If a randomized subject discontinues study treatment during the DB-WD part the subject will be asked to stay in the study and to perform the remaining visits of the DB-WD period. If a scheduled Week 40, Week 44 or Week 48 visit is within 7 days of the EOT or safety FU visit, this Week 40/44/48 visit can be skipped.

A subject who prematurely discontinues study treatment at any stage, and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. WD from the study and follow-up medical care of subjects withdrawn from the study are described in Sections 8.2 and 8.4, respectively.

5.1.11 Study-specific criteria for interruption / premature discontinuation of study treatment

All the following criteria apply after Randomization.

5.1.11.1 Hypertension

If mean SiSBP ≥ 180 mmHg and/or mean SiDBP ≥ 110 mmHg measured by AOBPM, i.e., essential hypertension grade 3 [Williams 2018], BP must be re-measured. The BP re-measurement can be at the next planned visit, or at an unscheduled visit. The time of re-measurement is at the investigator's discretion, taking into consideration the subject's medical history.

If grade 3 is confirmed by BP re-measurement, the study treatment must be permanently discontinued.

5.1.11.2 Renal failure

Study treatment must be permanently discontinued in the event of:

- Confirmed (within one week) eGFR< 15mL/min/1.73m^2 or
- Confirmed (within one week) increase of > 2 × from baseline in serum creatinine.

5.1.11.3 Persistent fluid retention

Study treatment must be permanently discontinued if the symptom(s) of fluid retention are not tolerable after increasing the dose of the existing diuretic or the addition of a new diuretic [Section 5.2.3.1].

5.1.11.4 Hemoglobin abnormalities

In the event of hemoglobin decrease from baseline of > 20 g/L, a hemoglobin retest must be performed within one week, with additional laboratory evaluations that include, but are not limited to, any of the following:

Red blood cell cellular indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), reticulocyte

count, iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation).

Study treatment must be permanently discontinued if clinically mandated based on the investigator's judgment, or in any of the following situations:

- A decrease in hemoglobin to < 80 g/L (< 4.9 mmol/L),
- A decrease in hemoglobin from baseline of > 50 g/L,
- The need for transfusion.

5.1.11.5 Liver aminotransferases abnormalities

Interruption of study treatment

Study treatment must be interrupted in the following case:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and ≤ 8 × the upper limit of normal (ULN)

Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase within one week. If AST and/or ALT elevation is confirmed, the re-test must be performed weekly until the value is within normal range or has returned to pre-treatment levels. Interruptions of study treatment are allowed up to 7 consecutive days during the DB part and the DB-WD part, and 14 consecutive days during the SB aprocitentan part [see Section 5.1.9].

Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Permanent discontinuation of study treatment

Study treatment must be permanently discontinued and its re-introduction is not to be considered in the following cases:

- Aminotransferases > 8 × ULN.
- Aminotransferases ≥ 3 × ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever).
- Aminotransferases ≥ 3 × ULN and associated increase in total bilirubin ≥ 2 × ULN.

Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (e.g., acetaminophen-related liver toxicity) should be considered and ruled out by performing the appropriate tests. To ensure the proper and comprehensive evaluation of hepatic events, additional subject data might be collected via the Idorsia Global Drug Safety department.

5.1.11.6 Pregnancy

At any time during the study, if a subject becomes pregnant, study treatment must be permanently discontinued. The investigator/delegate must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to the signature of the ICF.

A therapy that is study-concomitant is any treatment that is ongoing or initiated after the signature of the ICF, or initiated up to 30 days after study treatment discontinuation.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of randomized study treatment or is initiated during the randomized treatment period.

5.2.2 Mandatory concomitant therapy

During the screening period, at least 4 weeks before the start of the RI period, the 3 or more background antihypertensive medications that the subject had at entry in the study must be switched to a standardized background antihypertensive therapy which is a triple fixed combination of CCB (amlodipine), ARB (valsartan) and diuretic (HCTZ). The dose strength must be stable during the RI period.

Two dose strengths will be available: 10/160/25 and 5/160/25 mg (amlodipine, valsartan, HCTZ, respectively). The fixed combination will be provided to all subjects from time of the switch until EOS. The selection of the dose strength of the standardized background antihypertensive therapy for an individual subject (either 5 or 10 mg) is at the investigator's discretion and may vary during the screening period. It is required to use the maximal tolerated dose of the background antihypertensive therapy (i.e., 10 mg amlodipine, if there is no tolerability issue) from the start of the RI period. The dose strength must be kept stable for at least 1 week before Day –1 (end of the RI period) until the end of DB part (i.e., Week 4) and during the DB-WD part. The dose strength might be adjusted later on, during the SB aprocitentan part. If the highest dose of amlodipine (i.e., 10 mg) cannot be used, the reason should be documented in the eCRF. If standardized background antihypertensive therapy is interrupted by the subject for any reason, he/she must immediately inform the investigator. All interruptions must be recorded in the eCRF.

The standardized background antihypertensive therapy is supplied in blisters or bottles to cover the period up to the next scheduled visit. The subjects must be instructed to take one tablet orally o.d. irrespective of food intake every morning and not to take it on the morning of study visit days. The standardized background antihypertensive therapy will be supplied to all subjects by the sponsor and will be dispensed at the same time as the study treatment via the IRT system [see Section 5.1.4]. The protocol-mandated dispensing procedures for the standardized background antihypertensive therapy may be different in some countries depending on the number of tablets in one blister/bottle. In such a case, the detail on dispensing procedure will be provided in the site file.

Subjects are asked to return all used, partially used, and unused bottles/blisters at each visit. It must be kept in an appropriate, secure area and stored according to the conditions specified on the label. The storage condition must be explained to the subject.

Treatment adherence will be performed as study treatment, for details see Section 5.1.8.

5.2.3 Allowed concomitant therapy

Treatments considered necessary for the subject's well-being and not categorized as forbidden concomitant medications are allowed during the study and must be documented in the medical charts.

The following therapies are allowed with the provision that they have been initiated and the dose stable at least 4 weeks prior to the screening visit and that the dose is kept stable until the EOT:

- Beta blockers;
- Alfuzosin and tamsulosin (alpha-adrenergic receptor blockers) for prostatic symptoms;
- Hormonal contraceptives;
- Estrogen-replacement treatment;
- Sodium-glucose co-transporter 2 inhibitors;
- Erythropoiesis-stimulating agents;
- Psychiatric drugs;
- For selective serotonin reuptake inhibitors (SSRIs) and anxiolytics the instruction provided in the next paragraph must be followed;
- Low dose acetylsalicylic acid for prevention of cardiovascular disease.

In addition, the following therapies are allowed with the provision that they have been initiated at least 4 weeks prior to the screening visit and that the dose is kept stable until the end of DB part (i.e., Week 4):

- Non-steroidal anti-inflammatory drugs;
- SSRIs and anxiolytics (such as benzodiazepine).

After Week 4 (end of DB part) these medications can be used, if necessary, for the subject's well-being.

5.2.3.1 Antihypertensive rescue medication

In the SB aprocitentan part and DB-WD part (i.e., part 2 and part 3, respectively), if, in the investigator's opinion, the BP of a subject is not sufficiently controlled, antihypertensive rescue medication can be added according to local medical practice to the study treatment and the standardized background antihypertensive therapy, but only after confirmation of the BP value by a second measurement. The second measurement should be performed either at the next planned visit or at an unscheduled visit at the investigator's discretion. In addition, the urine analysis for detection of valsartan must confirm adherence to the standardized background antihypertensive therapy, otherwise additional antihypertensive medication should not be added.

Antihypertensive rescue medication is not allowed in the DB part of the study. Antihypertensive rescue medication must be recorded in the eCRF.

5.2.3.2 Diuretics for fluid retention

After Randomization, the dose of the existing diuretic (HCTZ) can be increased or a new diuretic can be added in the event of fluid retention judged by the investigator to be clinically relevant. The investigator's judgment should be guided by biomarkers such as subject's weight gain, NT-proBNP, and/or signs and symptoms.

The fluid retention must be reported as an AE in the eCRF. In this case fluid retention must be reported as the indication for the diuretic. If the symptom(s) of fluid retention are not tolerable the subject must discontinue the study treatment.

5.2.4 Forbidden concomitant therapy

To avoid concomitant administration of medications that would either compete with the same targeted receptors as aprocitentan, have an uncertain effect on BP, or trigger BP reduction or elevation, the following concomitant therapies are forbidden from the screening visit until the EOT visit:

- Any drug which may affect BP (except rescue and allowed medications described above), see Appendix 1;
- ERAs;
- Investigational drug, other than ID-080A301 study treatment.

If a randomized subject takes any of these forbidden medications, the investigator/delegate must contact the sponsor for further follow-up actions, including stopping/interrupting study treatment as appropriate.

For subjects who permanently discontinued study treatment the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local practice.

5.2.5 Reporting of previous / concomitant therapy in the eCRF

The generic name, start/end dates of administration, route, dose regimen, and indication will be recorded in the eCRF.

5.2.5.1 Antihypertensive therapies

All antihypertensive therapies stopped at Screening and/or ongoing at Screening will be recorded in the eCRF, i.e., start/end dates of administration, reason for discontinuation and dose regimen.

Antihypertensive treatments stopped in the last 12 months prior to Screening, start/end dates, dose regimen, and reason for discontinuation should be available in the hospital chart but will not be reported in the eCRF.

If a new antihypertensive therapy other than mandatory background therapy (i.e., the fixed combination of CCB, ARB and diuretic) and study treatment is (re-)initiated during the course of the study, the date of initiation, dose and detailed reason for (re-)initiation must be recorded in the eCRF.

5.2.5.2 Other therapies

The use of all other study-concomitant therapy (including traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) must be recorded in the eCRF.

Any other previous therapy must be recorded in the eCRF if discontinued less than 30 days prior to signing of the ICF.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint

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

Baseline is defined as the last available measurement before the start of DB treatment.

6.1.2 Secondary efficacy endpoints

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

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 SBP and DBP measured by ABPM;
- Change from Week 36 to Week 40 of DB-WD treatment in mean trough SiDBP measured by AOBPM;
- Changes from Week 36 to Week 40 of DB-WD treatment in 24 h mean SBP and DBP measured by ABPM.

6.1.3 Other efficacy endpoints

- 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;
- Changes from Week 36 to Week 38, Week 44 and Week 48 of DB-WD treatment in mean trough SiSBP/SiDBP measured by AOBPM;
- Changes from Week 36 to Week 40 in daytime and nighttime mean SBP and DBP;
- Changes from baseline to all assessed time points of DB, SB and DB-WD parts in urine albumin-to-creatinine ratio (UACR);
- Discontinuation of randomized study treatment due to confirmed grade 3 (i.e., mean SiSBP/SiDBP ≥ 180/110 mmHg, respectively) hypertension.
- Initiation of antihypertensive rescue medication in the SB aprocitentan part or DB-WD part.

6.2 Safety endpoints

- Treatment-emergent AEs;
- Treatment-emergent SAEs;
- Treatment-emergent AEs leading to premature discontinuation of study treatment;
- Treatment-emergent MACEs, defined as cardiovascular death, non-fatal MI, and non-fatal stroke [EMA 2016b]. Only those events confirmed by the CAC will be considered;

- Treatment-emergent MACE-plus, defined as cardiovascular death, non-fatal MI, non-fatal stroke and hospitalization for heart failure; only those events confirmed by CAC will be considered;
- Increase of the dose of an existing diuretic or addition of a new diuretic due to fluid retention;
- Changes from baseline to each visit up to EOS in body weight and HR;
- Treatment-emergent marked laboratory abnormalities[a] at each visit up to EOS;
- Changes from baseline to each visit up to EOS in laboratory variables;
- Changes from baseline to each visit up to EOS in 12-lead ECG variables.

[a] The selection of marked abnormalities considered for the analyses will be based on standard definitions and described in the Statistical Analysis Plan (SAP).

6.3 Pharmacokinetic endpoints

- Trough plasma concentration of aprocitentan at Week 4 of the DB part.

6.4 Biomarker endpoints

- Characterization of ET system activity biomarkers (e.g., CT-proET-1, ET-1, ET-3, renin and aldosterone) and NT-proBNP in the study population at Screening as well as at the end of RI;
- Changes from baseline to Week 4 in these biomarkers;
- Changes from baseline to time points up to Week 36 in NT-proBNP, mid-regional pro-atrial natriuretic peptide (MR-proANP) and Troponin I;
- Changes from Week 36 to time points up to Week 48 in NT-proBNP, MR-proANP and Troponin I.

6.5 Rationale for primary and secondary endpoints

Hypertension is an important public-health challenge worldwide. There is global recognition that favorable effects of antihypertensive agents on BP reduction translate into morbidity/mortality benefits, as acknowledged in the FDA's approved labels for all antihypertensive products. BP is a valid surrogate endpoint accepted by regulatory bodies for the development of antihypertensive agents [Desai 2006].

SBP is the main accepted target nowadays, especially in a population with an average age of around 61 years old and above. Landmark therapeutic clinical trials as SPRINT and PATHWAY-2 are based on SBP as the primary endpoint [Wright 2015, Williams 2015].

SBP measured by AOBPM is the primary and main secondary endpoint of this study. DBP is correlated with SBP and will be analyzed as a secondary endpoint.

The AOBPM was chosen as the method for measuring the primary efficacy endpoint and main secondary endpoint, based on the results of the recently completed Phase 2 study. AOBPM minimizes the white coat effect [Myers 2010] and allows immediate teletransmission of the BP readings and therefore offers better monitoring. In addition, AOBPM has less missing data compared to ABPM, which is known to be a burden for subjects. ABPM will be used for 24 h SBP/DBP recording as secondary endpoint.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits, their respective time windows and the assessments to be performed at each visit are listed in Table 2 and Table 3.

7.1.1 Screening/re-screening

7.1.1.1 Screening

The date of the screening visit is the date when the ICF is signed [see Section 12.3 for the informed consent procedure].

The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

If the signing of the ICF and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed.

If a study-specific procedure or assessment has been performed as part of routine assessments on the day of the screening visit prior to the subject signing the ICF, such procedure or assessment may be used and does not have to be repeated (e.g., vital signs). In such cases, it must be clear from the source documents when and for which reason the assessment was done prior to the signing of the ICF.

For convenience reasons, study-specific procedures or assessments can take place on different days/visits during the screening period.

Subjects who sign the ICF when the enrollment target has already been met may still be randomized.

7.1.1.2 Re-screening

Subjects who did not meet the criteria for participation in the study (i.e., screen failure) may be re-screened once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient time for optimization [i.e., maximal tolerated dose] of background antihypertensive medications, insufficient time window for allowed

medications, BP measurement technical issue[s]). Subjects who have switched to the standardized background antihypertensive therapy cannot be re-screened.

A new ICF must be signed prior to re-screening the subject if more than 3 months have elapsed since the first ICF signature. All screening assessments should then be repeated at the time of re-screening.

7.1.2 Placebo RI period

The RI period is a SB placebo treatment period. The study staff must not inform the subjects about the treatment they are receiving during this period.

If at any time during the RI period a subject must be discontinued from study treatment due to any reason, the end of RI visit must take place as soon as possible and no later than 7 days after the last dose of RI study treatment (i.e., placebo) and a safety FU call 30 (+ 3) days thereafter. The reason of the RI failure must be recorded in the eCRF.

7.1.3 Randomized treatment period

At end of RI visit (Day –1) all eligibility criteria for randomization must be checked [see Section 4.3]. If these criteria are met, the subject will be randomized the following day.

In case of premature discontinuation of randomized study treatment, the EOT visit must take place as soon as possible and no later than 7 days after the last dose of randomized study treatment and a safety FU visit 30 (+ 3) days thereafter.

Subjects who prematurely discontinue randomized study treatment for any reason will not be replaced.

7.1.4 Unscheduled visits

Unscheduled visits may be performed at any time during the study and corresponding data will be recorded in the eCRF. Body weight, BP, and HR must be measured and recorded in the eCRF at each unscheduled visit. These assessments are not required in case of re-test of laboratory parameters only. PK and biomarker sampling must not be performed during unscheduled visits unless the reason for this unscheduled visit is to retest NT-proBNP for confirmation of eligibility criterion at screening. Other assessments are performed at the discretion of the investigator.

After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

Table 2 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[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. See Section 7.1.4 for details.
[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). For subjects who do not fulfill Run-in eligibility criteria no urine sample to be collected.
[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), see Section 7.2.5 for details.
[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 central laboratory and one sample for local laboratory to measure hemoglobin, creatinine (to determine eGFR), and AST/ALT and to perform 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; RI = run-in; SAE = serious adverse event; UACR = urine albumin-to-creatinine ratio.

Table 3 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. See Section 7.1.4 for details.
[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), see Section 7.2.5 for details.
[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; EOT = End-of-Treatment; HR = heart rate; NT-proBNP = N-terminal pro-brain natriuretic peptide; PK = pharmacokinetic(s); RI = run-in; SAE = serious adverse event; UACR = urine albumin-to-creatinine ratio.

7.2 Study assessments

The study assessments are listed in Table 2 and Table 3. The assessments that are mandatory during a visit are marked with an 'X'.

All study assessments performed during study visits (scheduled or unscheduled) are to be done by the investigator/delegate and are recorded in the eCRF, unless otherwise specified.

The following order of assessments is recommended:

- Date and time of the last study treatment and standardized background antihypertensive therapy intake (i.e., the day prior to each study visit),
- AOBPM and HR measurements at trough[a];
- Blood sampling including PK and biomarker samples at trough[a];
- Urine sampling including sampling for drug monitoring at trough[a];
- Physical examination (including assessment of AEs/SAEs), and body weight;
- ECG;
- Start ABPM;
- Intake of the study treatment and standardized background antihypertensive therapy at the site in the presence of the study staff.

[a] Before taking the study treatment and the standardized background antihypertensive therapy.

If the Principal Investigator (PI) delegates any study procedure/assessment for a subject (e.g., ECG, blood / urine sampling) to an external facility, he/she should inform the sponsor to whom these tasks are delegated. The set-up and oversight will be agreed upon with the sponsor. The supervision of any external facilities remains the responsibility of the PI.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the screening of the first subject:

- BP monitoring devices (i.e., AOBPM and ABPM);
- Body weight scale;
- ECG devices;
- Temperature measurement devices for study treatment storage area and laboratory sample storage (e.g., freezer);
- Calibration certificates of other equipment must be available as per local requirements.

7.2.1 Baseline demographics and disease characteristics

Demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, ethnicity (if allowed in the country), weight and height. Relevant medical history / current medical conditions (e.g., chronic and ongoing acute conditions, serious past conditions) present before signing of the ICF will be recorded in the eCRF. In particular, the following conditions must be considered: DM, angina pectoris, heart failure, CKD, obstructive sleep apnea syndrome. Where possible, main diagnoses, instead of symptoms, will be recorded.

7.2.1.1 Hypertension history

True RHT disease characteristics, evidenced by documentation in the subject charts, as defined below will be recorded at Screening:

- Date of first diagnosis of hypertension;
- Secondary causes of hypertension that have been excluded;
- Current antihypertensive medications; i.e., ongoing at Visit 1 and stopped or modified if required at this visit.

7.2.1.2 Data to be collected for screening failure subjects

Blood samples for biomarker evaluation must be collected. The following data will be recorded in the eCRF if available:

- Date / time of ICF signature;
- Demographics (age, sex, race and ethnicity);
- Medical history;
- Reason for screen failure and associated assessments, if applicable;
- Antihypertensive medications; i.e., ongoing at Visit 1;
- All AEs and SAEs that occur after signing the ICF;

7.2.2 Efficacy assessments

7.2.2.1 Unattended automated office blood pressure measurement (AOBPM)

Accurate measurement of BP is essential to diagnose subjects with RHT and demonstrate the BP lowering effect of aprocitentan in true RHT subjects.

Fully automated BP measurement has several advantages over manual BP measurements, especially in routine clinical practice, by virtually eliminating office-induced increases in BP (i.e., white coat effect), improving accuracy, minimizing observer error, and providing a more standardized measurement technique [Myers 2010]. Therefore, BP will be measured throughout the study with an automatic oscillometric sphygmomanometer which will be provided to each site by the central BP laboratory.

At each study visit, BP will be measured non-invasively by the provided AOBPM device, which records multiple sitting BP readings, with the subject resting undisturbed, alone (unattended) in a quiet place. At each assessment, SiSBP and SiDBP will be measured using a pre-defined number of readings with preset time interval between them (timed from the start of one reading to the start of the next one). The BP device/system generates the average of the readings for SiSBP and SiDBP.

BP must always be measured at trough (i.e., before taking the study treatment and the standardized background antihypertensive therapy) at around the same clock time. In case an unscheduled visit is performed, BP must be measured using the AOBPM device.

The AOBPM device must be managed by qualified personnel and whenever possible, the same person should use the BP device for a given subject at each visit. It should be attempted to perform BP measurements at each visit always using the same arm of the subject and the appropriate cuff size, as determined during Screening.

Details on BP procedure including device to be used, subject preparation (e.g., arm selection, arm position, cuff size) will be provided in the BP laboratory manual and will follow the American Heart Association guidelines / Canadian Education Program on Hypertension [Pickering 2005, Daskalopoulou 2012]. AOBPM data will be electronically transferred to the central BP laboratory and subsequently to the sponsor.

Standing BP measurement

BP must also be measured in the standing position to monitor orthostatic hypotension [see Section 7.2.3.1.1]. Standing SBP/DBP is measured twice, with the AOBPM device, approximately one and three minutes after standing.

Pulse rate

Pulse rate will be measured at each visit, at the same time as BP measurements, with the AOBPM device, in a sitting position. The last pulse rate measurement will be used for analysis.

7.2.2.2 Ambulatory blood pressure monitoring

ABPM is performed over a 24 h period with the ABPM device set to record BP at a pre-defined inflation sequence over the 24 h period at the following visits:

- Baseline: At the end of the SB placebo RI period, i.e., Visit 4 / Day –1.
- End of DB part: At Visit 6 / Week 4 (Day 28, ± 2 days)
- End of the SB aprocitentan part: At Visit 11 / Week 36 (Day 252, ± 12 days).
- During the DB-WD part: At Visit 13 / Week 40 (Day 280, ± 4 days)

At visits during which ABPM assessments must be performed, the subject must go to the site on 2 consecutive days. On the first day after all visit assessments have been performed, the ABPM device will be applied to the subject. Thereafter, the subject will take the study treatment at the site, in the presence of study personnel (i.e., DOT). The following day (i.e., second day), the subject will come back to site to have the ABPM device removed.

The ABPM device will be provided to each site by the central BP laboratory for the duration of the study. ABPM data will be electronically transferred to the central BP laboratory and subsequently to the sponsor.

Details on ABPM procedure (installation, recording and transfer of data) including subject preparation will be provided in the BP laboratory manual.

7.2.2.3 Home blood pressure measurement

Each site will be provided with home BP monitoring devices. These can be lent to the subjects for the entire duration of the study, upon investigator's judgment, to monitor BP at home, if necessary.

The following instructions must be given to subjects who receive a home BP device:

- Explain how to use the device to measure the BP;
- Explain to measure BP if there are severe symptoms related to hypertension like headache, vomiting, nose bleeding, or symptoms related to orthostatic hypotension e.g., light-headedness, pre-syncope, dizziness, as follows:
  - Sit in a calm place for 5 minutes
  - Measure the SBP/DBP:
    - Three readings within 5–10 minutes in the morning before taking your study medications
    - Three readings within 5–10 minutes in the evening
  - Record the SBP/DBP values, time of measurement and time of study treatment intake in the subject's card, which will be provided with the device;
  - Measure the BP as described above for 3 days in a row;
  - If the symptoms are still present on the third day, contact the site.

The data recorded by the subject at home will be filed in the hospital charts. It will not be recorded in the eCRF or transferred to the sponsor.

The subject must give back the device at the EOS.

7.2.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs and pregnancies are described in Section 9.

7.2.3.1 Vital signs

7.2.3.1.1 Orthostatic hypotension

At each study visit, standing and sitting SBP and DBP will be measured with the AOBPM device [see Section 7.2.2.1].

Symptomatic orthostatic hypotension is defined as a SBP decrease of ≥ 20 mmHg or a DBP decrease of ≥ 10 mmHg from sitting to standing position, with symptoms of cerebral hypo-perfusion (e.g., light-headedness, dizziness, pre-syncope). The last sitting BP values (SBP and DPB) measured by AOBPM are compared to the last measured standing BPs.

Symptomatic orthostatic hypotension must be recorded as an AE in the eCRF.

7.2.3.2 Physical examination

Physical examination at Screening includes the examination of the general appearance, heart, lungs, abdomen, skin, extremities/peripheral vascular assessment, eyes, ears, nose, throat, neck, and lymph nodes. At subsequent visits, physical examination includes as a minimum the examination of general appearance, heart, and peripheral vascular assessment.

Other examinations will be performed if indicated, based on medical history and/or symptoms.

Information for all physical examinations must be included in the source documentation at the study site.

The physical examination will be reported in the eCRF as either normal or abnormal; in the latter case, the investigator should specify whether it is clinically relevant. Clinically relevant physical abnormalities present at the time of signing off the ICF must be reported on the medical history form of the eCRF. Physical examination findings, which meet the definition of an AE [Section 9.1.1] and are made after signing off the ICF, must be recorded on the AE form of the eCRF.

7.2.3.3 Weight and height

Height will be measured without shoes at Screening only.

Body weight must be carefully monitored during the study since it is one of the safety endpoints. Body weight must be measured at all visits in a standardized way, as follows: subjects should always be weighed under similar conditions, e.g., same scale, similar clothing (i.e., underwear only), and similar interval between weighing and last meal. The investigator will be asked to indicate on the body weight form in the eCRF whether an increase in body weight from the previous visit is judged to be clinically relevant and whether it could be a sign of fluid retention. In addition, subjects will be instructed to

monitor their body weight at home on a weekly basis and to contact the study site if they notice an unusual weight increase since the start of the study.

Body weight and height data measured at site will be recorded in the eCRF.

7.2.3.4 ECG assessment

ECGs will be performed with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement.

The following variables will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QTc (ms) will be calculated according to Bazett's and Fridericia's formula (QTcB = QT/(RR) ½ and QTcF = QT/(RR) ⅓, respectively).

Digital 12-lead ECG devices will be provided to each site by the central ECG vendor for the duration of the study. The central ECG vendor will be used for the evaluation of all protocol-mandated ECGs, including re-tests due to ECG abnormalities and ECGs performed at unscheduled visits. The site personnel will electronically transmit the ECGs to the central ECG vendor for central reading. The reports from the central ECG laboratory will be sent to the site within a few days.

All ECG reports must be reviewed, signed and dated by the investigator/delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the ECG report whether abnormal values or findings are considered clinically relevant or not. Clinically relevant ECG findings that are known at the time of signing of the ICF must be recorded in the medical history form of the eCRF. Any clinically relevant ECG abnormalities detected after signing of ICF must be reported as an AE or SAE as appropriate [see Sections 9.1.1, 9.1.2], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

Details on ECG procedure (recording, transfer of data and reporting to the site) will be provided in the ECG manual.

7.2.3.5 Laboratory assessments

7.2.3.5.1 Type of laboratory

A central laboratory or designated laboratory (see laboratory manual for contact details) will be used for all protocol-mandated laboratory tests (except PK and urine pregnancy tests), including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

At the end of the RI period (Day –1), two samples will be drawn:

- One sample for central laboratory, and

- One sample for local laboratory: to measure hemoglobin, creatinine (to determine eGFR), AST/ALT and pregnancy test for women of childbearing potential to confirm eligibility of subject for randomization. Decision on eligibility and randomization will be based on local laboratory results. These local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF.

For other exceptional circumstances (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency, or missing central laboratory results from a scheduled or unscheduled visit), local laboratory results of the parameters described in Section 7.2.3.5.2 with the corresponding normal ranges will be entered into the clinical database via dedicated eCRF forms.

If two or more consecutive central laboratory samples are lost or cannot be analyzed for whatever reason, the investigator can collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time-window and these test results are available (in which case they must be recorded in the eCRF).

Laboratory reports will be provided by the central laboratory to the investigator/delegate. All laboratory reports must be reviewed, signed and dated by the investigator/delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of ICF must be recorded in the medical history form of the eCRF. Any clinically relevant laboratory abnormalities detected after signing of the ICF must be reported as an AE or SAE as appropriate [see Sections 9.1.1 and 9.1.2], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the sponsor and the site personnel. Alert flags that will trigger such notifications are displayed in the laboratory guidelines.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.2.3.5.2 Blood tests

The amount of blood collected from an individual subject per visit will be described in the laboratory manual.

Hematology

- Hemoglobin
- Hematocrit
- Erythrocyte count
- Reticulocyte count
- Leukocyte count with differential counts
- Platelet count
- MCV, as part of a standard complete blood count, is used along with other red blood count indices (MCH and MCHC)

Blood chemistry

- ALT, AST, Alkaline phosphatase
- Total and direct bilirubin
- Cholesterol, triglyceride, high density lipoprotein, low density lipoprotein
- Creatinine, creatine kinase
- eGFR (estimated using the CKD-EPI creatinine equation [Levey 2009])
- Uric acid
- Albumin, Protein total
- Glucose
- Sodium, potassium
- NT-proBNP [see Section 7.2.5]

7.2.3.5.3 Urinalysis

Urine samples will be collected at each visit at trough before taking the study treatment and the standardized background antihypertensive therapy according to Table 2 and Table 3. The collected urine will be transferred into a standard urine collection tube for shipment to central laboratory. Details about the collection, sampling, storage, shipment procedures, transfer and reporting of results can be found in the laboratory manual.

7.2.3.5.3.1 UACR determination

A midstream, clean-catch urine specimen will be collected for the determination of UACR (mg/g).

7.2.3.5.3.2 Study treatment adherence

Urine samples will be analyzed by a designated central laboratory for the presence of valsartan (one of the components of the standardized background antihypertensive therapy).

7.2.3.5.4 Pregnancy tests

Serum pregnancy tests for women of childbearing potential will be performed during the study according to Table 3. Serum pregnancy tests will be sent to the central lab for analysis and the result will be sent to the investigator/delegate (see laboratory manual for details on collection, sampling, storage, shipment procedures, and reporting of results). Reporting procedures of pregnancy are described in Section 9.4.1.

During the SB aprocitentan part urine pregnancy tests will be performed between scheduled visits (i.e., monthly) with approved kits provided by the site to subject at home [see Table 3]. If pregnancy is suspected, the subject must immediately contact the site and a serum pregnancy test must be performed immediately at the site. The urine kit will be provided by the central laboratory to sites. The results of the urine pregnancy tests will not be collected in the eCRF.

Reporting procedures for pregnancy are described in Section 9.4.1.

7.2.4 Pharmacokinetic assessments

Pre-dose (i.e., trough) blood samples for determination of PK will be collected for all subjects to provide information about the concentration of aprocitentan in the target population. Blood samples will be drawn at trough (before dose of study treatment and the standardized background antihypertensive therapy) as defined in Section 7.2.4.

7.2.4.1 Sampling, labeling, storage and shipment

The date and exact actual clock time of collection of each blood sample, as well as the exact dates and time of the study treatment administration (including the background therapy of CCB, ARB and diuretic) prior to and after blood draw, will be entered in the eCRF.

Details about the collection, sampling, storage, and shipment procedures can be found in the laboratory manual. Sites will receive required material from the central laboratory before the start of the study (e.g., tubes, labels, shipment materials). The site personnel will take care of the shipment of the plasma samples to central laboratory who will forward the PK samples to the Idorsia bioanalytical laboratory at time intervals agreed with the sponsor.

7.2.4.2 Bioanalysis

The analysis of aprocitentan in plasma will be performed using a validated liquid chromatography coupled to tandem mass spectrometry assay. The foreseen limit of

quantification is 5 ng/mL. The analysis will be performed by the Idorsia bioanalytical laboratory.

The PK analysis will be performed in a time interval which is covered by plasma stability. The results will not be transferred to the study team until data base lock.

The samples will be destroyed upon signature of the Clinical Study Report (CSR).

7.2.5 Biomarker assessments

At Screening, end of RI (Day –1) and at the end of the DB part 1 (Week 4), plasma/serum samples will be collected for all subjects (if allowed per local/regulatory guidelines) to explore biomarkers that reflect the ET system activity. Such biomarkers may include, but are not limited to, CT-proET-1, ET-1, ET-3, renin and aldosterone for ET system activity. These assessments will provide information whether RHT is an ET-1 driven form of hypertension, whether these biomarkers can be used to characterize the study population, and whether these biomarkers are impacted by study treatment.

In addition, the following biomarkers will be evaluated at the end of RI (Day –1), at the end of DB part 1 (Week 4), during SB aprocitentan part 2 (Week 20 and Week 36) and during DB-WD part 3 (Week 40) to explore whether aprocitentan has an effect on micro- and macrovascular complications (e.g., edema, heart overload): Such biomarkers may include, but are not limited to, NT-proBNP MR-proANP, and Troponin I. In addition to these time points NT-proBNP will also be measured at Screening (Visit 1), Visit 7 (Week 6), Visit 8 (Week 12), Visit 10 (Week 28), Visit 14 (Week 44), Visit 15/EOT (Week 48), and Visit 16/EOS (EOT plus 30 days) as part of central laboratory assessments.

Samples will be measured by a designated central laboratory at frequencies defined by the stability of the samples. Details about the collection, sampling, storage and shipment procedures can be found in the laboratory manual. If consented by the subject, the collected biomarker samples will be stored in the sponsor´s research repository, which may be used for future research on the endothelin system activity. The stored samples will be destroyed within 18 months after the completion of the study.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

For an individual subject, the study is completed as per protocol when the 48-week randomized treatment period and the 30-day safety FU period have been completed.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further

participation in all components of the study (i.e., WD of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of WD onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. WD from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study [see Section 8.3].

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual have failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted in the event the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts (date, time and type of contact made), and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three attempts at contacts (e.g., telephone calls, or e-mails) must be placed to the last available telephone number or e-mail address, and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above he/she will be considered to be lost to follow-up.

The reason for premature WD from the study must be recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator should make his/her best efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but it will not be collected in the eCRF. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If a study is prematurely suspended or terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up, as described in Section 8.4. The sponsor may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates a study without prior agreement from the sponsor, the investigator must promptly inform the sponsor personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval / favorable opinion of a study, the investigator must promptly notify the sponsor personnel and provide a detailed written explanation of the termination or suspension.

Any suspension or premature termination of the study must be discussed with the IDMC.

8.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature WD from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Safety definitions

9.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days after study treatment discontinuation), whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study (i.e., signing of informed consent).

- Abnormal assessments (e.g., change on physical examination, ECG findings), if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

9.1.2 Definition of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: Refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons
- Hospitalization for pre-planned (i.e., planned prior to signing ICF) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

9.1.3 Definition of suspected unexpected serious adverse reaction

The expectedness of an adverse reaction is determined by the sponsor in the reference safety information (RSI) section provided in the most recent version of the IB. Any SAE that is assessed as related and unexpected against the RSI is defined as a SUSAR.

9.1.4 Definition of the intensity of adverse events

The intensity of AEs is graded on a three-point scale — mild, moderate, severe — as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

A mild, moderate, or severe AE may or may not be serious [see Section 9.1.2]. Seriousness, rather than intensity assessment, determines the regulatory reporting obligations [see Section 9.3.2].

9.1.5 Relationship to study treatment

Each AE/SAE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated.

9.1.6 Relationship to study design or protocol-mandated procedure

An AE/SAE is defined as related to study design or protocol-mandated procedure if it appears to have a reasonable possibility of a causal relationship to either the study design or to a protocol-mandated procedure (e.g., discontinuation of a subject's previous treatment leading to exacerbation of underlying disease). The determination of the likelihood that the study design / a protocol-mandated procedure caused the AE/SAE will be provided by the investigator.

9.2 Time period and frequency for AE/SAE assessment and follow-up

The occurrence of an AE/SAE may come to the attention of study personnel during study visits, phone calls and interviews of study participant presenting for medical care. At each

study visit (scheduled or unscheduled), the investigator will inquire about the occurrence of AE/SAEs since the last visit.

The clinical course of AEs/SAEs will be followed according to local standard medical practices.

9.2.1 Follow-up of adverse events

AEs still ongoing at the EOS must be followed up until they are no longer considered clinically relevant or until stabilization.

9.2.2 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided.

9.3 Reporting procedures

9.3.1 Reporting of adverse events

All AEs with an onset date after signing of the ICF and up to 30 days after study treatment discontinuation must be recorded on specific AE forms of the eCRF.

Information to be collected on an AE form in the eCRF includes date of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable), as well as PI's assessment of intensity and relationship to study treatment, standardized background antihypertensive therapy, study design or protocol mandated procedures.

If the intensity of an AE worsens during the study, a new AE should be reported in the eCRF with the higher intensity. If the intensity of an AE lessens during the study, no change in the intensity is required to be reported.

Follow-up information on ongoing AE obtained after the subject's EOS visit will not be collected in the eCRF.

9.3.2 Additional reporting procedures for serious adverse events

All SAEs must be reported by the investigator to the sponsor's Global Drug Safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs occurring after signing of the ICF up to 30 days after study treatment discontinuation must be recorded on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

The SAE forms must be sent to the sponsor's Global Drug Safety department (see contact details on the SAE form). The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The sponsor's Global Drug Safety personnel may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than that of the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

Follow-up information on an ongoing SAE obtained after a subject's EOS visit must be reported to the sponsor's Global Drug Safety department, but is not recorded in the eCRF.

New SAEs occurring after the 30-day FU period must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.3.3 Additional reporting procedures for SUSAR

The sponsor will report any SUSAR [see definition in Section 9.1.3] to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.4 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued [see Section 5.1.11]. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.4.1 Reporting of pregnancy

Any pregnancy occurring in a female subject after signing of the ICF and up to 30 days after study treatment discontinuation must be reported to the sponsor's Global Drug Safety department within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the sponsor Pregnancy form, which is faxed to the sponsor's Global Drug Safety department (see contact details provided on the Pregnancy form).

The investigator must complete the pregnancy form in English.

9.4.2 Follow-up of pregnancy

Any pregnancies must be followed-up to their conclusion and the outcome must be reported to the sponsor's Global Drug Safety department.

Any AE associated with the pregnancy occurring up to the EOS visit must be reported on separate AE forms in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.3.2.

9.5 Reporting of study treatment overdose, misuse, and abuse

Study treatment overdose, misuse, and abuse will be reported as an AE only if associated with signs or symptoms.

Overdose: Administration of a dose (per intake or cumulatively) which is above the instructions provided in the protocol. When applying this definition, clinical judgment should always be applied (e.g., just because a subject took two tablets instead of one it is not "overdose" as per definition).

Misuse: Intentional and inappropriate use which is different from the instructions provided in the protocol.

Abuse: Intentional excessive use with harmful physical or psychological effects.

9.6 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the sponsor (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical studies activities from protocol conception to database closure.

In addition, an IDMC is monitoring safety data on a study level [see Section 3.3.2].

10 STATISTICAL METHODS

10.1 Analysis sets

10.1.1 Screened Set

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

10.1.2 Run-in Set

The Run-in Set (RIS) includes all subjects from the SCR who received at least one dose of SB placebo in the RI period.

10.1.3 Full Analysis Set (FAS)

The FAS includes all subjects who were randomized and have a baseline SiSBP, measured by AOBPM. In order to adhere to the intent-to-treat principle as much as possible, subjects will be evaluated according to their assigned study treatment in the DB part: aprocitentan 25 mg, aprocitentan 12.5 mg or placebo.

10.1.4 Per Protocol Set

The PPS includes all subjects from the FAS without a major protocol deviation (to be defined in the SAP).

10.1.5 Modified FAS

The modified FAS (mFAS) includes all subjects in the FAS who were re-randomized in the DB-WD part of the study and who have a Week 36 SiSBP, measured by AOBPM. Subjects will be evaluated according to their assigned study treatment in the DB-WD part: aprocitentan 25 mg or placebo.

10.1.6 ABPM FAS

The ABPM FAS (aFAS) includes all subjects from the FAS who have a baseline 24 h mean SBP, measured by ABPM. Subjects will be evaluated according to their assigned study treatment in the DB part.

10.1.7 Modified ABPM FAS

The modified ABPM FAS (maFAS) includes all subjects from the aFAS who were re-randomized in the DB-WD part of the study and who have a Week 36 24 h mean SBP, measured by ABPM. Subjects will be evaluated according to their assigned study treatment in the DB-WD part.

10.1.8 Safety Analysis Set

The Safety Analysis Set (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.

10.1.9 Modified Safety Analysis Set

The modified SAF (mSAF) includes subjects from the SAF 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.

10.1.10 Pharmacokinetic Set

The PK set includes all subjects from the FAS with at least one valid PK assessment and no major protocol deviation pertaining to PK (to be defined in the SAP).

10.1.11 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 4.

Table 4 Role of the analysis sets

Study Part	DB	SB	DB-WD
Efficacy endpoints based on AOBPM	FAS (PPS)	-	mFAS
Efficacy endpoints based on ABPM	aFAS	-	maFAS
Safety endpoints	SAF	SAF	mSAF
PK 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; mSAF = modified Safety Analysis Set; PK = pharmacokinetic(s); PPS = Per Protocol Set; SAF = Safety Analysis Set; SB = single-blind; WD = withdrawal.

The SCR and RIS will be used for subject listings.

10.2 Variables

10.2.1 Primary efficacy variable

Refer to Section 6.1.1.

10.2.2 Secondary efficacy variables

Refer to Section 6.1.2. Details for the derivation of ABPM-based endpoints are given below. The criteria for ABPM readings to be evaluable for analysis will be listed in the SAP.

- *Changes from baseline to Week 4 of DB treatment in 24 h mean SBP and DBP measured by ABPM*. At each visit the 24 h mean SBP (DBP) is derived from the area under the SBP (DBP)-time curve, divided by the time span. The area under the curve is calculated by the trapezoidal rule. Time points later than 25 hours after the first time point will be excluded from the calculation. The change from baseline to Week 4 will be obtained by subtraction.
- *Changes from Week 36 to Week 40 of DB-WD treatment in 24 h mean SBP and DBP measured by 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 Week 36 and Week 40, respectively.

10.2.3 Safety variables

Refer to Section 6.2.

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

Three null hypotheses will be tested in this study. The first two hypotheses (H_{10} and H_{20}) will be tested in parallel using the Bonferroni correction. The third 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 group, 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 group, 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 Week 36 to Week 40 in mean trough SiSBP. The alternative hypothesis H_{2a} 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 Week 36 to Week 40 in mean trough SiSBP in the placebo and aprocitentan 25 mg group, 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 the H_{10} and H_{20} has been rejected. This way the overall type I error is protected at 0.05.

10.3.2 Analysis of the primary efficacy variable

The main analysis of the change from baseline to Week 4 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 10.3.1.

10.3.2.1 Main analysis in the DB part

AOBPM measurements obtained after premature discontinuation of DB 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 approach was chosen because it is anticipated that the effect of a treatment on BP will be lost soon 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].

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, time and treatment by time interaction and covariates for baseline SiSBP and the interaction between baseline and time. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject.

Least Squares Mean (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.

10.3.2.2 Handling of missing data in the DB part

Based on the Phase 2 study, AC-080A201, it is expected that 5% of subjects will have a missing Week 4 AOBPM. Missing data will not be imputed but will be handled by the mixed model assuming that the data are missing at random (MAR).

10.3.2.3 Sensitivity analyses for missing data in the DB part

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 missing not at random (MNAR) [Mallinckrodt 2013].

Multiple imputation analyses 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.

Two control-based multiple imputation analyses will be performed under MNAR: a Jump to Reference (J2R) and a Copy Reference (CR) approach [Carpenter 2013]. In these approaches, multiple imputation 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 SiSBP for the J2R approach; baseline as well as available post-baseline SiSBP for the CR 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 resulting multiple data sets are subsequently analyzed using the same mixed model as for the main analysis Results from these analyses are combined using Rubin's methodology [Rubin 1987].

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. Further details of the sensitivity analyses are given in the SAP.

10.3.2.4 Supportive analyses in the DB part

In a supportive analysis, all AOBPM measurements obtained after premature discontinuation of DB treatment will be included in the analysis, leading to a treatment policy strategy estimand in the terminology of [ICH E9 (R1)].

10.3.2.5 Subgroup analyses in the DB part

The aim of the subgroup analyses is to explore the consistency of treatment effect in relevant subgroups:

- Age (< 65 years vs ≥ 65 years),
- Sex (male/female),
- Race (Black, Caucasian, Other),
- Region (to be defined in the SAP),
- UACR at randomization visit (< 30 mg/g, 30–300 mg/g, > 300 mg/g),

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 10.3.2.1].
- A p-value for the interaction test obtained from the mixed model for the main analysis extended with factors for the subgroup and treatment by subgroup interaction.
- 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.

10.3.3 Analysis of the key secondary efficacy variable

The main analysis for the change from Week 36 to Week 40 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 in the re-randomization (i.e., randomized treatment in the DB part). The third null hypothesis (H_{30}) will be tested as described in Section 10.3.1.

10.3.3.1 Main analysis in the DB-WD part

For the main analysis in the DB-WD part the same approach was chosen as for the DB part for the reasons given in Section 10.3.2.1. In addition, the initiation of antihypertensive rescue medication (which is allowed in this part of the study) could influence the BP of a subject [O'Neill 2012]. For this reason, AOBPM measurements obtained after premature discontinuation of DB-WD treatment or initiation of antihypertensive rescue medication in the DB-WD part will be excluded from this analysis (i.e., considered as missing), leading to a hypothetical strategy estimand in the terminology of [ICH E9 (R1)].

Changes from Week 36 to visits up to Week 48 in mean trough SiSBP will be analyzed using a mixed model with factors for stratum, treatment group, time, and treatment by time interaction, covariates for Week 36 SiSBP and the interaction between Week 36 and time and an unstructured covariance matrix.

LSM differences vs placebo for the change from 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. LSM differences and their 95% CIs for changes from Week 36 to Weeks 44 and 48 will be obtained from the same model.

10.3.3.2 Handling of missing data in the DB-WD part

It is expected that 10% of subjects in the mFAS will have a missing Week 40 AOBPM. Missing data will not be imputed but will be handled by the mixed model assuming that the missing data are MAR.

10.3.3.3 Sensitivity analyses for missing data in the DB-WD part

The impact of deviations from the MAR assumption underlying the mixed model will be investigated in sensitivity analyses under MNAR as described for the DB part [Section 10.3.2.3].

10.3.3.4 Supportive analyses in the DB-WD part

In a supportive analysis, all AOBPM measurements obtained after premature discontinuation of DB-WD treatment or initiation of antihypertensive rescue medication in the DB-WD part will be included in the analysis, leading to a treatment policy strategy estimand in the terminology of [ICH E9 (R1)]. Additionally, an Analysis of Covariance (ANCOVA) will be performed for the change from Week 36 to Week 40 imputing missing data using last observation carried forward.

10.3.3.5 Subgroup analyses in the DB-WD part

Sub-group analyses in the DB-WD part will be performed as described for the DB part [Section 10.3.2.5]. In addition, subgroups based on the initiation of antihypertensive rescue medication prior to the DB-WD part (Y/N) will be considered. Subjects without antihypertensive rescue medication are considered an enriched sub-population of the mFAS.

10.3.4 Analysis of the other secondary efficacy variables

All other secondary efficacy variables will be tested at the two-sided significance level of 0.05.

- *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 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 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 model as specified for SiSBP (main analysis) in the DB-WD part.
- *Changes from 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 Week 36.

10.3.5 Analysis of other efficacy variables

The analyses of other efficacy variables will be described in detail in the SAP.

10.3.6 Analysis of the safety variables

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

Only treatment-emergent safety data up to EOT + 30 days will be considered in tables and figures. All safety data will be included in listings based on the SCR or RI (as appropriate), with flags for safety data not considered to be treatment-emergent.

10.3.6.1 Adverse events

10.3.6.1.1 Treatment-emergent AEs

Treatment-emergent AEs will be tabulated by study part (DB, SB or DB-WD), treatment group (within study part), system organ class (SOC) and preferred terms 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 preferred term will be displayed. AEs will also be summarized by decreasing frequency of preferred term. AEs will also be tabulated by maximum intensity and relationship to aprocitentan or placebo. 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. If, however, the intensity of the AE increases in the second part it is counted in that part as well.

10.3.6.1.2 Treatment-emergent SAEs

SAEs will be summarized in a similar manner as described in Section 10.3.6.1.1.

10.3.6.1.3 AEs leading to premature discontinuation of study treatment

(S)AEs leading to premature discontinuation of study treatment will be summarized in a similar manner as described in Section 10.3.6.1.1.

10.3.6.2 Laboratory data

10.3.6.2.1 Changes from baseline and Week 36 in laboratory variables

Changes from baseline for laboratory tests to visits in the DB and SB parts (henceforth, DB+SB) will be summarized using descriptive statistics by visit and treatment group (in the DB part). Changes from Week 36 to visits in the DB-WD part 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.

10.3.6.2.2 Treatment-emergent marked laboratory abnormalities

The number (%) of subjects with laboratory abnormalities will be tabulated by study part (DB+SB and DB-WD) and treatment group (within study part). Laboratory abnormalities will be defined in the SAP.

10.3.6.2.3 Ratios to baseline and Week 36 of NT-proBNP

Ratios to baseline of NT-proBNP will be log transformed (base e) and analyzed in the DB+SB parts using a mixed model for repeated measurements with factors for treatment group (in the DB part), visit (up to Week 36) and treatment by visit interaction and covariates for baseline log (NT-proBNP) and treatment by baseline interaction. Ratios to Week 36 of NT-proBNP in the DB-WD part will be analyzed similarly, but with baseline replaced by Week 36.

10.3.6.3 Vital signs

Descriptive statistics by study part (DB+SB or DB-WD), visit and treatment group (within study part) will be provided for observed treatment-emergent values and absolute changes from baseline and Week 36 in body weight and pulse rate.

10.3.6.4 ECG

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

Treatment-emergent marked abnormalities for selected 12-lead ECG variables (HR, PR, QT, QTcB, and QTcF) will be summarized by study part and treatment group.

In addition, summaries of treatment-emergent morphological ECG abnormalities that were not present before first study treatment intake (using data from the ECG provider) will be provided.

10.3.6.5 Treatment-emergent MACE and MACE-plus

The number (%) of subjects with MACE and MACE-plus will be tabulated by study part (DB, SB or DB-WD) and treatment group (within study part). Time from Randomization to (first) MACE will also be described using a Cox model with a time-dependent covariate for treatment. Times to event will be censored at EOT + 30 days. MACE-plus will be analyzed similarly.

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

This endpoint will be analyzed similarly to MACE.

10.3.7 Analysis of other variables

A full description of all other analyses will be provided in the SAP.

10.4 Interim analyses

No interim analysis is planned for this study.

10.5 Sample size

The sample size is driven by the power for the key secondary endpoint. The within-group standard deviation for the change from Week 36 to Week 40 in mean trough SiSBP as measured by AOBPM is expected to be around 15 mmHg (based on study AC-080A201). A difference vs placebo ('delta') of at least 5 mmHg is considered clinically relevant.

With a type I error of 0.05 (two-sided; if both H_{10} and H_{20} have been rejected), the size of the mFAS needed for 90% power to detect a difference of 5 mmHg between aprocitentan 25 mg and placebo would be 380 subjects (190 in each of the two groups in the DB-WD part). The sample size is based on the t-test but provides similar power for the mixed model.

The anticipated drop-out rate is 37% in the 9 months between Randomization and start of the DB-WD part (based on the AC-080A201 study). In order to have 380 subjects in the

DB-WD part a total of 600 subjects need to be randomized (200 in each of the three groups in the DB part of the study).

For the change from baseline to Week 4 in mean trough SiSBP as measured by AOBPM (primary endpoint) the clinically relevant difference vs placebo is around 6 mmHg. With 200 subjects per group in the DB part, the power to detect this difference is well over 90%.

Table 5 Power to detect a treatment difference for the primary endpoint

Delta (mmHg)	5.5	6.0	6.5
Power (alpha=0.025 two-sided)	92%	96%	98%

In case only one of the two doses in the DB part is statistically significantly better than placebo on the primary endpoint, the secondary endpoint must be tested at alpha=0.025 (two-sided). In that case the power for the DB-WD part is 84%. However, testing at alpha=0.025 is less likely than testing at alpha=0.05 (under the assumptions made in the sample size calculations the probabilities are approximately 80% and 20%, respectively). On average, the power for the DB-WD part is approximately 88%.

If the drop-out rate is greater than anticipated the sample size may be increased in order to ensure sufficient power for the DB-WD part. The sample size will not be decreased below 600.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timelines of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture. The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to the sponsor and any vendors or CROs, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other personal identifier. The investigator/delegate must keep a subject identification code list at the site, showing the screening/randomization number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to the sponsor, any vendor or CROs, and must be kept in strict confidence by the investigator/delegate.

11.3 Database management

eCRFs will be used for all subjects. The investigators will have write access to the site eCRF data until the database is locked. Thereafter, they will have read-only access, until they receive an electronic copy of the site eCRFs. The eCRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by the sponsor personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the issue and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database lock.

Laboratory samples, ECGs, AOBPM and ABPM will be processed through a central laboratory or vendor and the results of the randomized subjects will be electronically sent to the sponsor.

AEs and medical history are coded according to the latest MedDRA™ version used by the sponsor. Medications are coded according to the latest WHO Drug Dictionary version used by the sponsor.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made as described in the

appropriate sponsor QS docs. After database lock, the investigator will receive the CRFs of the subjects of his/her site (including the audit trail) as a portable document format file.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

The sponsor personnel and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the "Declaration of Helsinki", and with the laws and regulations of the country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board (IEC/IRB)

The investigator will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the site study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual subject participating in this study and/or his/her legally designated representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject to consider his or her decision to participate in the study and it shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

The ICF will be provided in the country local language(s).

Site personnel authorized (according to local regulation) to participate in the consent process and/or to obtain consent from the subject will be listed on the Delegation of Authority form.

The subject and authorized site personnel listed on the Delegation of Authority form must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

The informed consent process must be fully documented in the subject's medical records. This must include at a minimum the study reference, the subject number, the date and, if applicable, time when the subject was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional person present during the consent process (e.g., subject's family member[s]), and the information that a copy of the signed ICF was given to the subject.

12.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform the sponsor or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to the sponsor or (overruling) local requirements.

All protocol deviations will be reported in the CSR. IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

12.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. Several attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into two different categories of documents: ISF and subjects' source documents.

These records must be kept by the investigator for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided with personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The print-outs must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per the sponsor instructions. If it were not possible for the

CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

12.8 Monitoring

Prior to study start, at a site, all required approvals must be obtained. A site initiation visit (SIV) will be performed after the required essential study documents are approved by the sponsor. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV to assess the use of the eCRF.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. The sponsor monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data-collection times.

The PI must ensure that the eCRF is completed after a subject's visit (site visit or telephone call), and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. If a site does not enroll any subjects, the close-out visit may be performed prior to study closure at the discretion of the sponsor.

12.9 Investigator Site File

Each site will be provided with an ISF prior to the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of content listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. The ISF must be kept by the site for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), ICH-GCP and national and/or international regulations, whichever would be the longest period. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform the sponsor.

If the PI changes or if the site relocates the CRA must be notified as soon as possible.

12.10 Audit

The sponsor representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to the sponsor requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

12.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform the sponsor (usually via the CRA) that such a request has been made.

The investigator and site personnel must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

12.12 Reporting of study results and publication

The sponsor will post the key elements of this protocol and the summary of results within the required timelines on publicly accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by the sponsor's representatives and the Coordinating Investigator.

In accordance with the Good Publication Practices and ethical practice as outlined in internationally recognized guidance documents (e.g., European Medical Writers Association, American Medical Writers Association, International Society for Medical Publication Professionals), the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, the sponsor may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

13 REFERENCES

[D-18.046] A single-center, double-blind, randomized, placebo-controlled, two-way crossover study to evaluate potential body weight increase induced by fluid retention after administration of ACT–132577 in healthy male subjects on a high-sodium diet. Idorsia Pharmaceuticals Ltd; Clinical Study Report AC-080-102. Report in preparation.

[Aprocitentan IB] Investigator's Brochure for aprocitentan, version 5. Idorsia Pharmaceuticals Ltd; March 2018.

[Bangalore 2014] Bangalore S, Fayyad R, Laskey R, Demicco DA, Deedwania P, Kostis JB, et al. Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. Am J Med. 2014;127:71–81.

[Bhatt 2014] Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Eng J Med. 2014;370:1393–401.

[Cai 2017] Cai A, Calhoun DA. Resistant Hypertension: An Update of Experimental and Clinical Findings. Hypertension. 2017 Jul; 70(1):5–9.

[Calhoun 2008] Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant Hypertension: Diagnosis, Evaluation and Treatment. A Scientific Statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 2008:51:1403–19.

[Carpenter 2013] Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. Journal of Biopharmaceutical Statistics 2013;23:1352–71.

[Chobanian 2003] Chobanian AV, Backris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr,et al. National Heart Lung and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560–72.

[Chrysant 1979] Chrysant SG, Danisa K, Kem DC, Dillard BL, Smith WJ, Frohlich ED. Racial differences in pressure, volume and renin interrelationships in essential hypertension. Hypertension. 1979;(2):136–41.

[Daskalopoulou 2012] Daskalopoulou SS, Khan NA, Quinn RR, et al. The 2012 Canadian Hypertension Education Program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. Can J Cardiol 2012;28:270–87.

[Daugherty 2012] Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012 Apr 3;125(13):1635–42.

[Davenport 2016] Davenport AP, Hyndman KA, Dhaun N, Southan C, Kohan DE, Pollock JS, et al. Endothelin. Pharmacol 2016;68:357–418.

[De Nicola 2013] De Nicola L, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, et al. Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. J Am Coll Cardiol. 2013;61(24):2461–7.

[DeFelice 2008] DeFelice A, Willard J, Lawrence J, Hung J, Gordon MA, Karkowsky A, et al. The risks associated with short-term placebo-controlled antihypertensive clinical trials: a descriptive meta-analysis. J Hum Hypertens. 2008;22(10):659–68.

[Denolle 2014] Denolle T, Chamontin B, Doll G, Fauvel JP, Girerd X, Herpin D, et al [Management of resistant hypertension. Expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology]. Presse Med.2014;43:1325–31. French

[Desai 2006] Desai M, Stockbridge N, Temple R. Blood pressure as an example of a biomarker that functions as a surrogate. AAPS J. 2006;8(1):146–52.

[Dhaun 2008] Dhaun N, Goddard J, Donald E, Pollock DM, Schiffrin EL, Webb DJ. Role of Endothelin-1 in Clinical Hypertension – 20 Years on. Hypertension. 2008;52: 452–59.

[EMA 2016a] European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev.4), 23 June 2016. [accessed on 8 March 2018]. Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500209943

[EMA 2016b] European Medicines Agency. Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015) 25 February 2016. [accessed 8 March 2018]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203804.pdf

[Ergul 1996] Ergul S, Parish DC, Puett D, Ergul A. Racial differences in plasma endothelin-1 concentrations in individuals with essential hypertension. Hypertension. 1996;28(4):652–5.

[Gaddam 2008] Gaddam KK, Nishizaka MK, Pratt Ubunama MN, Pimenta E, Aban I, Oparil S, et al. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. Arch Intern Med. 2008;168(11):1159–64.

[Go 2013] Go AS, Mozzaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke statistics - 2013 update: a Report from the American Heart Association. Circulation 2013;127:e6-e245.

[ICH E9 (R1)] International Council for Harmonisation Guideline E9 (R1) Estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf

[Juurlink 2004] Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543–51.

[Kassel 2015] Kassel LE, Odum LE. Our Own Worst Enemy: Pharmacologic Mechanisms of Hypertension. Adv Chronic Kidney Dis. 2015 May;22(3):245–52.

[Kellum 2013] Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a kdigo summary (Part 1). Crit Care 2013 4;17(1):204.

[Kohan 2011] Kohan DE, Rossi NF, Inscho EW, Pollock DM. Regulation of blood pressure and salt homeostasis by endothelin. Physiol Rev 2011;91(1):1–77.

[Krogager 2017] Korgager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. Eu Heart J 2017;38:104–12.

[Kumbhani 2013] Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC, Crowley K, et al. Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. Eu Heart J. 2013;34(16):1204–14.

[Lancet 1981] Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Report of Medical Research Council Working Party on Mild to Moderate Hypertension. Lancet. 1981;12;(8246):539–43.

[Leung 2017] Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33(5): 557–76.

[Levey 2009] Levey AS, Cattran D, Friedman A, Miller WG, Sedor J, Tuttle K, et al. Proteinuria as a Surrogate Outcome in CKD: Report of a Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J kidney Diseases 2009;54:205–26.

[Lim 2012] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–60.

[Luft 1979] Luft FC, Grim CE, Fineberg N, Weinberger MC. Effects of volume expansion and contraction in normotensive whites, blacks, and subjects of different ages. Circulation. 1979 Apr;59(4):643–50.

[Mallinckrodt 2013] Mallinckrodt C, Roger J, Chuang-stein C, Molenberghs G, Lane PW, O'Kelly M. Missing data: turning guidance into action. Statistics in Biopharmaceutical Research 2013;4:369–82.

[McCormack 2013] McCormack T, Arden C, Begg A, Caulfield M, Griffith K, Williams H. Optimising hypertension treatment: NICE/BHS guideline implementation and audit for best practice. Br J Cardiol. 2013;20(suppl 1):S1–S16.

[Myat 2012] Myat A, Redwood SR, Qureshi AC, Spertus JA, Williams B. Resistant hypertension. BMJ 2012;345:e7473.

[Myers 2010] Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. et al. Measurement of blood pressure in the office recognizing the problem and proposing the solution. Hypertension. 2010;55:195-200.

[O'Neill 2012] O'Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: an FDA perspective on the importance of dealing with it. Clin Pharmacol Ther. 2012 Mar;91(3):550–4.

[Oparil 2015] Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res. 2015 Mar 13;116:1074–95.

[Palmer 2002] Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med 2002;347(16):1256–61.

[Pellicori 2017] Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, Zhang J, et al. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? Eur J Heart Fail. 2017 Jun;19(6):768–78.

[Pickering 2005] Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals part 1: Blood pressure measurement in humans, a statement for professionals from the subcommittee of professional and public education of the American Heart Association council on high blood pressure research. Circulation. 2005;111: 697–716.

[Poulter 2015] Poulter NR, Prabhakaran D, Caulfield M. Hypertension. Lancet. 2015;386:801–12.

[Ratitch 2013] Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models in SAS. Pharmaceutical Statistics 2013;12:337–47.

[Rimoldi 2013] Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: when, who, and how to screen? Eur Heart J. 2014 May 14; 35(19):1245–54.

[Rossignol 2015] Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, et. al. The double challenge of resistant hypertension and chronic kidney disease. Lancet. 2015;386(10003):1588–98.

[Rubin 1987] Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons, Inc. USA; 1987.

[Schiffrin 1998] Schiffrin EL. Endothelin and endothelin antagonists in hypertension. J Hypertens. 1998;16(12 Pt 2):1891–5.

[Sheppard 2017] Sheppard JP, Martin U, McManus RJ. Diagnosis and management of resistant hypertension. Heart 2017;103:1295–302.

[Solini 2014] Solini A, Zoppini G, Orsi E, Fondelli C, Trevisan R, Vedovato M, et al. Resistant hypertension in patients with type 2 diabetes: clinical correlates and association with complications. J Hypertens. 2014;32(12):2401–10.

[Strauss 1951] Strauss MB, Davies RK, Rosembaum JD, Rossmeisl EC. Water diuresis produced during recumbency by the intravenous infusion of isotonic saline solution. J Clin Invest 1951:30;862–8.

[Thomopoulos 2016a] Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens. 2016 34(10):1921–32.

[Thomopoulos 2016b] Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering treatment in hypertension: 8. Outcome reductions vs. discontinuations because of adverse drug events - meta-analyses of randomized trials. J Hypertens. 2016;34(8):1451–63.

[Tsioufis 2014] Tsioufis C, Kasiakogias A, Kordalis A, Dimitriadis K, Thomopoulos C, Tsiachris D, et al. Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study. J Hypertens 2014;32:415–22.

[Václavík 2011] Václavík J, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension 2011;57(6):1069–75.

[Weber 2009] Weber MA, Black H, Bakris G, Krum H, Linas S, Weiss R, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomized, double-blind, placebo-controlled trial. Lancet. 2009;347:1423–31.

[Weber 2014] Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community. J Clin Hypertens. 2014;16(1):14–26.

[Whelton 2017] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13 PMID: 29133356. ePub ahead of print.

[White 2014] White WB, Turner JR, Sica DA, Bisognano JD, Calhoun DA, Townsend RR, et al. Detection, evaluation, and treatment of severe and resistant hypertension: Proceedings from an American Society of Hypertension Interactive Forum held in Bethesda, MD, USA, October 10th 2013. J Am Soc Hypertension. 2014;8(10);743-57.

[Williams 2012] in BMJ 2012;345:e7473 doi: 10.1136/bmj.e7473 (Published 20 November 2012).

[Williams 2015] Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059–68.

[Williams 2018] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Aziz M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021–3104.

[Wright 2015] Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103–16.

14 APPENDICES

Appendix 1 Forbidden drugs

A) Medication which may affect BP:

- Inhibitors of vascular endothelial growth factor such as bevacizumab, or tyrosine kinase inhibitors such as sunitinib and sorafenib,
- Immunosuppressive agents: cyclosporine and tacrolimus (topical applications of tacrolimus are permitted),
- Sympathomimetics (any formulation),
    - Intermittent (not daily) use of topical (nasal/inhalers/drops) decongestants is permitted, except within 3 days prior to a study visit.
- Diet pills: phenylpropanolamine and sibutramine,
- Stimulants: amphetamines and cocaine (topical applications for local anesthesia are permitted),
- Herbal supplements: ephedra, ma huang, Yohimbine,
- Systemic corticosteroids (topical nasal/inhalers/drops/local injection applications are permitted),
- CYP17A1 inhibitors such as abiraterone,
- Phosphodiesterase type 5 inhibitors: except intermittent (not daily) use of sildenafil, vardenafil or tadalafil (e.g., [redacted]®, [redacted]®, [redacted]®) within 5 days prior to a study visit,
- Licorice.

For details information, please refer to Kassel et al [Kassel 2015].

B) Antihypertensive therapies except standardized background antihypertensive therapy, rescue medication including diuretics, and diuretics for treatment of clinically relevant fluid retention [see Section 5.2.2, 5.2.3.1, and 5.2.3.2], such as:

- Drugs that target the renin-angiotensin system;
    - ACEIs (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindropril, quinapril, ramipril, trandolapril).
    - ARBs (e.g., azilsartan, candesartan, eprosartan, ibresartan, losartan, olmesartan, telmisartan).

- Direct renin inhibitor (e.g., aliskiren).

- Diuretics;
  - Thiazide and thiazide like diuretics (e.g., bendrofluazide, bendroflumethiazide, chlorthalidone, hydroflumethiazide, indapamide, methylclothiazide, metolazone, polythiazide),
  - Loop diuretics (e.g., bumetanide, furosemide, piretanide, torsemide),
  - Potassium-sparing diuretics (e.g., amiloride, eplerenone, spironolactone, triamterene).

- CCBs;
  - Dihydropyridines (e.g., felodipine, isradipine, nicardipine, nifedipine, nitrendipine, nisoldipine).
  - Non dihydropyridines (e.g., diltiazem, verapamil).

- Alpha-adrenergic receptors blockers (e.g., doxazosin, phenoxybenzamine, phentholamine, prazosin, terazosin), with the exception of alfuzosin and tamsulosin for prostatic symptoms [see Section 5.2.3],
- Vasodilators (e.g., hydralazine, minoxidil),
- Central alpha-agonists (e.g., clonidine, clonidine patch, guanfacine, methyldopa, rilmenidine),
- Adrenergic depleters (e.g., reserpine).

C) ERAs (e.g., bosentan, macitentan, ambrisentan).

For detailed information, please refer to American Society of Hypertension guidelines [Weber 2014].