Protocol

AC-080A201

Multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2)

ClinicalTrials.gov Identifier: NCT02603809

This study was sponsored by Actelion Pharmaceuticals - study sponsorship was transferred to Idorsia Pharmaceuticals Ltd.

ACT-132577

Essential Hypertension

Protocol AC-080A201

Multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2)

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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment number

ACT-132577

Indication

Essential hypertension

Protocol number, study title

AC-080A201, Multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2).

I approve the design of this study.

TITLE	NAME	DATE	SIGNATURE
Clinical Trial Physician	[redacted]		
Clinical Trial Statistician			

INVESTIGATOR SIGNATURE PAGE

Treatment number

ACT-132577

Indication

Essential hypertension

Protocol number, study title

AC-080A201, Multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2).

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (eCRF), 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. I will obtain approval by an Institutional Review Board or Independent Ethics Committee (IRB/IEC) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB/IEC and ensure approval by regulatory authorities (if applicable) have been obtained before the implementation of changes described in the amendment. I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

	Country	Site number	Town	Date	Signature
Principal Investigator				_____	_____

TABLE OF CONTENTS

SPONSOR CONTACT DETAILS 2

ACTELION CONTRIBUTORS TO THE PROTOCOL 2

CONTRACT RESEARCH ORGANIZATIONS INFORMATION 3

LIST OF ABBREVIATIONS AND ACRONYMS 13

SUBSTANTIAL GLOBAL AMENDMENT 2 16

PROTOCOL SYNOPSIS AC-080A201 21

1 BACKGROUND 31

1.1 Indication 31
1.2 Study treatment(s) 32
1.2.1 Phase 1 studies 32
1.3 Purpose and rationale of the study 34

2 STUDY OBJECTIVES 34

2.1 Primary objective(s) 34
2.2 Secondary objectives 34
2.3 Other objectives 34

3 OVERALL STUDY DESIGN AND PLAN 35

3.1 Study design 35
3.2 Study design rationale 37
3.3 Study committees 38

4 SUBJECT POPULATION 38

4.1 Subject population description 38
4.2 Rationale for the selection of the study population 38
4.3 Inclusion criteria 38
4.4 Exclusion criteria 39
4.5 Criteria for women of childbearing potential 41
4.5.1 Definition of childbearing potential 41
4.5.2 Acceptable methods of contraception 41
4.6 Medical history 42

5 TREATMENTS 42
5.1 Study treatment 42
5.1.1 Investigational treatment: description and rationale 42
5.1.2 Comparator(s): description and rationale 43
5.1.3 Placebo: description and rationale 43
5.1.4 Study treatment administration 43
5.1.4.1 Run-in period (single-blind placebo) 44
5.1.4.2 Double-blind treatment period 44
5.1.4.3 Withdrawal period (single-blind placebo) 44
5.1.5 Treatment assignment 45
5.1.6 Blinding 45
5.1.7 Unblinding 46
5.1.7.1 Unblinding for final analyses 46
5.1.7.2 Unblinding for SUSARs 46
5.1.7.3 Emergency procedure for unblinding 46
5.1.8 Study treatment supply 47
5.1.8.1 Study treatment packaging and labeling 47
5.1.8.2 Study treatment distribution and storage 47
5.1.8.3 Study treatment dispensing 47
5.1.8.4 Study treatment return and destruction 47
5.1.9 Study treatment accountability and compliance with study treatment 47
5.1.9.1 Study treatment accountability 47
5.1.9.2 Study treatment compliance 48
5.1.10 Study treatment dose adjustments and interruptions 48
5.1.11 Premature discontinuation of study treatment 49
5.1.12 Study-specific criteria for interruption / premature discontinuation of study treatment 50
5.2 Previous and concomitant therapy 52
5.2.1 Definitions 52
5.2.2 Reporting of previous/concomitant therapy in the eCRF 52
5.2.3 Allowed concomitant therapy 52
5.2.4 Forbidden concomitant therapy 53

6 STUDY ENDPOINTS 53
6.1 Efficacy endpoints 53
6.1.1 Primary efficacy endpoint(s) 53
6.1.2 Secondary efficacy endpoints 53
6.1.3 Other efficacy endpoints 54
6.2 Safety endpoints 54

6.3 Pharmacokinetic and pharmacodynamic endpoints 55
6.3.1 Pharmacokinetic endpoints 55
6.3.2 Pharmacodynamic endpoints 55

7 STUDY ASSESSMENTS 55

7.1 Screening/baseline assessments 56
7.2 Efficacy assessments 57
7.2.1 Blood pressure measurement 57
7.2.1.1 Office blood pressure measurement 57
7.2.2 Home blood pressure measurement 58
7.2.3 Ambulatory blood pressure monitoring 58
7.3 Safety assessments 59
7.3.1 Vital signs 59
7.3.1.1 Orthostatic hypotension 59
7.3.1.2 Heart rate 59
7.3.2 Weight and height 59
7.3.3 ECG assessments 60
7.3.4 Physical examination 60
7.3.5 Laboratory assessments 60
7.3.5.1 Type of laboratory 60
7.3.5.2 Laboratory tests 61
7.4 Pharmacokinetic and pharmacodynamic assessments 63
7.4.1 Blood sampling 63
7.4.2 Labeling and shipment 64
7.4.3 Bioanalysis 64

8 SCHEDULE OF VISITS 64

8.1 Screening and run-in periods 65
8.1.1 Visit 1 / Week –6 65
8.1.2 Visit 2 / Week –4 67
8.1.3 Visit 3 / Week –1 68
8.1.4 Visit 4 / Day –1 to Day 1 69
8.1.4.1 Day –1 (Visit 4 / Pre-randomization) 69
8.2 Double-blind period 70
8.2.1 Day 1 (Visit 4 / Randomization) 70
8.2.2 Visit 5 / Week 2 70
8.2.3 Visit 6 / Week 4 71
8.2.4 Visit 7 / Week 8 DB-EOT 72
8.2.4.1 Visit 7 / Part 1 72
8.3 Withdrawal period 72

8.3.1 Visit 7 / Part 2 72
8.3.2 Visit 8 / Week 10 withdrawal EOT 73
8.4 Premature End-of-Treatment visit (Visit 9) 73
8.5 Follow-up period 74
8.6 Unscheduled visits 74

9 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE 75

9.1 Study completion 75
9.2 Premature withdrawal from study 75
9.3 Premature termination or suspension of the study 76
9.4 Medical care of subjects after study completion / withdrawal from study 76

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS 77

10.1 Adverse events 77
10.1.1 Definitions of adverse events 77
10.1.2 Intensity of adverse events 78
10.1.3 Relationship to study treatment 78
10.1.4 Adverse events associated to study design or protocol-mandated procedures 79
10.1.5 Reporting of adverse events 79
10.1.6 Follow-up of adverse events 79
10.2 Serious adverse events 79
10.2.1 Definitions of serious adverse events 79
10.2.1.1 Serious adverse events 79
10.2.2 Reporting of serious adverse events 80
10.2.3 Follow-up of serious adverse events 80
10.2.4 After the 30-day follow-up period 80
10.2.5 Reporting procedures 80
10.3 Pregnancy 81
10.3.1 Reporting of pregnancy 81
10.3.2 Follow-up of pregnancy 81
10.4 Study safety monitoring 81

11 STATISTICAL METHODS 82

11.1 Analysis sets 82
11.1.1 Screened Analysis Set 82
11.1.2 Full Analysis Set 82
11.1.3 Per-Protocol Set 82

11.1.4 Safety Set 82
11.1.5 Pharmacokinetic Set 82
11.1.6 Usage of the analysis sets 82
11.2 Variables 83
11.2.1 Primary efficacy variable(s) 83
11.2.2 Secondary efficacy variables 83
11.2.3 Other efficacy variables 83
11.2.4 Safety variables 83
11.2.5 Other variables 84
11.2.5.1 Pharmacokinetic variables 84
11.2.5.2 Pharmacodynamic variables 84
11.3 Description of statistical analyses 84
11.3.1 Overall testing strategy 84
11.3.2 Analysis of the primary efficacy variable(s) 85
11.3.2.1 Hypotheses and statistical model 85
11.3.2.2 Handling of missing data 85
11.3.2.3 Main analysis 85
11.3.2.4 Supportive/sensitivity analyses 86
11.3.2.5 Subgroup analyses 87
11.3.3 Analysis of the secondary efficacy variable(s) 87
11.3.4 Analysis of the other efficacy variables 88
11.3.5 Analysis of the safety variable(s) 88
11.3.5.1 Adverse events 88
11.3.5.2 Laboratory parameters 89
11.3.5.3 12-lead ECG 90
11.3.5.4 Vital signs and body weight 90
11.3.6 Analysis of other variable(s) 90
11.4 Interim analyses 90
11.5 Sample size 90
11.5.1 Sample size justification 90
11.5.2 Sample size sensitivity 91
11.5.3 Blinded sample size re-estimation 92

12 DATA HANDLING 93

12.1 Data collection 93
12.2 Maintenance of data confidentiality 94
12.3 Database management and quality control 94

13 PROCEDURES AND GOOD CLINICAL PRACTICE 95

13.1 Ethics and Good Clinical Practice 95

13.2 Independent Ethics Committee / Institutional Review Board 95
13.3 Informed consent 95
13.4 Compensation to subjects and investigators 96
13.5 Protocol adherence/compliance 96
13.6 Protocol amendments 97
13.7 Essential documents and retention of documents 97
13.8 Monitoring 98
13.9 Investigator site file 99
13.10 Audit 99
13.11 Inspections 100
13.12 Reporting of study results and publication 100

14 REFERENCES 102

15 APPENDICES 106

LIST OF TABLES

Table 1 Visit and assessment schedule 29
Table 2 Power to demonstrate a dose-response relationship with n = 70 per group (PPS) 91
Table 3 Power for the supportive ANCOVA with n = 70 per group (PPS) 91
Table 4 Sample size (PPS) needed for 80–95% power to detect a dose-response for various SDs 92
Table 5 Number and proportion of subjects in PPS and 95% CIs for the proportion at the time of the sample size re-estimation 93
Table 6 Threshold for marked laboratory abnormalities 107

LIST OF FIGURES

Figure 1 Study design 37
Figure 2 Examples of dose-response relationships 86

LIST OF APPENDICES

Appendix 1 Marked laboratory abnormalities 106
Appendix 2 Central laboratory alert flags 109
Appendix 3 Forbidden concomitant medication 110
Appendix 4 Strong CYP3A4 inhibitors and inducers (FDA guidelines for drug interaction studies, February 2012) 112

LIST OF ABBREVIATIONS AND ACRONYMS

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
BP	Blood pressure
CCB	Calcium channel blocker
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRO	Contract Research Organization
CYP3A4	Cytochrome P450 3A4
DB	Double-blind
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
E_{max}	Maximum effect
EOS	End-Of-Study
EOT	End-Of-Treatment
ERA	Endothelin receptor antagonist
ET	Endothelin
ET_A	Endothelin type A receptor
ET_B	Endothelin type B receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LDH	Lactate dehydrogenase
MCP-Mod	Multiple Comparison Procedure – Modeling
MCT	Multiple Contrast Test
MedDRA	Medical Dictionary for Regulatory Activities
o.d.	Once a day
OBPM	Office blood pressure measurement
PD	Pharmacodynamic(s)
PDE5	Phosphodiesterase type-5
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
PT	Preferred Term
RHT	Resistant hypertension
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SB	Single-blind
SBP	Systolic blood pressure
SD	Standard deviation
SiDBP	Sitting diastolic blood pressure
SiSBP	Sitting systolic blood pressure
SIV	Site initiation visit
SOC	System Organ Class
SOP	Standard operating procedure
SSRIs	Selective serotonin reuptake inhibitors

SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent elimination half-life
TSH	Thyroid stimulating hormone
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of the normal range
WD	Withdrawal

SUBSTANTIAL GLOBAL AMENDMENT 2

Amendment rationale

This amendment applies to global protocol AC-080A201 Version 2 dated 18 November 2015. The resulting amended global protocol is Version 3 dated 30 May 2016.

The main reasons for this amendment are to:

1 Remove the requirements for systolic blood pressure (SBP) ≥ 140 mmHg from inclusion criterion 3;

2 Modify the randomization eligibility criterion 1 by reducing the requirement of diastolic blood pressure (DBP) to 90 mmHg and eliminating the delta of 5 mmHg;

3 Modify the study-specific interruption / premature discontinuation of study treatment criterion for grade 3 hypertension, by requiring a further confirmation of grade 3 hypertension;

4 Add a sample size re-estimation.

The changes are as follows:

1. The inclusion criterion 3 has been modified to:
    - Allow selection of subjects based only on DBP (i.e., mean DBP ≥ 90 mmHg) at screening, since 1) the randomization criterion is only based on DBP; and 2) the primary objective of the study is to explore the dose-response of ACT-132577 on DBP.
    - Align with the Seventh Joint National Committee and European Society of Hypertension Classification [Chobanian 2003, Mancia 2013], which classifies the blood pressure (BP) based on either SBP ≥ 140 and/or DBP ≥ 90 mmHg.
2. The randomization eligibility criterion 1 has been modified to:
    - Reduce the lower limit of the DBP in the first part of the criterion to 90 instead of 95 mmHg (i.e., "mean [sitting diastolic blood pressure] SiDBP ≥ 90 to < 110 mmHg measured by [office blood pressure measurement] OBPM", and
    - Remove the second part of the criterion: "mean SiDBP values (measured by OBPM) from Visit 3 and Visit 4 must not differ by more than 5 mmHg".

Randomization eligibility criterion 1 (including both parts of the criterion mentioned above) was initially introduced based on experience with classical standard manual OBPM, and landmark studies [e.g., Calhoun 2011].

In this study an automated office BP device (i.e., BpTRU) is used which automatically measures BP 6 times and provides the mean of 5 measurements [see Section 7.2.1.1]. This has several advantages over manual BP measurements by virtually eliminating office-induced increases in BP (white coat effect), improving accuracy, minimizing observer error, and providing a more standardized measurement technique [Myers 2010]. It is also reported that automated OBPM readings are normally 3–4 mmHg lower than manually measured BPs [Edwards 2013].

Therefore, the lower limit of DBP criterion is decreased to 90 instead of 95. This is also more in line with the definition of grade 1 and 2 hypertension (i.e., SBP ≥ 140 and/or DBP ≥ 90 mmHg) according to hypertension guidelines.

In addition, due to the above-mentioned advantages (such as improved accuracy) the automated office BP device (i.e., BpTRU) eliminates variability between BP measured at two consecutive visits. Therefore, the second part of the criterion "mean SiDBP values (measured by OBPM) from Visit 3 and Visit 4 must not differ by more than 5 mmHg" has been removed.

3. The study-specific criterion for permanent discontinuation from study treatment for hypertension is very conservative, i.e., discontinuation from study as soon as mean SBP is ≥ 180 and/or mean DBP is ≥ 110 mmHg. This criterion has been changed to allow for confirmation of the values by a second BP measurement. If the second measurement confirms the value (i.e., mean SBP ≥ 180 and/or mean DBP ≥ 110 mmHg) the subject must be permanently discontinued from study treatment.

4. The sample size for this study assumed a standard deviation (SD) for the primary endpoint (change from baseline to Week 8 in mean trough SiDBP, measured by OBPM) of 9 mmHg, based on several published studies using conventional office BP devices. With BpTRU the variability may be lower. For this reason, the SD of the primary endpoint will be estimated in a blinded fashion based on the first 100 randomized subjects and the sample size will be adjusted accordingly, while also taking into consideration the need for sufficient exposure to allow proper evaluation of the safety of the compound (e.g., fluid retention) in this indication. The number of randomized subjects is expected to be between 300 and the originally planned 540.

Additional changes have been made in order to allow more flexibility before and during the screening procedure (i.e., possibility for subjects without a confirmed diagnosis of

hypertension to undergo a pre-screening process to confirm the diagnosis of hypertension before entering the study).

The confirmation of diagnosis before screening is due to the fact that BP is measured with an automated office BP device (i.e., BpTRU) in this study, which reduces the well-known white coat effect that results in lower BP values compared to BP measured by conventional BP devices. Many subjects have been diagnosed with other less precise devices (e.g., office-based manual measurement); therefore, to reduce the burden on subjects, for the present study a confirmation of the diagnosis has been introduced before consent to participation in the study is given. This means that at pre-screening the subject will simply consent to the confirmation of diagnosis by measuring the BP with an automated office BP device. Measurements should be done at trough, in case the patient is on anti-hypertensive treatment(s). If hypertension is confirmed, the subject will then be proposed to enter the study and full consent to participation in the study will be given.

Finally some clarifications (i.e., allowed and forbidden medications) have been provided, minor errors corrected, and changes in staff accounted for.

Changes to the protocol

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

3.1	**Study design**
4.1	**Subject population description**
4.3	**Inclusion criteria**
4.4	**Exclusion criteria**
5.1.12	**Study-specific criteria for interruption / premature discontinuation of study treatment**
5.2.3	**Allowed concomitant therapy**
5.2.4	**Forbidden concomitant therapy**
8	**SCHEDULE OF VISITS**
8.1	**Screening and run-in periods**

8.1.1 Visit 1 / Week −6

8.1.2 Visit 2 / Week −4

8.1.3 Visit 3 / Week −1

8.1.4.1 Day −1 (Visit 4 / Pre-randomization)

8.2.2 Visit 5 / Week 2

8.2.3 Visit 6 / Week 4

8.2.4.1 Visit 7 / Part 1

8.3.2 Visit 8 / Week 10 withdrawal EOT

8.4 Premature End-of-Treatment visit (Visit 9)

11.5.3 Blinded sample size re-estimation

13.3 Informed consent

14 REFERENCES

Appendix 2 Central laboratory alert flags

Appendix 3 Forbidden concomitant medication

Appendix 4 Strong CYP3A4 inhibitors and inducers (FDA guidelines for drug interaction studies, February 2012)

Changes to the Informed Consent Form

- The core Informed Consent Form dated 18 November 2015 was amended to introduce detailed explanations on screening period procedure (i.e., measurement of BP at trough at Visit 1), and the procedure for costs and compensation.

- A new Informed Consent Form was created, "Diagnosis of mild-to-moderate hypertension by measuring blood pressure with an automated device".

  The establishment of the diagnosis of mild-to moderate hypertension is not part of this protocol. Only subjects who have been previously diagnosed with the disease [see Section 4.1 and Section 4.3] can enter the screening. This Informed Consent Form has been created in order to facilitate the screening procedure for subjects without a confirmed diagnosis.

Summary of previous amendments

Amendment	Date	Main reason(s)
1	18 November 2015	• A new exclusion criterion was added to the protocol to make it clearer and more explicit that "subjects with co-morbidities taking anti-hypertensive medications for reasons other than blood pressure are excluded from the study". • Harmonization of the methods of contraception in this protocol by implementing the most conservative approach.

PROTOCOL SYNOPSIS AC-080A201

TITLE	Multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2)
OBJECTIVES	**Primary objective** The primary objective of the study is to explore the dose-response of ACT-132577 on diastolic blood pressure (DBP) in subjects with essential hypertension (grade 1 and 2). **Secondary objectives** Evaluate the dose-response of ACT-132577 on: • Systolic blood pressure (SBP) • Control and response rates of blood pressure (BP) • 24-h ambulatory blood pressure monitoring (ABPM) Evaluate the safety and tolerability of a once a day (o.d) oral regimen of 4 doses of ACT-132577. **Other objectives** Other objectives are described in Section 2.3.
DESIGN	Prospective, multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study
PERIODS	**Pre-screening:** Subjects without a confirmed diagnosis of hypertension are offered the possibility of having their BP measured (at trough if subjects are on anti-hypertensive treatment) with an automated office BP device before entering the screening period. **Screening:** Visit 1 (screening period) lasts up to 72 h to allow for informed consent to be obtained and study assessments to be performed (e.g., laboratory tests) to determine whether the subject is eligible for the study. **Run-in Period (Period I)** is a single-blind (SB) placebo period of 4 to 6 weeks. It commences at the end of Visit 1 and ends at Visit 4 / Randomization (after completion of the baseline 24-h ABPM

	recording on the last dose of SB study treatment (placebo). For subjects on anti-hypertensive treatment at first visit (Visit 1) the SB placebo period is 6 weeks including a 2-week wash-out period for anti-hypertensive treatment. For anti-hypertensive treatment-naïve subjects at first visit, the SB placebo period is 4 weeks. Visit 1 is combined with Visit 2. **Treatment Period (Period II)** is a double-blind (DB) treatment period of 8 weeks which starts at Visit 4 / Randomization with the first dose of DB study treatment and ends at Visit 7 / Part 2 (after completion of 24-h ABPM recording on the last dose of DB study treatment). **Withdrawal Period (Period III)** is an SB placebo period of 2 weeks which starts at Visit 7 / Part 2 with the first dose of SB study treatment (placebo) and ends at Visit 8 (withdrawal End-of-Treatment [WD-EOT]). **Follow-up Period** starts after the last dose of withdrawal study treatment and ends at least 2 weeks thereafter, by the follow-up telephone call, or follow-up visit only for women of childbearing potential to perform a pregnancy test at the site. **End-of-Study (EOS)** for a single subject is defined as the date of the follow-up telephone call or the date of the follow-up visit. If a subject withdraws consent and does not wish to participate in further visits, the date of consent withdrawal is EOS for this subject. If a subject is declared lost to follow-up [see also Section 9.2], the date of last contact is EOS for this subject. The overall study is considered completed when all subjects have completed their safety follow-up telephone call or follow-up visit.
PLANNED DURATION	Approximately 16 months from first subject first visit (i.e., Screening Visit) to last subject last visit (i.e., 30-day follow-up telephone call / visit).

SITE(S) / COUNTRY(IES)	Approximately 100 sites in 3 to 4 countries in North America and Israel (planned).
SUBJECTS / GROUPS	Approximately 1000 subjects will be enrolled in the SB placebo run-in period, in order to have at least 540 subjects randomized in 6 groups (90 subjects per group) in a 1:1:1:1:1:1 ratio. At least 420 subjects (70 per group) are expected to complete the trial.
INCLUSION CRITERIA	This study will enroll adult male and female subjects aged 18 to 75 years with mild-to-moderate (grade 1 and 2) essential hypertension with or without ongoing anti-hypertensive treatment. Women of childbearing potential must have a negative pregnancy test at screening and randomization, and must agree to use reliable methods of contraception from Visit 1 (Screening) until up to 30 days after DB study treatment discontinuation. Eligible subjects must be able and willing to give informed consent for participation in the clinical study. For the complete list of inclusion criteria, please see Section 4.3.
EXCLUSION CRITERIA	Subjects with severe hypertension (grade 3) or secondary hypertension. Subjects with clinically relevant medical or surgical conditions that, in the opinion of the investigator, would put the subject at risk by participating in the study. For the complete list of exclusion criteria, please see Section 4.4.

STUDY TREATMENTS	**Investigational treatment** ACT-132577 5 mg, 10 mg (2 × 5 mg), 25 mg, and 50 mg administered as capsules orally o.d. in the morning irrespective of food intake during the DB treatment period. **Comparator** Lisinopril is used as active reference drug. It is administered as 20 mg capsules orally o.d. in the morning irrespective of food intake during the DB treatment period. **Placebo** Placebo matching ACT-132577 and placebo matching lisinopril capsules will be administered concomitantly orally o.d. during the SB placebo run-in period and SB placebo withdrawal period to all subjects and during the DB treatment period to those subjects who have been randomized to the placebo group.
CONCOMITANT THERAPY	**Allowed concomitant therapy** Treatments considered necessary for the subject's wellbeing and not categorized as prohibited concomitant medications are allowed during the study. Intermittent use of topical/nasal corticosteroid applications are allowed during the study. In addition, the following therapies are allowed with the provision that they have been initiated at least one month prior to the Screening visit (Visit 1) and that the dose is kept stable until the WD-EOT visit (i.e., Visit 8): • Hormonal contraceptives. • Estrogen-replacement treatment. • Non-steroidal anti-inflammatory drugs (e.g., low dose acetylsalicylic acid for prevention of cardiovascular disease). • Selective serotonin reuptake inhibitors and anxiolytics. **Forbidden concomitant therapy** The following concomitant therapies are forbidden from Screening visit (i.e., Visit 1) until the WD-EOT visit (i.e., Visit 8), see Section 5.2.4:

	• Any drug, including ophthalmic preparation, which may affect blood pressure; see Appendix 3. • Endothelin receptor antagonists and phosphodiesterase type-5 inhibitors. • Strong inhibitors or inducers of cytochrome P450 3A4 isoenzyme (CYP3A4); see Appendix 4.
ENDPOINTS	**Primary efficacy endpoint(s)** The primary efficacy variable is the change from baseline to Week 8 of DB treatment period (Period II) in mean trough sitting DBP (SiDBP), measured by office blood pressure measurement (OBPM). **Secondary efficacy endpoints** Secondary efficacy variables include (measured by OBPM, unless specified otherwise): • Change from baseline to Week 8 of DB treatment period (Period II) in mean trough sitting systolic BP (SiSBP); • Control and response rates at Week 8 of DB treatment period (Period II) based on trough SiDBP [defined as in Section 7.2.1.1]; • Control and response rates at Week 8 of DB treatment period (Period II) based on trough SiSBP [defined as in Section 7.2.1.1]; • Change from baseline to Week 8 of DB treatment period (Period II) in 24-h mean DBP, measured by ABPM; • Change from baseline to Week 8 of DB treatment period (Period II) in 24-h mean SBP, measured by ABPM; • Trough to peak ratio for DBP based on ABPM. **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Safety endpoints** • Treatment-emergent adverse events (AEs); • AEs leading to premature discontinuation of study treatment; • Treatment-emergent deaths; • Treatment-emergent serious adverse events; • Treatment-emergent ECG abnormalities;

	• Treatment-emergent marked laboratory abnormalities; • Changes from baseline to Weeks 2, 4 and 8 of DB treatment period (Period II) in laboratory parameters; • Changes from baseline to Weeks 4 and 8 of DB treatment period (Period II) in ECG parameters (PR, QRS, QT, QTcB, QTcF); • Changes from baseline to Weeks 2, 4 and 8 of DB treatment period (Period II) in body weight and heart rate. See Section 10.1.1 for definition of 'treatment-emergent'. **Pharmacokinetic/pharmacodynamic endpoints** Pharmacokinetic / pharmacodynamic endpoints are described in Section 6.3.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	The Full Analysis Set (FAS) includes all subjects randomized to a study treatment, who have a baseline mean trough SiDBP. The Per-Protocol Set (PPS) includes all subjects from the FAS who have a mean trough SiDBP at Week 8 of DB treatment period (Period II) and do not have any major protocol deviation. Major protocol deviations will be described in the Statistical Analysis Plan. The Safety Set includes all subjects who received at least one dose of study treatment in DB treatment period (Period II). **Statistical hypotheses** The null hypothesis to be tested is that there is no dose-response for the primary endpoint. H_0: $\mu_0 = \mu_1 = \mu_2 = \mu_3 = \mu_4$ Here, μ_i denotes the mean change from baseline to Week 8 in mean trough SiDBP (μ) for ACT-132577 dose (i) (where $i = 0$ corresponds to placebo). A value of $\mu_i < 0$ corresponds to a decrease in SiDBP. The alternative hypothesis is that there is a monotonic dose-response for the primary endpoint. H_1: $\mu_0 \geq \mu_1 \geq \mu_2 \geq \mu_3 \geq \mu_4$ and $\mu_i > \mu_j$ for at least one $i > j$ or $\mu_0 \leq \mu_1 \leq \mu_2 \leq \mu_3 \leq \mu_4$ and $\mu_i < \mu_j$ for at least one $i > j$

	Note that larger values of μ_i –corresponding to less decrease (or more increase) from baseline to Week 8 in mean trough SiDBP with increasing dose of ACT-132577– are less favorable. The first part of the alternative hypothesis corresponds to ACT-132577 being superior to placebo. **Type I and II errors and power** The type I error (α) is set to 0.05 (two-sided). The type II error is set to 0.10 and therefore the power to 90%. **Primary analysis** The primary analysis will be conducted on the PPS. Change from baseline to Week 8 in mean trough office SiDBP will be analyzed using the MCP-Mod approach. In brief, it consists of a set of Multiple Contrast Tests (MCTs) to establish the existence of a dose-response and a set of pre-specified dose-response models to describe the dose-response curve. Six candidate dose-response models will be considered: linear, linear in log-dose, quadratic, E_{max}, sigmoidal E_{max} and logistic. The analysis will be performed using the R-package *DoseFinding*. A dose-response relationship is demonstrated if at least one of the six MCTs has an adjusted p-value < 0.05. Supportive and sensitivity analyses will be conducted on the PPS and FAS. Change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiDBP (imputed by last observation carried forward, if applicable) will also be analyzed using an analysis of covariance model with a factor for treatment group (placebo and four doses of ACT-132577) and a covariate for baseline mean trough SiDBP. Each of the four doses of ACT-132577 will be compared to placebo applying the Dunnett's test. **Secondary analyses** Secondary efficacy variables will be analyzed for the PPS at $\alpha = 0.05$ (two-sided) using 95% confidence intervals (CIs). No correction for multiple testing will be applied for these analyses. **Safety analyses** Safety analyses will be performed on the Safety Set. Safety data will be summarized using descriptive statistics.

	Interim analysis No formal interim analysis is planned. **Sample size** In a previous study with macitentan in essential hypertension (AC-055-201) the within-group standard deviation (SD) for the change from baseline to Week 8 in SiDBP was 7.4 mmHg (90% CI: 7.0–8.0). [redacted] It is assumed that the maximum difference versus placebo is achieved at the highest dose of ACT-132577. For the sample size it was required that the power to demonstrate the existence of a dose-response relationship — conservatively assuming a maximum difference versus placebo of 4 mmHg and an SD = 9 mmHg — is 90%. A total of 70 subjects per group in the PPS (i.e., 420 subjects in total) satisfied this condition and would also allow for sufficiently precise estimation of the dose-response curve. Assuming a drop-out rate of approximately 20%, a total of 90 patients per group would need to be randomized (i.e., 540 in total). A blinded sample size re-estimation will be performed by the sponsor after 100 subjects have been randomized and their Week 8 BP data are available for analysis. The sample size will be recalculated considering the overall SD of the primary endpoint (change from baseline to Week 8 in mean trough SiDBP, measured by OBPM) in the PPS. The recalculated size of the PPS is expected to be between 280 subjects and the originally foreseen 420 subjects. The associated number of subjects to be randomized will also be re-estimated and is expected to be between 300 subjects and the originally planned 540 subjects. See Section 11.5.3 for more details.
STUDY COMMITTEES	An Independent Liver Safety Data Review Board (an external expert committee of hepatologists) provides ongoing assessment and advice regarding any hepatic events that may require further evaluation during the study.

Table 1 Visit and assessment schedule

PERIODS	Name / duration	Period I: Run-in / 4–6 weeks[6]			Period II: Double-blind / 8 weeks				Period III: withdrawal / 2 weeks		Premature EOT		Follow-up
VISITS	Number Name	1[6] Week –6	2[6] Week –4	3 Week –1	4		5 Week 2	6 Week 4	7 Week 8		8 Week 10	9	U1, 2, 3, etc.[10]	Telephone call[9] or visit[11]
	Name	Screening**			Randomization				DB-EOT		WD-EOT	Within 7 days after last study treatment intake	Unscheduled	EOS
	TIME / Week	Day –42	Day –28 (± 3 d)	Day –7 (± 4 d)	Pre-Day –1	Day 1	2 Day 14 (± 3 d)	4 Day 28 (± 3 d)	Part 1 Day 55 (± 5 d)	Part 2 Day 56	10 Day 70 (± 3 d)		Any time	30–33 d after last dose of DB treatment
Informed consent		X												
Eligibility		X	X	X	X									
Medical history		X												
Physical examination		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
HR*, body weight, height[1]		X	X	X	X		X	X	X		X	X	X	
12-lead ECG*		X[4]			X[9]			X	X		X	X[9]	X	
Laboratory incl. pregnancy tests*[2]		X[5]		X[9]	X[9]		X	X	X		X	X[9]	X	X[2]
Urinalysis			X[7, 9]		X[9]		X	X	X		X	X[9]	X	
Office BP measurement*		X	X	X	X		X	X	X		X	X	X	
Home BP device[12]		X	→											
Ambulatory BP measurement*					X				X					
PK and PD sampling[13]							X	X	X					
Compliance with study treatment			X[9]	X[9]	X		X	X	X		X	X	X	
Study treatment dispensing/return		X	X[8]		X	X		X	X	X	X	X	X	
Adverse events[3]		X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[3]		X	X	X	X	X	X	X	X	X	X	X	X	X

*Electronically transferred to sponsor.
** Visit 1 (screening) can last up to 72 h for obtaining informed consent and performing required assessments.

1. Height is only measured at Visit 1.
2. Serum pregnancy test only for women of childbearing potential. Result is transferred electronically to sponsor.
3. All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after last DB study treatment intake must be reported.
4. Historical ECG is accepted if not older than 6 months.
5. Historical blood laboratory data is accepted to check exclusion criterion 15, if not older than 3 months. In such a case, for women of childbearing potential a urine pregnancy test must be performed. If no historical report is available, a blood sample to be taken for laboratory analysis (including pregnancy test for women of childbearing potential) by central laboratory.
6. Run-in period is 4 weeks before randomization for anti-hypertensive treatment naïve subjects. Visit 1 is combined with Visit 2. Run-in period is 6 weeks before randomization for subjects on anti-hypertensive treatment. Visit 1 and Visit 2 must be performed.
7. Only urine pregnancy test for women of childbearing potential. Result is captured in the eCRF.
8. Only for subjects who were on anti-hypertensive drugs at Visit 1 (i.e., had to perform a Visit 2).
9. If subject discontinued study treatment during run-in period (i.e., between run-in visits) or at an in-person run-in visit (e.g., Visit 3), these tests may not be performed.
10. Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.
11. For women of childbearing potential a visit must be organized instead of the telephone call to perform the serum pregnancy test at the site. However, if a woman of childbearing potential discontinued study treatment during the run-in period, a follow-up telephone call can be made instead of the visit.
12. Upon investigator's judgment, a home monitoring device will be dispensed to monitor BP at home, if necessary.
13. Sample to be taken at trough (i.e., prior to study treatment intake).

AE = adverse event; BP = blood pressure; DB = double-blind; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; HR = heart rate; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; WD = withdrawal.

PROTOCOL

1 BACKGROUND

1.1 Indication

Hypertension represents a significant global public health concern and is defined in adults by (office) systolic/diastolic blood pressure (BP) ≥ 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 [Mancia 2013, Chobanian 2003].

Hypertension 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 anti-hypertensive drugs of different pharmacological classes and combinations of drugs, hypertension remains inadequately controlled in many patients. A number of these uncontrolled patients are considered to have so-called "resistant hypertension" (RHT). RHT is defined as the failure to lower (office) systolic/diastolic BP to target in patients adhering to lifestyle measures and to the optimal doses of an appropriate regimen of three anti-hypertensive drugs from different classes, including a diuretic [Calhoun 2008]. The National Health and Nutrition Examination Survey estimated prevalence of RHT is 8.9% of all adults with hypertension and 12.8% of all drug-treated hypertensive adults in the US [Persell 2011].

RHT is an important clinical problem concerning a population with high cardiovascular risks [Daugherty 2012, Kumbhani 2013, Irvin 2014]. There is still a medical need for additional pharmacological treatment acting on pathway(s) different from those classically used (renin angiotensin aldosterone blockers, sympathic system inhibitors, calcium channel blockers [CCBs], diuretics) and interfering with the RHT pathogenesis [Dhaun 2008, Oparil 2015].

Endothelin receptor antagonists (ERAs) might be of particular relevance in subjects with RHT already receiving standard anti-hypertensive therapies, since:

- Endothelin (ET)-1 is a potent vasoconstrictor that is implicated in the pathogenesis of hypertension, including the hypertension that is often associated with chronic kidney disease and the metabolic syndrome which are both known to be independent predictors of RHT development [Dhaun 2008, Moorhouse 2013].
- There is no evidence that the vasoconstrictor effects of ET at ET type A (ET_A) receptors are successfully inhibited by other agents (e.g., angiotensin-converting enzyme inhibitors and CCBs [Weber 2009, ACT-132577 IB].

1.2 Study treatment(s)

ACT-132577 is an orally active, potent dual ET_A and ET type B (ET_B) receptor antagonist. It is the active metabolite of macitentan (ACT-064992). Macitentan 10 mg (Opsumit®) is approved for the treatment of pulmonary arterial hypertension.

ACT-132577 was selected for further development in hypertension for the following reasons [ACT-132577 IB]:

- In hypertensive rats, ACT-132577 demonstrated long-lasting BP decrease after single dose administration, without heart rate (HR) increase.
- In hypertensive rats, a "synergistic" effect of ACT-132577 and the angiotensin receptor blocker valsartan on BP reduction was observed without an effect on HR.
- The BP-lowering effects were observed in different models of hypertension, with a stronger effect in volume-dependent and salt-sensitive models.

For detailed information, please see the most recent version of the ACT-132577 Investigator's Brochure (IB) [ACT-132577 IB].

1.2.1 Phase 1 studies

One Phase 1 study in healthy subjects has been clinically completed:

- A single-center, three-part study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACT-132577 in healthy male and female subjects.
  - Part A – Pilot: One group of 3 male and 3 female subjects received an oral dose of 5 mg ACT-132577 in fasted conditions in an open-label design.
  - Part B – Single Ascending Dose: Four groups of 8 subjects each (4 male and 4 female subjects) received oral doses of placebo or 25 mg, 100 mg, 300 mg, and 600 mg ACT-132577 in fasted conditions in a double-blind, randomized design. In each group, 6 subjects (3 male and 3 female subjects) received active treatment and 2 (one male and one female subject) received placebo. For the 100 mg dose group, following a 2-week washout period, subjects received the same single administration of ACT-132577 or placebo following a standardized high-fat, high-calorie breakfast.
  - Part C – Multiple Ascending Dose: In this part of the study, 3 groups of healthy male and female subjects received oral doses of 5, 25, or 100 mg ACT-132577 in fasted conditions once daily for 10 days in a double-blind, randomized design. In each group, 6 subjects (3 male and 3 female subjects) received active treatment and 2 (one male and one female subject) received placebo. The dose of 100 mg ACT-132577 once daily for 10 days was also investigated in a group of elderly healthy subjects.

The pharmacokinetic (PK) properties of ACT-132577 after single- and multiple-dosing were similar. After absorption of ACT-132577 with maximum plasma concentrations (C_{max}) reached between 3 and 9 h for the different doses, elimination is slow with an apparent elimination half-life ($t_{1/2}$) of approximately 44 h. The PK of ACT-132577 were not affected by food to a clinically relevant extent and therefore ACT-132577 can be administered with or without food. Steady-state conditions were reached by Day 8 and accumulation when compared to Day 1 was approximately 3-fold. At steady state, exposure expressed in C_{max} as well as area under the curve during a dosing interval (AUC_{τ}) were dose proportional over the tested dose range. Compared to young subjects, elderly subjects had a higher C_{max} and AUC_{τ} (1.3- and 1.2-fold that of healthy subjects respectively), which was not considered to be clinically relevant.

ET-1 concentrations increased with dose up to the highest tested dose of 100 mg ACT-123577. This dose-dependent increase was more pronounced on Day 10, when steady-state conditions of ACT-132577 were reached.

ACT-132577 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 once daily.

After single-dose administration, under fasted conditions, more subjects reported adverse events (AEs) with increasing dose. The most frequently reported AEs were headache, nausea, and postural orthostatic tachycardia, with headache reported by all subjects treated with 600 mg ACT-132577. AEs were mostly of a mild to moderate intensity, and none of those led to a discontinuation of the study. There were no relevant differences in safety findings between subjects in fed and fasted condition.

After multiple-dose administration, when compared to placebo, subjects treated with ACT-132577 reported more AEs. The most frequently reported AEs were headache, somnolence, and nasal congestion. Reporting of headache increased with dose and was not observed in subjects treated with placebo. Most AEs were of mild to moderate intensity and resolved at the end of study. One elderly female subject, treated with 100 mg ACT-132577, experienced increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 2.5 and 3.8 × upper limit of the normal range (ULN), respectively, that returned close to baseline values approximately 2.5 weeks after last dosing.

Hemoglobin showed a treatment-related decrease after both single-and multiple-dose administration. Compared to placebo and lower doses of ACT-132577, 100 mg ACT-132577 appeared to increase body weight in both healthy and healthy elderly subjects after multiple-dose treatment. No other clinically relevant findings were observed for any of the other hematology, clinical laboratory, vital signs, and ECG

parameters. No clinically relevant differences were observed when comparing healthy elderly subjects to healthy subjects.

For detailed information, please see the most recent version of the ACT-132577 IB [ACT-132577 IB].

1.3 Purpose and rationale of the study

Study AC-080A201 is a dose-finding study exploring the efficacy as well as safety and tolerability of 4 different doses of ACT-132577 in subjects with essential hypertension.

The results of study AC-080A201 will allow selection of dosages to be investigated in the Phase 3 program in RHT patients.

The dose selection of ACT-132577 is explored as monotherapy in order to identify the dose(s) with the best efficacy/tolerability ratio in a homogeneous hypertensive patient population (i.e., grade 1 and 2 essential hypertension). This approach is justified as dose recommendations of all anti-hypertensive therapies used in RHT are the same as those in uncomplicated hypertension [Weber 2014]. The sponsor does not anticipate a different efficacy/tolerability ratio for a given dose of ACT-132577 from a monotherapy to an add-on therapy situation (RHT).

2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective of the study is to explore the dose-response of ACT-132577 on diastolic blood pressure (DBP) in subjects with grade 1 or 2 essential hypertension.

2.2 Secondary objectives

- Evaluate the dose-response of ACT-132577 on:
  - Systolic blood pressure (SBP)
  - Control and response rate of BP
  - 24-h ambulatory blood pressure monitoring (ABPM).
- Evaluate the safety and tolerability of a once a day (o.d.) oral regimen of 4 doses of ACT-132577.

2.3 Other objectives

- Evaluate steady-state [redacted] plasma concentrations of ACT-132577 [redacted] in hypertensive subjects.
- Evaluate steady-state trough ET-1 in hypertensive subjects.
- Investigate the correlation between ET-1 and ACT-132577 plasma concentrations.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

Study AC-080A201 is a prospective, multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2).

Approximately 640 subjects will be enrolled into the study, in order to have at least 540 subjects randomized in the 6 following groups in a 1:1:1:1:1:1 ratio; placebo, 5 mg ACT-132577, 10 mg ACT-132577, 25 mg ACT-132577, 50 mg ACT-132577, lisinopril 20 mg. At least 420 subjects are expected to complete the trial.

The study consists of the following study periods:

Pre-screening:

Subjects without a confirmed diagnosis of mild-to-moderate hypertension are offered the possibility of having their BP measured (at trough if subjects are on anti-hypertensive treatment) with an automated office BP device before entering the screening period. These subjects must sign the "confirmation of diagnosis" Informed Consent Form (ICF) before BP measurement. If hypertension is confirmed then the subject will be proposed to enter the study.

Screening:

Screening lasts up to 72 h starting from the signature of the "study" ICF until the run-in period eligibility decision.

Run-in period (Period I)

Period I is a single-blind (SB) placebo period of 4 to 6 weeks starting at the end of Visit 1 and ends at Visit 4 Randomization (after completion of the baseline 24-h ABPM recording on the last dose of SB study treatment [placebo]).

The run-in period is 4 weeks for anti-hypertensive treatment naïve subjects at Screening (Visit 1). Visit 1 is combined with Visit 2.

The run-in period is 6 weeks for subjects on anti-hypertensive treatment at Screening (Visit 1) including a 2-week wash-out period for anti-hypertensive treatment. In such a case, anti-hypertensive treatment must be discontinued (according to its label) at Visit 1, if there is no contra-indication to stop it.

Treatment period (Period II)

Period II is a double-blind (DB) treatment period of 8 weeks which starts at Visit 4 / Randomization with the first dose of DB study treatment and ends at Visit 7 / Part 2 (after completion of the 24-h ABPM recording on the last dose of DB study treatment).

Withdrawal period (Period III)

Period III is a SB placebo period of 2 weeks which starts at Visit 7 / Part 2 with the first dose of withdrawal (WD) study treatment (placebo), and ends at Visit 8 (WD-EOT).

Follow-up period

The follow-up period starts after the last dose of SB withdrawal study treatment (placebo) and ends at least 2 weeks (i.e., 30 days after the last dose of the DB treatment) thereafter, by the follow-up telephone call, or follow-up visit only for women of childbearing potential to perform the pregnancy test at the site.

End-of-Study

End-of-Study (EOS) for a single subject is defined as the date of the follow-up telephone call or follow-up visit.

If a subject withdraws consent and does not wish to participate in the study visits, the date of consent withdrawal is EOS for this subject. If a subject is declared lost to follow-up [see also Section 9.2], date of last contact is EOS for this subject.

In addition, unscheduled visits may take place at any time during the study, in which case appropriate assessments [as specified in Table 1] may be performed at the discretion of the investigator and must be recorded in the electronic Case Report Form (eCRF).

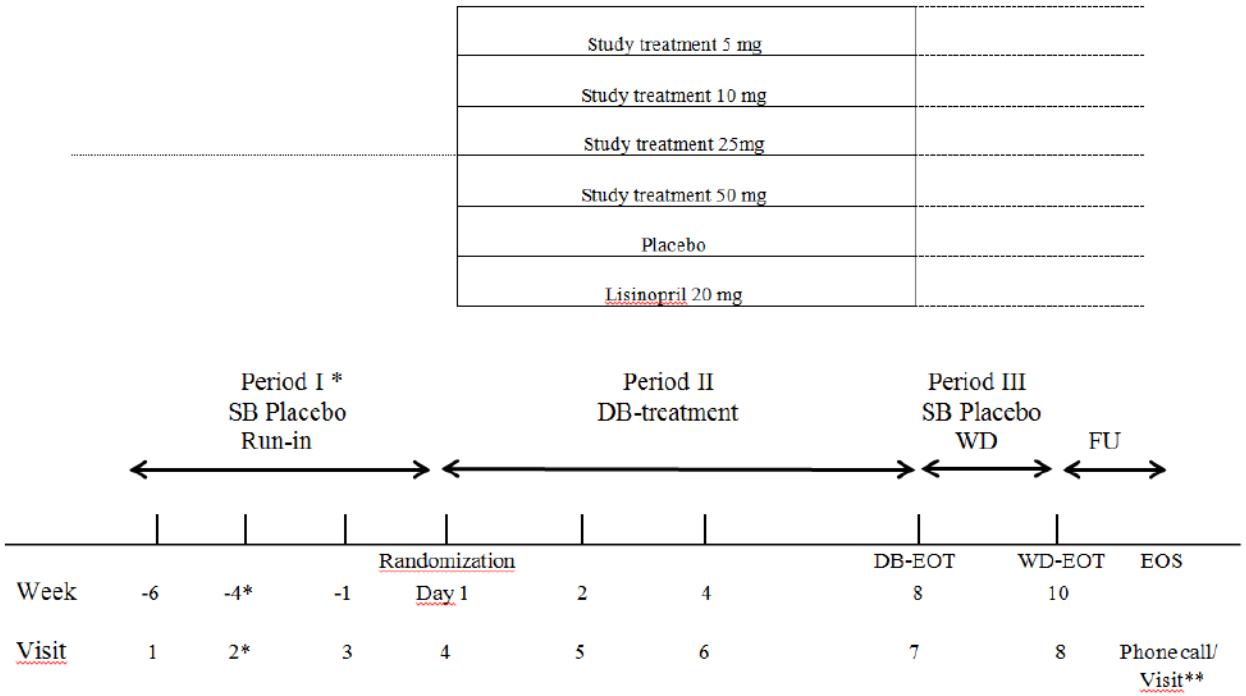
At the end of the study, the investigator/delegate will explain to the subject what treatment(s)/medical care is necessary and available according to local regulations.

Study duration

Subject participation in the study will be up to 16–18 weeks.

The overall study design is depicted in Figure 1.

Figure 1 Study design



*SB placebo run-in period is 4 weeks for anti-hypertensive treatment naïve subjects; Visit 1 is combined with Visit 2.
** Only for women of childbearing potential.
DB = double-blind; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up, SB = single-blind, WD = withdrawal.

3.2 Study design rationale

This study is designed to select doses to be investigated in the Phase 3 program. The design of this dose-finding study meets the requirements laid out by international guidelines [ICH 2000a, ICH 2000b, EMA 2010] and literature [Rose 1990, Myers 2001].

In accordance with the regulatory guidelines, the study has a placebo run-in period of 4 to 6 weeks. The administration of placebo during this period minimizes bias due to the regression-toward-the-mean phenomenon [EMA 2010]. The placebo run-in period is 4 weeks for anti-hypertensive treatment-naïve subjects at Visit 1. For subjects receiving anti-hypertensive treatment at Visit 1, a 2-week placebo wash-out period is added to the 4-week run-in period. For these subjects the SB placebo run-in period is 6 weeks.

A 2-week SB placebo withdrawal period is introduced at the end of the study to investigate the withdrawal phenomena, i.e., rebound effect on BP.

3.3 Study committees

An Independent Liver Safety Data Review Board (ILSDRB; an external expert committee of hepatologists) provides ongoing assessment and advice regarding any hepatic events that may require further evaluation during the study.

4 SUBJECT POPULATION

4.1 Subject population description

Subjects diagnosed with mild-to-moderate essential hypertension (i.e., grade 1 and grade 2) according to the seventh joint national committee and European Society of Hypertension classification [Chobanian 2003, Mancia 2013] are participating in the study.

Grade 1, 2, and 3 definitions are:

Grade 1: SBP greater than or equal to (≥) 140 and/or DBP ≥ 90.

Grade 2: SBP ≥ 160 and/or DBP ≥ 100 mmHg.

Grade 3: SBP ≥ 180 and/or DBP ≥ 110 mmHg.

4.2 Rationale for the selection of the study population

The selection of study population follows the recommendation of regulatory guidelines [EMA 2010] for evaluation of efficacy or safety of new anti-hypertensive drugs.

Therefore, in this study subjects with mild-to-moderate essential hypertension (grades 1 and 2) are included in order to select the ACT-132577 monotherapy dose(s) in a homogenous hypertensive population.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject:

<u>At Screening visit (Visit 1):</u>

1. Signed informed consent prior to any study-mandated procedure.
2. Male and female subjects aged from ≥ 18 to ≤ 75 years.
3. Mild-to-moderate essential hypertension with or without ongoing anti-hypertensive treatment(s):
   - DBP ≥ 90mmHg, as a mean of 5 measurements with office BP measurements (OBPM).
   - No contra-indication to stop (according to label) anti-hypertensive treatment(s).
4. 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., Randomization).
- Agreement to undertake pregnancy tests during the study and up to 30 days after DB study drug discontinuation [see Table 1].
- Agreement to use methods of birth control as described in Section 4.5 from Screening up to at least 30 days after DB study treatment discontinuation.

At Visits 2 and 3:

1. Mean sitting DBP (SiDBP) < 110 mmHg measured by OBPM.

Randomization (Visit 4):

1. Mean SiDBP ≥ 90 to < 110 mmHg measured by OBPM.
2. Subjects demonstrating ≥ 80% compliance (pill counting) during run-in period (Period I).

4.4 Exclusion criteria

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

Disease

1. Severe hypertension (grade 3): mean sitting systolic/diastolic BP (SiSBP/SiDBP; measured by OBPM) ≥ 180/110 mmHg, respectively.
2. Secondary hypertension (e.g., untreated obstructive sleep apnea, history or presence of drug related hypertension, renal parenchymal disease, renal artery stenosis, primary aldosteronism, thyroid disease (hyper- and hypothyroidism), and pheochromocytoma).
3. Known hypertensive retinopathy greater than Keith-Wagener Grade 2.
4. Myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft within 12 months prior to randomization.
5. Unstable angina within 6 months prior to randomization.
6. Heart failure New York Heart Association class III and IV.
7. Valvular defects (such as severe aortic or mitral valve disease) and/or hemodynamically relevant rhythm disturbances.
8. Clinical evidence of cerebrovascular insufficiency or a cerebrovascular accident within 6 months prior to randomization.
9. *Subjects working night shifts.
10. Body mass index < 20 kg/m^2 or > 40 kg/m^2

* A maximum of 2 night shifts per week is permitted except within 3 days prior to a study visit.

Treatments

11. Treatment with any medication which may affect BP (e.g., treatment of psychiatric diseases, ophthalmic preparations); see Appendix 3.
11a. Subject with co-morbidities taking anti-hypertensive medications for reasons other than BP.
12. Treatment with strong cytochrome P450 3A4 (CYP3A4) isoenzyme inhibitors or inducers; see Appendix 4.
13. Treatment with guanethidine and/or mineralocorticoid receptor antagonists within 1 month prior to Screening (Visit 1).
14. Treatment with another investigational treatment within 1 month prior to Screening (Visit 1).

Laboratory assessments

15. Evidence of the following at Screening (Visit 1)* and Visit 3:
    a. Hepatic disease: i.e., ALT or AST > 3 times the upper limit of normal range.
    b. Severe renal impairment, i.e., serum creatinine ≥ 2.26 mg/dl (200 µmol/l) or creatinine clearance <30 mL/min/1.73 m^2.
    c. Hemoglobin <100 g/L.

* Historical laboratory data acceptable, if not older than 3 months.

Others

16. Known and documented moderate or severe hepatic impairment.
17. History of dialysis or history of nephrotic syndrome.
18. Insulin-dependent, or known and documented uncontrolled diabetes mellitus.
19. History or concomitant diagnosis of alcohol or drug abuse within 2 years prior to randomization.
20. Any contraindication to lisinopril treatment (according to its label) or drugs of the same class.
21. Known hypersensitivity to ACT-132577 or lisinopril or drugs of the same classes, or any of their excipients.
22. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results such as drug or alcohol dependence or psychiatric disease or noncompliance with medical regimens or unwillingness to comply with the trial protocol.
23. Known concomitant life-threatening disease with a life expectancy < 12 months.
24. Any planned surgical intervention during the study period, except minor interventions (e.g., tooth extraction).

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

* Childbearing potential status will be assessed at each visit and recorded in the eCRF.

4.5.2 Acceptable methods of contraception

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

The use of one of the following options is regarded as reliable contraception:

Option 1	Option 2	Option 3	Option 4
One method from this list:	**One method from this list:**	**One method from this list:**	**One method from this list:**
Standard intrauterine device (IUD) (Copper T380A IUD)	Estrogen and progesterone oral contraceptives ("the Pill")	Diaphragm with spermicide	Partner's vasectomy
Intrauterine system (LNg 20IUS: progesterone IUS)	Estrogen and progesterone transdermal patch	Cervical cap with spermicide	**PLUS one method from this list:**
Progesterone implant	Vaginal ring	**PLUS one method from this list:**	Male condom
Tubal sterilization	Progesterone injection	Male condom	Diaphragm with spermicide
	PLUS one method from this list:		Cervical cap with spermicide
	Male condom		Estrogen and progesterone oral contraceptives ("the pill")
	Diaphragm with spermicide		Estrogen and progesterone transdermal patch
	Cervical cap with spermicide		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 one month prior to the Screening visit (Visit 1), see Section 5.2.3.

4.6 Medical history

Relevant medical history, as defined below, must be recorded in the eCRF:

- Chronic medical conditions (e.g., diabetes, angina pectoris, heart failure) and new acute medical conditions in the past 6 months;
- Acute medical conditions present at screening or occurring in the past with sequelae;
- Childbearing potential status at Screening.

Hypertension disease characteristics, evidenced by documentation in the subject charts, as defined below will be collected at Screening visit:

- Date of first diagnosis.
- Current anti-hypertensive treatments, if any.

5 TREATMENTS

5.1 Study treatment

Study treatments include the following doses of ACT-132577: 5 mg, 10 mg (2 × 5 mg), 25 mg, 50 mg, as well as placebo and lisinopril 20 mg. The ACT-132577 and its matching placebo will be provided as identical capsules of size "0".

Lisinopril 20 mg tablet, as active reference, is over-encapsulated (capsule size "0"). Matching placebo to lisinopril capsules will be provided as identical capsules of size "0", see Section 5.1.4.2.

5.1.1 Investigational treatment: description and rationale

Four fixed doses of ACT-132577 (5 mg, 10 mg [2 × 5 mg], 25 mg, and 50 mg) covering a dose range of 10-fold are selected for the present dose finding study. The study treatment must be taken orally o.d. based on the PK profile of ACT-132577 ($t_{1/2}$ of approximately 44 h). ACT-132577 can be administered irrespective of food as the PK of ACT-132577 were not affected by food [ACT-132577 IB].

In the AC-080-101 Phase 1 study, a dose-dependent increase in ET-1 plasma concentrations was observed after several days of treatment up to the highest tested dose of 100 mg ACT-132577.

At a dose of 5 mg, ET-1 plasma concentrations did not differ from subjects treated with placebo, whereas 25 mg induced a clear increase in ET-1 plasma concentration. Therefore, 5 mg and 10 mg are selected to cover the lower-part of the dose-response curve. 25 mg and 50 mg are selected to complete the dose-response curve. The exposure margins and the nonclinical safety program support this Phase 2 clinical trial at doses up to 50 mg o.d. for a treatment period of 8 weeks [ACT-132577 IB].

5.1.2 Comparator(s): description and rationale

The regulatory guidelines and scientific standards recommend use of a reference drug [ICH 2000a, ICH 2000b, EMA 2010].

Lisinopril is the active reference drug. An o.d. dose of 20 mg provides statistically and clinically significant decreases in SBP/DBP at trough after 6 weeks of treatment compared to placebo [Gomez 1989].

5.1.3 Placebo: description and rationale

Placebo is used as the control group in the DB period as recommended by health authorities [ICH 2000a, ICH 2000b, EMA 2010] for short-term studies (4–12 weeks).

The use of placebo is justified due to the following reasons:

- Only mild-to-moderate (grade 1 and 2) hypertensive subjects will be enrolled into this study.
- Subjects are closely followed throughout the study (8 to 9* visits at site).
- Study-specific discontinuation criteria have been set-up [see Section 5.1.12].
- No irreversible harm was reported during this short term period 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].

Placebo matching ACT-132577 and placebo matching lisinopril capsules will be concomitantly administered orally o.d. during the SB placebo run-in and SB placebo withdrawal periods to all subjects and during the double-blind treatment period to those subjects who have been randomized to the placebo group.

* Nine visits: Only for women of childbearing potential.

5.1.4 Study treatment administration

Study treatment is supplied in bottles containing 36 capsules to provide 36 days of treatment to cover a 4-week treatment period and the time window to the next visit.

Study treatment consists of 2 bottles. The subjects must be instructed to take one capsule from each bottle (i.e., total of 2 capsules) orally o.d. irrespective of food intake every morning between 7:00 and 10:00 a.m., and not to take it on the morning of study visit days.

See Table 1 and Section 8 for details on study treatment dispensing.

5.1.4.1 Run-in period (single-blind placebo)

Subjects will receive 2 bottles; one bottle contains placebo capsules matching ACT-132577 and the other bottle contains placebo capsules matching lisinopril. The subjects must be instructed to take one capsule from each bottle (i.e., total of 2 capsules) o.d. every morning from the morning of the Screening visit (Visit 1) to the morning of Visit 4 / Pre-randomization (Day –1). The run-in period is an SB period (subject-blinded). Accordingly, site staff must not inform the subject of the treatment received during this period.

5.1.4.2 Double-blind treatment period

All subjects will receive 2 bottles and must be instructed to take one capsule from each bottle (i.e., total of 2 capsules) o.d. every morning from the morning of Visit 4 / Randomization (i.e., Day 1, after completion of the baseline 24-h ABPM recording) to the morning of Visit 7 / Part 1. Depending on the DB study treatment arm the study treatment consists of:

- ACT-132577 5 mg: One bottle of ACT-132577 5 mg capsules + one bottle of placebo capsules matching lisinopril.
- ACT-132577 10 mg: Two bottles of ACT-132577 5 mg capsules.
- ACT-132577 25 mg: One bottle of ACT-132577 25 mg capsules + one bottle of placebo capsules matching lisinopril.
- ACT-132577 50 mg: One bottle of ACT-132577 50 mg capsules + one bottle of placebo capsules matching lisinopril.
- Lisinopril 20 mg: One bottle of lisinopril 20 mg capsules + one bottle of placebo capsules matching ACT-132577.
- Placebo: One bottle of placebo capsules matching ACT-132577 + one of placebo capsules matching lisinopril.

5.1.4.3 Withdrawal period (single-blind placebo)

All subjects will receive 2 bottles; one bottle contains placebo capsules matching ACT-132577 and the other bottle contains placebo capsules matching lisinopril. The subjects must be instructed to take one capsule from each bottle (i.e., total of 2 capsules) o.d. every morning from the morning of Visit 7 / Part 2 (i.e., after completion of the DB-EOT 24-h ABPM recording) to the morning of the day before Visit 8 (i.e., the WD-EOT visit). The WD period is an SB period (subject-blinded). Accordingly, site staff must not inform the subject of the treatment received during this period.

5.1.5 Treatment assignment

After informed consent has been signed, the investigator/delegate contacts the Interactive Response Technology system (IRT) at Visit 1 (Screening visit) to get a subject number. After having confirmed the eligibility of the subject, the investigator/delegate contacts the IRT to receive the bottle numbers for the SB placebo run-in period.

For subjects on anti-hypertensive treatment, the investigator/delegate re-contacts the IRT at Visit 2 (Week –4) to get a new study treatment number (i.e., bottle numbers) for the remaining 4 weeks of the SB placebo run-in period. See Section 8 for more details.

At the end of the run-in period, after having confirmed the eligibility of the subject and prior to the start of DB treatment period, the investigator/delegate contacts the IRT at Visit 4 / Randomization (Day 1) to randomize the subject. The IRT assigns a randomization number to the subject and bottle numbers to match the treatment arm assigned by the randomization list. Randomization will be in a 1:1:1:1:1:1 ratio (ACT-132577 5 mg; ACT-132577 10 mg; ACT-132577 25 mg; ACT-132577 50 mg; lisinopril 20 mg; placebo). At Visit 6 (Week 4), the investigator/delegate re-contacts the IRT to get a new study treatment number (i.e., bottle numbers) for the remaining 4 weeks of the DB treatment period. See Section 8 for more details.

At the end of the DB treatment period (Visit 7), the investigator/delegate contacts the IRT to get the study treatment number (i.e., bottle numbers) for the SB placebo withdrawal period.

The randomization list is generated by an independent Contract Research Organization (CRO), [redacted] using SAS version 9.3.

5.1.6 Blinding

This study will have an SB placebo run-in period prior to randomization. After randomization, the study will be performed in a DB fashion. This is followed by an SB placebo withdrawal period. During the placebo run-in and placebo WD periods, only the subject will be blinded to the treatment.

The investigator and study staff, the subjects, the monitors, Actelion staff, and CROs involved in the conduct of the study will remain blinded to the study treatment during the double-blind treatment period and until study closure. Actelion staff responsible for clinical trial supply distribution will need to be unblinded to ensure adequate distribution of study treatment. 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 meetings after study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential and accessible only to authorized persons, (i.e., Global Quality Management, IRT provider), who are not involved in the conduct of the study.

The investigational treatment, active reference and the respective matching placebos are indistinguishable and all study treatments will be packaged in the same way.

5.1.7 Unblinding

5.1.7.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure in accordance with Actelion standard operating procedures (SOPs).

5.1.7.2 Unblinding for SUSARs

When a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information will be anonymized and provided to Actelion Global Drug Safety, respective health authorities and Institutional Review Boards / Independent Ethics Committees (IRBs/IECs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.7.3 Emergency procedure for unblinding

The investigator, study staff and sponsor staff must remain blinded to the subject's study 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 randomization code for study treatment allocation through the IRT. 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 Actelion.

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

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

5.1.8 Study treatment supply

Manufacturing, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice, Good Clinical 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.

5.1.8.1 Study treatment packaging and labeling

5.1.8.1.1 Study treatment packaging

Study treatment is provided as capsules and supplied in childproof bottles for all periods.

5.1.8.1.2 Study treatment labeling

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

5.1.8.2 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.

5.1.8.3 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. The protocol-mandated study treatment dispensing/return procedures may not be altered without prior written approval from Actelion. An accurate record of the date and amount of study treatment dispensed to and returned from each subject must be available for inspection at any time.

5.1.8.4 Study treatment return and destruction

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused subject bottles, which will be sent to the warehouse, where Actelion 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 Actelion or the deputy, and written permission for destruction has been obtained from Actelion.

5.1.9 Study treatment accountability and compliance with study treatment

5.1.9.1 Study treatment accountability

The inventory of study treatment dispensed and returned (i.e., study treatment accountability) must be performed by the study staff on the day of the subject visit and before providing further study treatment. It is recorded on the Investigational Medicinal

Product dispensing and accountability log and in the eCRF and checked by the monitor 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 (bottle) dispensed to the subject:

- Dispensed bottle numbers
- Date dispensed / Number of capsules dispensed
- Date returned / Number of capsules returned

All study treatment supplies, including partially used or empty bottles must be retained at the site for review by the monitor.

If the subject forgets to bring the remaining study treatment to a study visit, he/she must be instructed to bring it at the next visit.

5.1.9.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated by site for each study visit and period using the formula defined below:

Compliance = [(number of capsules* dispensed – number of capsules* returned) / Total number of capsules* that should have been taken during a period] × 100

* From both bottles

At the end of the run-in period, eligibility with regard to study treatment compliance during run-in period [see Section 4.3] will be assessed as follows: Subject is considered compliant and therefore is eligible for randomization if accountability-based compliance is ≥ 80%. In order to minimize misuse of study medication by the subject (e.g., throwing out capsules from the returned bottles) and to properly evaluate this inclusion criterion, the study staff must not inform the subject about this criterion.

After randomization, compliance is still expected to be between 80% and 120%. If out of range value(s) are noticed (from study treatment accountability), they will be considered as a protocol deviation. The investigator must check with the subject the reasons for this non-compliance and discuss actions to be taken to avoid re-occurrence at the next visit.

5.1.10 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.12.

If study treatment intake is interrupted by the subject for any reason, she/he must immediately inform the investigator.

Interruptions of study treatment should be kept as short as possible. If treatment is stopped for more than 4 consecutive days, re-introduction is not permitted and treatment must be permanently discontinued [see Section 5.1.12].

Study treatment interruptions must be recorded in the eCRF.

5.1.11 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Actelion. The main reason and whether discontinuation of study treatment is the decision of the subject, the investigator, or Actelion must be documented in the eCRF.

A subject has the right to prematurely discontinue study treatment at any time by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study, see Section 9.2).

The investigator should 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 treatment may be discontinued in response to an AE, lack of efficacy (including treatment failure, worsening of subject's condition), a protocol deviation (including eligibility failure, non-compliance with study requirements), a diagnostic or therapeutic procedure, or for administrative reasons.

Study-specific criteria for discontinuation of study treatment are described in Section 5.1.12.

A subject who prematurely discontinues study treatment is NOT considered withdrawn from the study and will be asked to return for a premature EOT visit (Visit 9) within 7 days of last intake of study treatment and thereafter might be contacted for the safety follow-up telephone call or follow-up visit [see Sections 8.4 and 8.5], provided that the subject's consent for this limited participation in the study has not been withdrawn.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered withdrawn from the study. Subjects who die or are lost to follow-up are also considered withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

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

A) Hypertension

At any time throughout the study if mean SiDBP ≥ 110 mmHg and/or mean SiSBP ≥ 180 mmHg is measured by OBPM, i.e., essential hypertension grade 3 [Mancia 2013], BP must be re-measured. If the value (i.e., mean SiSBP ≥ and/or DBP ≥ 110 mmHg measured by OBPM at the site) is confirmed, subject must permanently discontinue study treatment.

The BP re-measurement can be during the same visit (e.g., within 1 h), or at the next planned visit, or at an unscheduled visit. The time of re-measurement is at investigator's discretion, taking into consideration the subject's medical history.

B) Pregnancy

If a female subject becomes pregnant while on study treatment, study treatment must be discontinued immediately, and a Pregnancy Form must be completed [see Section 10.3].

C) Liver aminotransferases abnormalities

Interruption of study treatment
After randomization study treatment must be interrupted in the following cases:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and ≤ 8 × ULN

Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase within 48 h. If AST and/or ALT elevation is confirmed, the re-introduction of study treatment is not to be considered.

Interruptions must be for less than 5 consecutive days; longer interruptions must lead to permanent discontinuation of study treatment [see Section 5.1.10].

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

Permanent discontinuation of study treatment
Study treatment must be stopped 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 drug 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.

All liver aminotransferases abnormalities leading to study drug interruption or discontinuation must be recorded as AEs [see Section 10].

An ILSDRB provides ongoing assessment and advice regarding any hepatic events that may require further evaluation during the study.

To ensure the proper and comprehensive evaluation of hepatic events, additional subject data might be collected via Actelion Global Drug Safety.

D) Hemoglobin abnormalities

In the event of hemoglobin decrease from baseline* of > 20 g/L, a hemoglobin retest must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

- Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), peripheral blood smear, reticulocyte count, iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation), lactate dehydrogenase (LDH), indirect bilirubin.

Study drug should be stopped 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.

* Baseline hemoglobin: last value obtained prior to first intake of DB study treatment.

E) Initiation of forbidden medications

Study treatment must be permanently discontinued if any forbidden therapy as listed in Section 5.2.4 is started during the study.

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 start of study (i.e., signing of informed consent).

A therapy that is study-concomitant is any treatment that is ongoing or initiated after signing of informed consent, or initiated up to 30 days after the DB study treatment discontinuation.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of DB study treatment (i.e., Day 1 – Visit 4 / Randomization) or is initiated during the DB treatment period (i.e., up to Visit 7).

5.2.2 Reporting of previous/concomitant therapy in the eCRF

The use of all study-concomitant therapy (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous therapy must be recorded in the eCRF if discontinued less than 14 days prior to the start of study (i.e., signing of the informed consent). The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency and indication will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

Treatments considered necessary for the subject's wellbeing and not categorized as prohibited concomitant medications are allowed during the study.

Intermittent use of topical/nasal applications of corticosteroids are allowed during the study.

In addition, the following therapies are allowed with the provision that they have been initiated at least one month prior to the Screening visit (Visit 1) and that the dose is kept stable until the WD-EOT visit (i.e., Visit 8):

- Hormonal contraceptives.
- Estrogen-replacement treatment.
- Non-steroidal anti-inflammatory drugs (e.g., low dose acetylsalicylic acid* for prevention of cardiovascular disease).
- Selective serotonin reuptake inhibitors (SSRIs) and anxiolytics.

* Intermittent (not daily) use of acetylsalicylic acid is permitted except within 2 days prior to a study visit.

5.2.4 Forbidden concomitant therapy

To avoid concomitant administration of medications that either compete with the same targeted receptors as ACT-132577, or with uncertain effect on BP, or that can themselves trigger BP reduction or elevation, or increase or decrease exposure to ACT-132577, the following concomitant therapies are forbidden from Screening visit (i.e., Visit 1) until the WD-EOT visit (i.e., Visit 8):

- Any drug which may affect BP e.g., ophthalmic preparation, sympathomimetics (any formulation of decongestants*), corticosteroids (intermittent use of topical/nasal applications excluded), cyclosporin, tacrolimus, erythropoietin, diet pills, herbal supplements, homeopathic compounds, treatment for psychiatric diseases [see Appendix 3].
- ERAs, and **PDE5 inhibitors.
- Strong inhibitors or inducers of CYP3A4 [see Appendix 4].

* Intermittent (not daily) use of topical decongestants is permitted except within 3 days prior to a study visit.

** Intermittent (not daily) use of sildenafil, vardenafil or tadalafil (e.g., Viagra®, Levitra®, Cialis®) is permitted except within 5 days prior to a study visit.

If a subject takes any of these forbidden medications during the course of the study, study treatment must be permanently discontinued.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the change from baseline to Week 8 of DB treatment period (Period II) in mean trough (i.e., 24 h post-dose) SiDBP, measured by OBPM.

6.1.2 Secondary efficacy endpoints

- Change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiSBP, measured by OBPM;
- Control[1] and response rates at Week 8 of DB treatment period (Period II) based on trough SiDBP, measured by OBPM;
- Control[2] and response rates at Week 8 of DB treatment period (Period II) based on trough SiSBP, measured by OBPM;
- Change from baseline to Week 8 of DB treatment period (Period II) in 24-h mean DBP, measured by ABPM;

- Change from baseline to Week 8 of DB treatment period (Period II) in 24-h mean SBP, measured by ABPM;
- Trough to peak ratio for DBP based on ABPM.

[1] Control and response rates at Week 8 on trough SiDBP are defined as:

- Controlled, if mean SiDBP < 90 mmHg.
- Responder, if the reduction from baseline in mean SiDBP ≥ 10 mmHg.

[2] Control and response rates at Week 8 on trough SiSBP is defined as:

- Controlled, if mean SiSBP < 140 mmHg.
- Responder, if the reduction from baseline in mean SiSBP ≥ 20 mmHg.

See Section 7.1 for definition of 'baseline'.

6.1.3 Other efficacy endpoints

- Changes from baseline to Weeks 2 and 4 of DB treatment period (Period II) in mean trough SiSBP and SiDBP, measured by OBPM;
- Change from baseline to Week 8 of DB treatment period (Period II) in mean day time ABPM;
- Change from baseline to Week 8 of DB treatment period (Period II) in mean night time ABPM;
- Trough to peak ratio for SBP based on ABPM;
- Changes from baseline to Week 2 of withdrawal period (Period III) in mean trough SiSBP and SiDBP, measured by OBPM;
- Changes from Week 8 of Period II to Week 2 of withdrawal period (Period III) in mean trough SiSBP and SiDBP, measured by OBPM.

See Section 7.1 for definition of 'baseline'.

6.2 Safety endpoints

- Treatment-emergent AEs
- AEs leading to premature discontinuation of study treatment;
- Treatment-emergent deaths;
- Treatment-emergent serious adverse events (SAEs);
- Treatment-emergent ECG abnormalities;
- Treatment-emergent marked laboratory abnormalities;
- Changes from baseline to Weeks 2, 4 and 8 of DB treatment period (Period II) in laboratory parameters.

- Changes from baseline to Week 4 and Week 8 of DB treatment period (Period II) in ECG parameters (PR, QRS, QT, QTcB, QTcF).
- Changes from baseline to Weeks 2, 4 and 8 of DB treatment period (Period II) in body weight and HR.

See Section 7.1 for definition of 'baseline' and Section 10.1.1 for definition of 'treatment-emergent'.

6.3 Pharmacokinetic and pharmacodynamic endpoints

6.3.1 Pharmacokinetic endpoints

- [redacted] plasma concentrations of ACT-132577 [redacted], measured at steady state at Weeks 2, 4 and 8 in DB treatment period (Period II).

6.3.2 Pharmacodynamic endpoints

- Trough plasma concentrations of ET-1, measured at steady state at Weeks 2, 4 and 8 in DB treatment period (Period II).

7 STUDY ASSESSMENTS

All study assessments are performed by a study staff member: medical, nursing, or specialist technical staff, and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF. When applicable, the assessments should be performed in the following order:

- BP measurement and HR
- Physical examination
- ECG
- Blood/urine sampling.

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

Calibration certificates for the following equipment used to perform study assessments must be available prior to the screening of the first subject:

- Temperature measurement devices for study treatment storage area and laboratory sample storage (e.g., freezer).
- Body weight scale.
- BP monitoring devices (i.e., OBPM and ABPM).
- ECGs.

7.1 Screening/baseline assessments

Unless otherwise specified, baseline for a given assessment is defined as the last assessment prior to Randomization (Day 1).

Prior to performing any study-specific procedures or assessments, the subject must provide written informed consent to participate in the study. If the signing of informed consent 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 and the results are available prior to the subject's signing of informed consent, such procedure or assessment may be used to assess eligibility and does not have to be repeated (e.g., 12-lead ECG [see Section 7.3.3], laboratory assessment [see Section 7.3.5.2]). In such cases, it must be clear from the source document when and for which reason the assessment was done prior to the signing of the informed consent.

The following assessments will be recorded in the eCRF:

- Subject information and consent form: Date and time of signature as well as date of withdrawal (when applicable).
- Demographics: Age, race/ethnicity, sex, weight and height.
- Medical history (previous and ongoing clinically significant diseases, as described in Section 4.6).
- Date of diagnosis of essential hypertension and treatment of hypertension ongoing at Visit 1 and stopped at this Visit (if any).
- Previous and concomitant medication [as described in Section 5.2].
- Methods of contraception (for females of childbearing potential only).
- Reason why a female is not considered to be of childbearing potential.
- Urine pregnancy test.
- Physical examination.
- AEs/SAEs.

The results of the following assessments will be transferred to Actelion through external providers (for details see appropriate sections):

- BP and HR measurements [see Section 7.2.1]
- Laboratory tests: Hematology, blood chemistry including serum pregnancy test (for women of childbearing potential) and urine albumin-to-creatinine ratio (UACR) [see Section 7.3.5]
- 12-lead ECG [see Section 7.3.3].

7.2 Efficacy assessments

7.2.1 Blood pressure measurement

Accurate measurement of BP is essential to classify individuals and record study treatment effect in AC-080A201; consequently BP should be measured by an automatic BP device at the site identical for all participating sites and managed by qualified personnel.

The same person should use the BP device for a given subject at each visit whenever possible.

It should be attempted to perform BP measurements at each visit always using the same arm of the subject and the appropriate cuff size, determined during Visit 1.

The BP must be measured at trough (i.e., before study drug intake) and around the same clock time between 7:00 and 10:00 a.m. +/– 1 h.

Details on BP procedure (measurement, and transfer of data) including 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].

7.2.1.1 Office blood pressure measurement

Systolic and diastolic BP will be measured non-invasively at each study visit.

OBPM is the mean of multiple BP readings recorded with a fully automated device with the patient resting quietly in the office/clinic. It has several advantages over manual BP measurements, especially in routine clinical practice, by virtually eliminating office-induced increases in BP, improving accuracy, minimizing observer error, and providing a more standardized measurement technique [Myers 2010].

The OBPM device is the BpTRU ([redacted]), which will be provided to each site by the central BP laboratory for the duration of the study.

Sitting BP measurement

At each pre-dose assessment, SiSBP and SiDBP will be measured at a pre-defined number of readings. There is a preset interval between measurements (timed from the start of one reading to the start of the next one). The first reading will be discarded and the mean of the remaining readings will be the mean sitting OBPM value [Myers 2006, Myers 2008].

The BpTRU device is an automatic oscillometric sphygmomanometer designed to record an initial 'test' reading and then a series of readings [Myers 2006, Myers 2008]. Prior to

the measurement, the subject has to rest in a sitting position for a minimum of 5 minutes in a quiet room.

Standing BP measurement

BP must be measured in the standing position to monitor orthostatic hypotension [see Section 7.3.1.1]. Standing SBP/DBP is measured by OBPM device (BpTRU) automatically twice, approximately one and three minutes after standing.

7.2.2 Home blood pressure measurement

Each site will be provided with home BP monitoring devices. These can be lent to the Subjects at Visit 1 for the entire duration of the study (i.e., until Visit 8), 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
- Explain how to measure BP if the subject experiences severe symptoms related to hypertension or orthostatic hypotension like headache, vomiting, nose bleeding, or dizziness, as follows:
  - Sit in a calm place for 5 minutes
  - Measure the SBP/DBP
    - Three readings within 5–10 minutes in the morning between 7:00 and 10:00 am before taking your study medications
    - Three readings within 5–10 minutes in the evening between 7:00 and 10:00 pm
  - Record the SBP/DBP values, time of measurement and time of study treatment intake in the subject's card (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.

Upon investigator's judgment based on discussion with the subject, an unscheduled visit can be performed. The data recorded by the subject at home will not be recorded in the eCRF.

The subject must give back the device at Visit 8.

7.2.3 Ambulatory blood pressure monitoring

Two 24-h ABPMs will be performed:

- Baseline ABPM: At the end of the SB placebo run-in period; 24 h before Day 1 (Visit 4 / Randomization).
- End of DB treatment ABPM: At the end of the DB treatment period; 24 h after Visit 7 / Part 1.

The ABPM device (Mobil-o-Graph) will be provided to each site by the central BP laboratory for the duration of the study.

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.

ABPM data will be electronically transferred to the central BP laboratory and subsequently to Actelion.

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

7.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs (and pregnancies) are described in Section 10.

7.3.1 Vital signs

7.3.1.1 Orthostatic hypotension

At each study visit standing SBP and DBP will be measured with the OBPM device (i.e., BpTRU) in addition to sitting measurements [see Section 7.2.1.1].

Orthostatic hypotension is defined as a BP decrease of SBP $\geq$ 20 mmHg or DBP $\geq$ 10 mmHg from sitting to standing position with symptoms of cerebral hypo-perfusion (e.g., light-headedness, dizziness, pre-syncope). The last SiDBP and SiSBP values measured by OBPM are compared to the last measured standing BPs.

Any value meeting the criteria of orthostatic hypotension must be recorded as an AE.

7.3.1.2 Heart rate

At each visit, HR will be measured with the OBPM device (i.e., BpTRU) at the same time as BP measurements, in the sitting position. The last HR measurement will be used for analysis.

7.3.2 Weight and height

Height will be measured at screening only (Visit 1) and recorded in the eCRF.

Body weight will be measured at each visit and recorded in the eCRF. The subject should always be weighed under similar conditions, i.e., same scale, similar clothing (i.e., underwear only), and similar interval between weighing and last meal.

7.3.3 ECG assessments

A standard 12-lead ECG is performed as defined in Table 1, Schedule of Assessments. Historical ECG is accepted for Visit 1, if not older than 6 months. Digital 12-lead ECG devices will be provided to each site by the central ECG laboratory for the duration of the study.

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).

ECG findings made after study start which meet the definition of an AE [Section 10.1.1] must be recorded by the investigator on the AE page of the eCRF.

The data records will be electronically transmitted to the central ECG laboratory for central reading. The reports from the central ECG laboratory will be sent to the site within a few days. Details on ECG procedure (recording, transfer of data and reporting to the site) will be provided in the ECG manual.

ECG data will be electronically transferred from the ECG laboratory database to Actelion.

7.3.4 Physical examination

Physical examination (i.e., inspection, percussion, palpation, and auscultation) is to be performed during the course of the study. The observations should be reported according to body system in the eCRF as either normal or abnormal. If an abnormality is found it should be specified on the corresponding eCRF page, describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings (other than those related to hypertension) that are present at study start (i.e., signing of informed consent) must be recorded on the Medical History eCRF page. Physical examination findings made after study start which meet the definition of an AE [Section 10.1.1] must be recorded by the investigator on the AE page of the eCRF.

7.3.5 Laboratory assessments

7.3.5.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests (except PK), including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be automatically transferred from the central laboratory database to Actelion's clinical database. In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency, or missing central laboratory values)

local* laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated eCRF pages.

* Except historical local laboratory data of Visit 1.

If a central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator will 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.

Central laboratory reports will be sent to the investigator. In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion and the concerned site. Alert flags that will trigger such notifications are displayed in Appendix 2.

All laboratory reports must be signed and dated by the investigator or delegate within 5 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 signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant laboratory abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10], 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. Further laboratory analyses should be performed as indicated and according to the judgment of the investigator.

At Screening (Visit 1) historical laboratory data can be used to check exclusion criterion 15 [see Section 4.4], if not older than 3 months. If not available, a blood sample must be taken for analysis by central laboratory.

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

7.3.5.2 Laboratory tests

The total amount of blood collected during the study is provided in the laboratory manual. This is approximately 96 mL (10 mL for hematology / clinical chemistry including pregnancy test [if applicable], 8 mL for PK and pharmacodynamic [PD] samples, and 2 mL for pregnancy test at follow-up visit):

- At Visit 1: One sample, only if no historical (within 3 months to this visit) laboratory data available;
- At Visits 3 and 4: One sample;

- At Visits 5, 6, and 7: Two samples; one for the hematology / clinical chemistry / pregnancy analysis, and one for PK and PD analysis); and
- At Visit 8: One sample.
- Follow-up visit, only for women of childbearing potential: One sample for serum pregnancy test.

Hematology

- Hemoglobin, hematocrit
- Erythrocyte count
- Leukocyte count with differential counts
- Platelet count.

Clinical chemistry

- Aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, LDH
- Creatinine, creatinine clearance
- Uric acid
- Glucose
- Sodium, potassium
- Protein, albumin
- Free T3, free T4, thyroid stimulating hormone (TSH).

Urinalysis

At Visits 4, 5, 6, 7 and 8 a midstream, clean-catch urine specimen (about 10 mL) will be collected for dipstick analysis and determination of UACR.

UACR determination:

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.

Dipstick analysis:

- Bilirubin, urobilinogen
- Blood
- Glucose
- Ketone
- Leukocytes
- Nitrite

- pH
- Protein.

Urine dipsticks provided by the central laboratory will be used to perform the urinalysis. The test should be performed and analyzed at the site. The results must be documented in the source documents / subject charts. No data will be collected in the eCRF. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1] will be recorded accordingly on the AE page of the eCRF.

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed at Visit 3, Visit 4 (Day –1), Visits 5, 6, 7, 8, and Follow-up visit. If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

A urine pregnancy test will be performed at Visits 1 (Screening)* and 2 with validated kits provided by the site.

* If blood must be taken for hematology / clinical chemistry laboratory analysis, a serum pregnancy test must be performed.

7.4 Pharmacokinetic and pharmacodynamic assessments

Blood samples for determination of PK and PD will be collected for all subjects to provide information about the concentration of the drug in the target population and its effect on the PD marker ET-1. Blood samples will be drawn at trough (before morning dose) at Week 2 (Visit 5), Week 4 (Visit 6) and Week 8 (Visit 7).

No genetic analysis will be conducted.

7.4.1 Blood sampling

Blood samples will be drawn at trough (before morning dose) at Week 2 (Visit 5), Week 4 (Visit 6) and Week 8 (Visit 7) [See Table 1]. Blood sampling will take approximately 1 minute. Procedures for sampling for PK and PD measurements are as follows: blood (4 mL for ACT-132577 [redacted] measurements and 4 mL for ET-1 measurements) will be collected by direct venipuncture or via an i.v. catheter placed in an antecubital vein in the arm in Vacutainer® or equivalent tubes containing K3-EDTA. Immediately following collection of the required blood volume, the Vacutainer® will be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution, and immediately cooled in an ice water bath. Within 30 minutes of collection, the Vacutainer® will be centrifuged at approximately 1500 g for 10 minutes at 4 °C. The plasma for PK (approximately 1.5 mL) will be transferred into one labeled polypropylene tube to avoid carryover of erythrocytes. The PD plasma sample (about 500 µL) will be

transferred into 1 labeled polypropylene tube. All samples will be stored in an upright position at –80 ± 20 °C. The date and exact actual clock time of collection of each blood sample will be entered in the eCRF as well as the exact dates and time of the drug administration prior and after blood draw.

7.4.2 Labeling and shipment

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 bioanalytical laboratory at time intervals agreed with the sponsor.

7.4.3 Bioanalysis

ACT-132577 [redacted] will be measured using liquid chromatography with tandem mass spectrometry by Actelion. The foreseen limit of quantification is 1 ng/mL.

Pharmacodynamic measurements of ET-1 will be measured in plasma by central laboratory after the study has clinically been completed.

8 SCHEDULE OF VISITS

Please refer to Table 1 for more details.

It is the responsibility of the investigator to obtain written informed consent(s) from each subject participating in this study after adequate explanation of the objective, methods, and potential hazards of the study [see Section 7.1].

Subjects without a confirmed diagnosis of mild-to-moderate hypertension are offered the possibility of having their BP measured (at trough if subjects are on anti-hypertensive treatment) with an automated office BP device (i.e., BpTRU) before entering the screening period.

In such cases, the specific written ICF ("Confirmation of mild-to-moderate hypertension by measuring blood pressure with an automated device") must be obtained before the BP measurement. If the subject has confirmed hypertension, he/she will be proposed to enter the study and a complete ICF provided.

The subject can only enter screening once the "study" ICF is signed.

It is permitted to re-screen subjects once, if the subject did not take any study medication and if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication, etc.), provided that documented

authorization has been received from Actelion. All screening assessments should then be repeated at the time of re-screening.

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

To ensure compliance, at each visit the study personnel must remind women of childbearing potential to use the methods of contraception defined for this study. The reminders must be documented in the subject's chart.

8.1 Screening and run-in periods

Screening lasts up to 72 h, starting with the signature of the "study" ICF and lasting until the Visit 1 eligibility assessments (i.e., eligibility to enter the run-in period) are completed.

The run-in period takes place 4 to 6 weeks prior to Day 1 (Visit 4 / Randomization) and starts with the Screening visit (Visit 1) and ends with the Randomization visit. The run-in period is an SB placebo treatment period; the study staff must not inform the subjects about the treatment they are receiving during the run-in period.

The run-in period is 4 weeks for anti-hypertensive treatment naïve subjects at Screening (Visit 1). Visit 1 is combined with Visit 2.

The run-in period is 6 weeks for subjects on anti-hypertensive treatment at Screening (Visit 1), including a 2-week wash-out period for anti-hypertensive treatment. In such a case, anti-hypertensive treatment must be discontinued (according to label) at Visit 1 if there is no contra-indication to stop it.

8.1.1 Visit 1 / Week –6

Visit 1 starts with the subject signing the ICF and lasts up to 72 h, i.e., until eligibility assessments are completed.

The following assessments are to be performed at the Screening visit. It is recommended to perform the screening assessments in the following order; however the order can be adapted to site and subject convenience:

- Subject information and consent form.
- Access IRT to get a subject number. The subject number will identify the subject throughout the study. In case of re-screening [see Section 8.1], the subject number assigned during the first screening procedure will be retained.

- Demographics: age, race/ethnicity, sex, and weight and height.
- Medical history and disease characteristics.
- Sitting BP and HR, and standing BP, measured by OBPM device.
  - Subjects on anti-hypertensive treatment(s) must have their BP measured at trough (i.e., before intake of anti-hypertensive treatment[s]). Therefore, the subject should be asked to withhold the anti-hypertensive treatment(s) dose(s) in the morning of BP measurement at site.
- Physical examination.
- 12-lead ECG: Historical ECG is acceptable if not older than 6 months. Otherwise, perform a 12-lead ECG.
- Assessment of childbearing potential and recording of contraception methods, if applicable.
- Laboratory tests: Historical blood laboratory analysis is accepted to check exclusion criterion 15, if not older than 3 months.
  - If historical laboratory data are available, perform a **urine** pregnancy test for women of child-bearing potential.
  - If historical laboratory data are not available, laboratory tests (i.e., hematology, blood chemistry) and **serum** pregnancy test (only for women of child bearing potential) must be performed.
- Recording of AEs and SAEs.
- Previous and concomitant medication.

The investigator must check inclusion/exclusion criteria and decide on the subject's eligibility for the study [see Sections 4.3 and 4.4, respectively].

If the subject is eligible:

- If the subject is treated with anti-hypertensive drugs and there is no contra-indication to stop these medications, stop all ongoing medications that can affect BP [see Section 5.2.4] according to their labels.
- Access IRT to get bottle numbers.
- Dispense the run-in period bottles. Instruct subject to take one capsule from each bottle irrespective of food intake every morning between 7:00 and 10.00 a.m.
- Study treatment intake at site.
- Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.
- If judged necessary, provide a home BP device to the subject, instruct how to operate it, where to record the measured BP values, when to monitor BP and whom to contact [see Section 7.2.2], if necessary.

- If subject was anti-hypertensive treatment-naïve, Visit 1 is combined with Visit 2 (i.e., Visit 2 does not take place), the next visit will be the Week –1 visit (Visit 3).

If the subject is not eligible:

- Date of eligibility assessment will be collected in the eCRF; additionally, the reasons for screening failure are documented in the eCRF (screening information is collected for all screen failure subjects).
- Subjects on anti-hypertensive treatment(s) who withhold the anti-hypertensive treatment(s) dose(s) for trough BP measurement should take the treatment at site.

8.1.2 Visit 2 / Week –4

This visit will be performed only for subjects who had anti-hypertensive drugs at Visit 1.

The visit will be performed at Day –28 ± 3 days.

The subject must not take study treatment at home on the morning of Visit 2.

Visit 2 includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- *Urine pregnancy test for women of childbearing potential.
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- *Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- *Record the date and time of last study treatment intake before this visit.
- *Check compliance with study treatment.

The investigator checks the exclusion criteria and the following eligibility criterion and decides on the potential eligibility of the subject for the next visit (Visit 3):

  - mean SiDBP measured by OBPM device < 110 mmHg

1) If this criterion is not met, the subject must be discontinued from the study. In such case, tests highlighted by * are optional and performed as deemed necessary per medical practice. The investigator has to record the reason of the run-in failure in the eCRF. A follow-up telephone call must be performed in 2 weeks to check any potential AEs/SAEs.

2) If the criterion is met, study treatment must be taken at site (i.e., one capsule from each bottle) from the bottles dispensed at Visit 1. Record the study treatment intake date and time. Retrieve the 2 bottles.

- Access IRT to get bottle numbers.
- Dispense 2 new bottles, and instruct subject to take one capsule from each bottle irrespective of food intake every morning between 7:00 and 10.00 a.m.
- Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.

8.1.3 Visit 3 / Week –1

This visit will be performed at Day –7 ± 4 days.

The subject must not take study treatment at home on the morning of Visit 3.

Visit 3 includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- *Laboratory test (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- *Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- *Record the date and time of last study treatment intake before this visit.
- *Check compliance with study treatment.

The investigator checks the exclusion criteria and the following eligibility criterion and decides on the potential eligibility of the subject for the next visit (Visit 4):

- mean SiDBP measured by OBPM device < 110 mmHg

1) If this criterion is not met, the subject must be discontinued from the study. In such case, tests highlighted by * are optional and performed as deemed necessary per medical practice. The investigator has to record the reason of the run-in failure in the eCRF. A follow-up telephone call must be performed in 2 weeks to check any potential AEs/SAEs.

2) If the criterion is met, study treatment must be taken at site (i.e., one capsule from each bottle). Record the study treatment intake date and time and instruct subject to continue taking one capsule from each bottle irrespective of food intake every morning between 7:00 and 10.00 a.m. Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.

8.1.4 Visit 4 / Day –1 to Day 1

The assessments of this visit will be performed over 2 consecutive days.

Day –1: Visit 4 / Pre-randomization is the end of run-in period. At Day –1, eligibility criteria will be checked. Subjects who are eligible must perform the baseline 24-h ABPM under run-in period study treatment (placebo) before randomization on Day 1.

Day 1: Visit 4 / Randomization is the start of DB treatment period. The DB period consists of Visit 4 / Randomization to 7 / DB-EOT (i.e., Day 1, Week 2, Week 4, and Week 8 visits).

8.1.4.1 Day –1 (Visit 4 / Pre-randomization)

The Day –1 visit must be scheduled 7 days ± 2 days after Visit 3.

Visit 4 / Pre-randomization includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- *12-lead ECG.
- *Laboratory tests (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- *Urinalysis (dipstick by site / UACR by central laboratory).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- *Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- *Record the date and time of last study treatment intake before this visit
- Check compliance with study treatment.

The investigator checks the following eligibility criteria and decides on the eligibility of the subject for randomization:

- Mean SiDBP ≥ 90 to < 110 mmHg measured by OBPM device.
- Treatment compliance ≥ 80% during run-in period.

1) If one of these criteria is not met, the subject must be discontinued from the study. In such case, tests highlighted by * are optional and performed as deemed necessary per medical practice. The investigator has to record the reason of the run-in failure in the eCRF. A follow-up telephone call must be performed in 2 weeks to check any potential AEs/SAEs.

2) If all these criteria are met, perform the following:

- Apply the ABPM device according to the BP manual for 24 h recording and review the subject's instruction handout with the study participant.
- Administer the last doses of the run-in period study treatment. Record the study treatment intake date and time and retrieval of study treatment bottles.
- Instruct subject to return to the site the next morning.

8.2 Double-blind period

8.2.1 Day 1 (Visit 4 / Randomization)

Day 1 is the start of DB treatment period for subjects eligible after Day –1 assessments (Visit 4 / Pre-randomization).

Day 1 includes:

- Remove the 24-h ABPM device.
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- Access IRT and obtain randomization and bottle numbers. Dispense the DB period study treatment.
- Instruct subject to take one capsule from each bottle irrespective of food intake every morning between 7:00 and 10:00 a.m.
- Study treatment intake at site.
- Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.

8.2.2 Visit 5 / Week 2

This visit will be performed at Day 14 ± 3 days. The subject must not take study treatment at home on the morning of Visit 5.

Visit 5 includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- Laboratory test (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- [redacted].
- Urinalysis (dipstick by site / UACR by central laboratory).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.

- Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- Record the date and time of last study treatment intake before this visit.
- Check compliance with study treatment.
- Study treatment intake at site. Record the study treatment intake date and time.
- Instruct subject to continue taking one capsule from each bottle irrespective of food intake every morning between 7:00 and 10:00 a.m.
- Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.

8.2.3 Visit 6 / Week 4

This visit will be performed at Day 28 ± 3 days. The subject must not take study treatment at home on the morning of Visit 6.

Visit 6 includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- 12-lead ECG.
- Laboratory test (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- [redacted].
- Urinalysis (dipstick by site / UACR by central laboratory).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- Record the date and time of last study treatment intake before this visit.
- Check compliance with study treatment and retrieve study treatment bottles.
- Access IRT to obtain new bottle numbers and dispense 2 new study bottles.
- Study treatment intake at site. Record the study treatment intake date and time.
- Instruct subject to take one capsule from each bottle irrespective of food intake every morning between 7:00 and 10:00 a.m.
- Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.

8.2.4 Visit 7 / Week 8 DB-EOT

The assessments of this visit will be performed over 2 consecutive days.

Visit 7 / Part 1 is the end of DB treatment period. On this day, the EOT 24-h ABPM under DB study treatment will be performed.

Visit 7 / Part 2 is the start of the SB placebo withdrawal period.

8.2.4.1 Visit 7 / Part 1

Visit 7 / Part 1 must be scheduled at Day 55 ± 5 days.

Part 1 includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- 12-lead ECG.
- Laboratory test (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- [redacted].
- Urinalysis (dipstick by site / UACR by central laboratory).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- Record the date and time of last study treatment intake before this visit.
- Check compliance with study treatment.
- Apply the ABPM device according to the BP manual for 24-h recording and review the subject's instruction handout with the study participant.
- Intake of the last doses of the DB period study treatment and retrieve study treatment bottles. Record the study treatment intake date and time.
- Instruct subject to return to the site in the next morning.

8.3 Withdrawal period

8.3.1 Visit 7 / Part 2

Visit 7 / Part 2 is the start of SB placebo withdrawal period.

This period is a SB treatment period, the study staff must not inform the subjects about the treatment they are receiving during this period.

Part 2 includes:

- Remove the 24-h ABPM device.

- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- Access IRT and obtain bottle numbers. Dispense the withdrawal period study treatment (placebo).
- Study treatment intake. Record the study treatment intake date and time.
- Instruct subject to take one capsule from each bottle irrespective of food intake every morning between 7:00 and 10:00 a.m.
- Remind the subject to bring back both bottles to the next visit and not take study treatment on the day of study visit prior to coming to the site.

8.3.2 Visit 8 / Week 10 withdrawal EOT

The visit will be performed at Day 70 ± 3 days. The subject must not take study treatment at home on the morning of Visit 8.

Visit 8 includes:

- Sitting BP and HR, and standing BP, measured by OBPM device at trough.
- Physical examination and body weight.
- 12-lead ECG.
- Laboratory test (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- Urinalysis (dipstick by site / UACR by central laboratory).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- Assessment of childbearing potential and recording of changes in contraception methods, if applicable.
- Record the date and time of last study treatment intake before this visit.
- Retrieve study treatment bottles.
- Check compliance with study treatment.
- If home BP device provided to the subject, retrieve the device.
- Make an appointment for the follow-up telephone call, or, for women of childbearing potential, an appointment for the follow-up visit.

8.4 Premature End-of-Treatment visit (Visit 9)

All subjects who prematurely discontinue study treatment must have Visit 9 performed as soon as possible but not longer than 7 days after the last dose of study treatment, provided that the subject's consent for this limited participation in the study has not been withdrawn.

The following assessments are to be performed at premature EOT / Visit 9:

- Sitting BP and HR, and standing BP, measured by OBPM device.
- Physical examination and body weight.
- *12-lead ECG.
- *Laboratory test (i.e., hematology, blood chemistry, and pregnancy test if applicable).
- *Urinalysis (dipstick by site / UACR by central laboratory).
- Reporting of AEs and SAEs.
- Recording of changes in concomitant medications.
- *Assessment of childbearing potential and recording of changes in contraception methods.
- Check compliance with study treatment.
- Retrieve study treatment bottles.
- Make an appointment for the follow-up telephone call or, *for women of childbearing potential, an appointment for the follow-up visit.

* If subject discontinued study treatment during run-in period,

- This test may not be performed, and
- For women of childbearing potential, a follow-up telephone call can be made instead of the follow-up visit.

8.5 Follow-up period

A follow-up telephone call must be performed 30 days after the last dose of the DB treatment and the following must be checked with the subject:

- Any changes in concomitant medication.
- Any AEs and SAEs.

For women of childbearing potential:
A visit must be scheduled 30 days after the last dose of the DB treatment instead of telephone call to perform a serum pregnancy test, in addition to the above mentioned assessments.

8.6 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., loss of efficacy, AE, etc.), appropriate assessments [as specified in Table 1] may be performed based on the judgment of the investigator and must be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

9 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

9.1 Study completion

End-of-Study for a single subject is defined as the date of the 30-day follow-up telephone call / visit.

If a subject withdraws consent and does not wish to participate in further visits, the date of consent withdrawal is the EOS for this subject. If a subject is declared lost to follow-up [see also Section 9.2], the date of last contact is the EOS for this subject.

The overall study is considered completed when all subjects have completed their 30-day safety follow-up telephone call/visit.

Enrollment and screening failure rates will be monitored in order to limit the inclusion of subjects in excess of the planned number of randomized subjects. If some subjects are still in the run-in period when the planned number of randomized subjects is reached they will be allowed to continue until the Randomization visit (Visit 4) and beyond if they fulfill the randomization criteria.

9.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study 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., withdrawal 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 withdrawal 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. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual fail. 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 case 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, and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number 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., site staff visit 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.

If premature withdrawal occurs for any reason, the reason for premature withdrawal from the study, along with who made the decision (subject, investigator, or Actelion) must be recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject was withdrawn from the study, the investigator should make efforts to schedule a last appointment/phone 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/phone 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 9.4.

9.3 Premature termination or suspension of the study

Actelion 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, Actelion will promptly inform the investigators, the IRBs/IECs, 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 Actelion must promptly inform all enrolled subjects, and ensure their appropriate treatment and follow-up, as described in Section 9.4. Actelion 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 Actelion, the investigator must promptly inform Actelion and the IRB/IEC, and provide both with a detailed written explanation of the termination or suspension.

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

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

After the subject's study completion or premature withdrawal 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. Such care may include the use of drugs which were forbidden during the study. Female subjects of childbearing

potential will be reminded of the need to maintain reliable contraception method for one month after study treatment stop and to perform a pregnancy test one month after study treatment termination.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

An AE is any adverse change, 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 (i.e., from signing of the informed consent), 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 in run-in period until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

Adverse events 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.

Overdose, misuse, and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study drug accountability log of the eCRF.

10.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the intensity reporting is required.

If the intensity of an AE with an onset date between informed consent signature and start of study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE must be completed in the eCRF. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- **Mild**

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

A mild, moderate, or severe AE may or may not be serious [see Section 10.3.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study treatment

Each AE 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. The determination of the likelihood that the study treatment caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated to study design or protocol-mandated procedures

An AE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease.

10.1.5 Reporting of adverse events

All AEs occurring after study start (i.e., signing of informed consent) and up to 30 days after DB study treatment discontinuation must be recorded on specific AE pages of the eCRF.

10.1.6 Follow-up of adverse events

Adverse events still ongoing more than 30 days after DB study treatment discontinuation must be followed up until they are no longer considered clinically relevant.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 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 inpatient 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 exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) 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 (for example if a complication prolongs hospitalization).

10.2.2 Reporting of serious adverse events

All SAEs occurring after study start (i.e., signing of informed consent) up to 30 after DB study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

10.2.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

10.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period [consistent with the definition in Section 10.2.2] must be reported to the Actelion drug safety department within 24 h 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.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 h of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be faxed to the Actelion drug safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 h of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

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

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to health authorities, IRBs/IECs, and investigators is the reference safety information section of the Investigator's Brochure [ACT-132577 IB].

10.3 Pregnancy

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

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring after study start (i.e., signing of informed consent) up to 1 month following study treatment discontinuation must be reported within 24 h of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on a pregnancy page in the eCRF.

10.3.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Actelion drug safety department.

Any AE and SAE associated with the pregnancy occurring during the follow-up period (up to 1 month) after study treatment discontinuation must be reported on the AE page in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.3.1.

10.4 Study safety monitoring

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

An ILSDRB (an external expert committee of hepatologists) provides ongoing assessment and advice regarding any hepatic event that may require further evaluation during the study.

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion. A Statistical Analysis Plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

11.1 Analysis sets

11.1.1 Screened Analysis Set

This analysis set includes all subjects who were screened and received a subject number.

11.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects randomized to a study treatment, who have a baseline mean trough SiDBP. Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received).

11.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) includes all subjects from the FAS who have a mean trough SiDBP at Week 8 of Period II and do not have any major protocol deviations. Major protocol deviations will be described in the SAP. Subjects are evaluated according to the study treatment they have been assigned to.

11.1.4 Safety Set

The Safety Set includes all subjects who received at least one dose of study treatment in Period II. Subjects are evaluated according to the study treatment they have received.

11.1.5 Pharmacokinetic Set

The Pharmacokinetic (PK) Set includes all subjects from the PPS who had at least one evaluable PK trough sample.

11.1.6 Usage of the analysis sets

The primary efficacy analysis will be performed on the PPS based on treatment as randomized. Secondary and exploratory efficacy analyses will also be performed on the PPS. The FAS and PPS will be used for supportive and sensitivity analyses.

Safety analyses will be performed on the Safety Set based on treatment as treated.

Subject listings will be based on the Safety Set, unless otherwise specified. Subject disposition will be described for the Screened Analysis Set.

Pharmacokinetic analyses will be performed on the PK set.

11.2 Variables

11.2.1 Primary efficacy variable(s)

The primary efficacy variable is the change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiDBP, measured by OBPM.

11.2.2 Secondary efficacy variables

Secondary efficacy variables include (measured by OBPM, unless specified otherwise):

- Change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiSBP;
- Control and response rates at Week 8 of DB treatment period (Period II) based on trough SiDBP [defined as in Section 6.1.2];
- Control and response rates at Week 8 of DB treatment period (Period II) based on trough SiSBP [defined as in Section 6.1.2];
- Change from baseline to Week 8 of DB treatment period (Period II) in 24-h mean DBP, measured by ABPM;
- Change from baseline to Week 8 of DB treatment period (Period II) in 24-h mean SBP, measured by ABPM;
- Trough to peak ratio for DBP based on ABPM.

11.2.3 Other efficacy variables

Other efficacy variables include:

- Changes from baseline to Week 2 and Week 4 of DB treatment period (Period II) in mean trough SiSBP and SiDBP (measured by OBPM);
- Change from baseline to Week 8 of DB treatment period (Period II) in mean day time ABPM;
- Change from baseline to Week 8 of DB treatment period (Period II) in mean night time ABPM;
- Trough to peak ratio for SBP based on ABPM;
- Changes from baseline to Week 2 of withdrawal period (Period III) in mean trough SiSBP and SiDBP (measured by OBPM);
- Changes from Week 8 of Period II to Week 2 of withdrawal period (Period III) in mean trough SiSBP and SiDBP (measured by OBPM).

11.2.4 Safety variables

Safety variables include:

- Treatment-emergent AEs;
- Adverse events leading to premature discontinuation of study treatment;

- Treatment-emergent deaths;
- Treatment-emergent SAEs;
- Treatment-emergent ECG abnormalities;
- Treatment-emergent marked laboratory abnormalities [as defined in Appendix 1];
- Changes from baseline to Weeks 2, 4 and 8 of DB treatment period (Period II) in laboratory parameters;
- Changes from baseline to Week 4 and Week 8 of DB treatment period (Period II) in ECG parameters (PR, QRS, QT, QTcB, QTcF);
- Changes from baseline to Weeks 2, 4 and 8 of DB treatment Period (Period II) in body weight and HR.

Treatment-emergent is defined in Section 10.1.1.

11.2.5 Other variables

11.2.5.1 Pharmacokinetic variables

- [redacted] plasma concentrations of ACT-132577 [redacted], measured at steady state at Weeks 2, 4 and 8 in DB treatment period (Period II).

11.2.5.2 Pharmacodynamic variables

- Trough plasma concentrations of ET-1, measured at steady state at Weeks 2, 4 and 8 in DB treatment period (Period II)

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

The primary analysis will be performed at a type I (false-positive) error of $\alpha = 0.05$ (two-sided) using 95% confidence intervals (CIs). Secondary efficacy variables will also be analyzed at $\alpha = 0.05$ (two-sided). Dunnett's test will be applied when comparing multiple doses of ACT-132577 versus placebo. The active comparator will be excluded from all statistical tests related to dose-response, but will be compared separately versus placebo.

11.3.2 Analysis of the primary efficacy variable(s)

11.3.2.1 Hypotheses and statistical model

The null hypothesis to be tested is that there is no dose-response for the primary endpoint.

H_0: $\mu_0 = \mu_1 = \mu_2 = \mu_3 = \mu_4$

Here, μ_i denotes the mean change from baseline to Week 8 in mean trough SiDBP (μ) for ACT-132577 dose (i) (where i = 0 corresponds to placebo). A value of $\mu_i < 0$ corresponds to a decrease in SiDBP.

The alternative hypothesis is that there is a monotonic dose-response for the primary endpoint.

H_1: $\mu_0 \geq \mu_1 \geq \mu_2 \geq \mu_3 \geq \mu_4$ and $\mu_i > \mu_j$ for at least one $i > j$ or
$\mu_0 \leq \mu_1 \leq \mu_2 \leq \mu_3 \leq \mu_4$ and $\mu_i < \mu_j$ for at least one $i > j$

Note that larger values of μ_i –corresponding to less decrease (or more increase) from baseline to Week 8 in mean trough SiDBP with increasing dose of ACT-132577– are less favorable. The first part of the alternative hypothesis corresponds to ACT-132577 being superior to placebo, whereas the second part corresponds to ACT-132577 being worse than placebo.

11.3.2.2 Handling of missing data

In subjects without a post-baseline mean trough SiDBP the baseline will be carried forward (i.e., the change from baseline will be set to zero). In subjects without a post-baseline mean trough SiDBP obtained at Week 8, the last post-baseline measurement will be carried forward. Note there will be no missing data for the primary efficacy variable in the PPS.

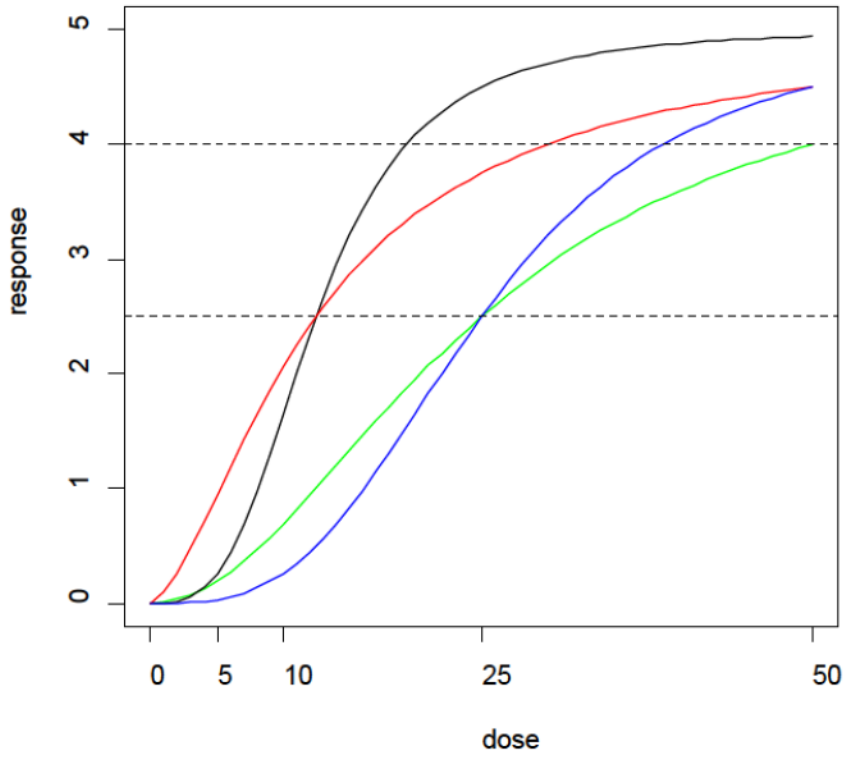
11.3.2.3 Main analysis

The primary analysis will be conducted on the PPS.

The change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiDBP will be analyzed using the MCP-Mod approach [Bretz 2005, Pinheiro 2006]. In brief, this consists of a set of Multiple Contrast Tests (MCTs) to establish the existence of a dose-response and a set of pre-specified dose-response models to describe the dose-response curve.

Some examples of dose response relationships are given in Figure 2 below, where it is assumed that the minimum response will be obtained with placebo (0 mg) and the maximum response (4–5 mmHg, placebo corrected) will be reached at the highest dose of ACT-132577 (50 mg).

Figure 2 Examples of dose-response relationships



Six candidate dose response models will be considered: linear, linear in log-dose, quadratic, E_{max}, sigmoidal E_{max} and logistic. The analysis will be performed using the R-package *DoseFinding* [Bornkamp 2015]. A dose-response relationship is demonstrated if at least one of the six MCTs has an adjusted p-value < 0.05. The best fitting model based on Akaike's Information Criterion will be used to estimate the minimum effective dose, defined as the dose that achieves a placebo-corrected mean reduction from baseline of at least 4 mmHg with a 95% CI excluding 0.

11.3.2.4 Supportive/sensitivity analyses

Supportive and sensitivity analyses will be conducted on the PPS and FAS.

Supportive analysis. Change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiDBP (imputed by last observation carried forward, if applicable) will also be analyzed using an analysis of covariance (ANCOVA) model with a factor for

treatment group (placebo and four doses of ACT-132577) and a covariate for baseline mean trough SiDBP. Each of the four doses of ACT-132577 will be compared to placebo applying Dunnett's test). The active comparator will be compared separately versus placebo using an ANCOVA model with a factor for treatment group (placebo or active comparator) and a covariate for baseline mean trough SiDBP.

Sensitivity analysis. Changes from baseline to Weeks 2, 4 and 8 of DB treatment period (Period II) in mean trough SiDBP will also be analyzed using repeated measurements model. A mixed model will be applied with factors for treatment group, time (Week 2, 4 or 8), treatment by time interaction and a covariate for baseline mean trough SiDBP. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. At Week 8 each of the four doses of ACT-132577 will be compared to placebo applying Dunnett's test.

11.3.2.5 Subgroup analyses

Subgroup analyses will be performed by age (≤ 65 versus > 65 years), race and country. This will be done based on the ANCOVA and the repeated measurements model described above. Additional subgroup analyses will be described in the SAP.

11.3.3 Analysis of the secondary efficacy variable(s)

Secondary efficacy variables will be analyzed for the PPS at $\alpha = 0.05$ (two-sided) using 95% CIs. No correction for multiple testing will be applied for these analyses.

Change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiSBP will be analyzed similarly to the primary endpoint (SiDBP), i.e., MCP-Mod will be applied, supplemented by the ANCOVA and the repeated measurements model described above.

Control and response rates at Week 8 of DB treatment period (Period II) based on trough SiDBP will be analyzed using a logistic regression model with a factor for treatment group and a covariate for baseline mean trough SiDBP. Control and response rates at Week 8 of Period II based on trough SiSBP will be analyzed similarly.

Change from baseline to Week 8 of DB treatment period (Period II) in 24 h mean DBP based on ABPM will be analyzed using an ANCOVA with a factor for treatment group and a covariate for baseline 24 h mean DBP. Change from baseline to Week 8 of DB treatment period (Period II) in 24 h mean SBP based on ABPM will be analyzed similarly.

Trough to peak ratios for DBP at Week 8 of DB treatment period (Period II) based on ABPM will be log transformed and analyzed using an ANCOVA model with a factor for treatment group and a covariate for log baseline trough to peak ratio.

11.3.4 Analysis of the other efficacy variables

Changes from baseline to Week 2 and Week 4 of DB treatment period (Period II) in mean trough SiSBP and SiDBP (OBPM) will be obtained from the same repeated measurements model as described in Section 11.3.2.4 under *sensitivity analysis*.

Change from baseline to Week 8 of DB treatment period (Period II) in mean day time ABPM will be analyzed using an ANCOVA with a factor for treatment group and a covariate for baseline mean day time ABPM. Change from baseline to Week 8 of DB treatment period (Period II) in mean night time ABPM will be analyzed similarly.

Trough to peak ratios for SBP at Week 8 of DB treatment period (Period II) based on ABPM will be analyzed similarly to trough to peak ratio for DBP based on ABPM.

Changes from baseline to Week 2 of withdrawal period (Period III) in mean trough SiSBP and SiDBP (OBPM) will be obtained by extending the repeated measurements model described in Section 11.3.2.4 with a timepoint for Week 2 of withdrawal period (Period III). Changes from Week 8 of Period II to Week 2 of withdrawal period (Period III) in mean trough SiSBP and SiDBP will be obtained from the same model using appropriate treatment and time contrasts.

11.3.5 Analysis of the safety variable(s)

All safety analyses described below will be performed on the Safety Set including data from DB treatment period (Period II). All safety analyses will also be performed on the subset of subjects who participated in the withdrawal period, including data from withdrawal period (Period III). Additionally, summaries will be provided for safety data from Period I based on the Screened Analysis Set. All safety data will be listed, with flags for quantitative abnormalities.

11.3.5.1 Adverse events

A treatment-emergent AE is any AE temporally associated with the use of a study drug. Treatment-emergent is defined as in Section 10.1.1. The number and percentage of subjects experiencing treatment-emergent AEs and SAEs at least once will be tabulated by treatment group and by:

- MedDRA System Organ Class (SOC) and individual Preferred Term (PT) within each SOC, in descending order of incidence.
- Frequency of subjects with events coded with the same PT, in descending order of incidence.

Furthermore, treatment-emergent AEs and SAEs will be tabulated as described above by severity and relationship to study drug.

AEs leading to premature discontinuation of study drug and death will also be summarized as described above.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study drug, and for AEs leading to death.

The number and percentage of subjects with treatment-emergent ECG abnormalities will be tabulated by treatment group.

11.3.5.2 Laboratory parameters

Descriptive summary statistics by visit and treatment group will be provided for observed values and absolute changes from baseline, in both hematology and blood chemistry and urine (only UACR) laboratory tests. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments will be assigned to the most appropriate visit timepoint according to the best fitting time-window for that assessment.

Actelion internal guidelines will be used for the definitions of marked abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables are transformed to standard units. All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

Marked laboratory abnormalities will be summarized for each laboratory parameter by treatment group providing their incidence and frequency. Absolute values and changes from baseline of laboratory parameter values during the course of the study will be summarized using the usual location and scale summary statistics by treatment group.

Laboratory parameters include:

- Hematology: hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential counts, platelet count.
- Blood chemistry: AST, ALT, alkaline phosphatase, total and direct bilirubin, LDH, creatinine, creatinine clearance, uric acid, glucose, sodium, potassium, protein, albumin, free T3, free T4, TSH.
- Urine: UACR.

The number and percentage of subjects with treatment-emergent laboratory abnormalities will be tabulated by treatment group.

11.3.5.3 12-lead ECG

Descriptive statistics by visit and treatment group will be provided for observed values and absolute changes from baseline, in numeric 12-lead ECG values (PR, QRS, QT, QTcB and QTcF). In order to minimize missing data and to allow for unscheduled visits, all recorded assessments will be assigned to the most appropriate visit time point according to the best fitting time-window for that assessment.

In addition, treatment-emergent morphological ECG abnormalities will be summarized.

11.3.5.4 Vital signs and body weight

Vital signs parameters, HR and body weight will be summarized at each study visit using the usual location and scale summary statistics by treatment group for both absolute values and changes from baseline. Subjects for whom no post-baseline value is available are excluded from the analysis of the changes from baseline.

11.3.6 Analysis of other variable(s)

PK and PD data will be listed by subject number and PK endpoints will be analyzed descriptively by treatment. PK trough and ET-1 plasma concentrations at each visit will be summarized by treatment using arithmetic mean, minimum, median, maximum, standard deviation (SD), standard error, and two-sided 95% CI of the mean.

If possible, the exploratory PK/PD analysis will be performed in which the relationship between ACT-132577 plasma concentrations and ET-1 levels is investigated.

Whenever possible, a model will be established to describe these relationships. Exploratory data-driven analysis may be performed, with the caveat that any statistical inference will not have any confirmatory value. The results of this analysis will be reported separately.

11.4 Interim analyses

No formal interim analysis is planned.

11.5 Sample size

11.5.1 Sample size justification

In a previous study with macitentan in essential hypertension (AC-055-201) the within-group SD for the change from baseline to Week 8 in SiDBP was 7.4 mmHg (90% CI: 7.0–8.0). In the sample size calculations SDs of 7–9 mmHg are considered.

[redacted]

It is assumed that the maximum difference versus placebo is achieved at the highest dose of ACT-132577. For the dose-response curves four scenarios were considered [see Figure 2]. These are, in fact, sigmoidal E_{max} curves.

For the sample size it was required that the power to demonstrate the existence of a dose-response relationship is 90% for each of the four scenarios. A total of 70 subjects per group in the PPS (i.e., 420 subjects in total) satisfied this condition and would also allow for sufficiently precise estimation of the dose-response curve. Assuming a drop-out rate of approximately 20%, a total of 90 patients per group would need to be randomized (i.e., 540 in total).

The power for the MCP-Mod approach to demonstrate the existence of a dose-response relationship with 70 subjects per group (PPS) is given in Table 2 for various combinations of placebo-corrected differences and SDs.

Table 2 Power to demonstrate a dose-response relationship with n = 70 per group (PPS)

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Delta*	4.9	4.5	4.5	4.0
SD				
7	99%	99%	99%	99%
8	99%	99%	99%	99%
9	98%	96%	98%	97%

*Maximum difference versus placebo (mmHg) PPS = Per-Protocol Set

Conservatively assuming that the difference versus placebo is 4 mmHg and the SD is 9 mmHg, the power for the MCP-Mod approach is > 95% for the four scenarios considered.

11.5.2 Sample size sensitivity

The power for the supportive ANCOVA to demonstrate that at least one of the four ACT-132577 doses is better than placebo is given in Table 3 for the same combinations of placebo-corrected differences and SDs.

Table 3 Power for the supportive ANCOVA with n = 70 per group (PPS)

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Delta*	4.9	4.5	4.5	4.0
SD				
7	99%	98%	97%	97%
8	95%	94%	91%	91%
9	89%	87%	82%	82%

*Maximum difference versus placebo (mmHg) ANCOVA = analysis of covariance; PPS = Per-Protocol Set.

Again assuming that the difference versus placebo is 4 mmHg and the SD is 9 mmHg, the power for the pairwise comparisons is > 80% for the four scenarios considered. It can be seen that ANCOVA is less powerful than the MCP-Mod approach.

11.5.3 Blinded sample size re-estimation

A blinded sample size re-estimation will be performed by the sponsor after 100 subjects have been randomized and their Week 8 BP data are available for analysis (or DB treatment discontinuation before Week 8 is confirmed, where applicable). The sample size recalculation will consider the overall SD of the primary endpoint (change from baseline to Week 8 in mean trough SiDBP, measured by OBPM) in the PPS as well as a more common requirement for the power to detect a dose-response, still allowing for sufficient precision to estimate the dose-response curve [Table 4].

Table 4 Sample size (PPS) needed for 80–95% power to detect a dose-response for various SDs

	SD = 6.0	SD = 6.5	SD = 7.0	SD = 7.5	SD = 8.0	SD = 8.5	SD = 9.0
80% power							
- PPS size	126	150	174	198	222	252	282
- per group*	21	25	29	33	37	42	47
90% power							
- PPS size	174	198	234	264	300	336	378
- per group*	29	33	39	44	50	56	63
95% power							
- PPS size	210	252	288	330	372	420	474
- per group*	35	42	48	55	62	70	79

*Expected number. Power based on the MCT test in the MCP-Mod procedure as implemented in the R *DoseFinding* package, averaged over the four dose-response curves in Figure 2.
MCP-Mod = Multiple Comparison procedure - Modeling; MCT = Multiple Contrast Test; PPS = Per-Protocol Set; SD = standard deviation.

Here, SD is the overall standard deviation of the primary endpoint. It is acknowledged that this could be an overestimation of the (unobserved) within group SD, but, given the range of anticipated treatment group differences, this overestimation is likely to be small (< 5%). The recalculated size of the PPS is expected to be between 280 subjects and the originally foreseen 420 subjects.

The number of subjects to be randomized will be calculated by dividing PPS size by the proportion of randomized subjects who were included in the PPS. That proportion will be estimated based on the same 100 randomized subjects considered for the sample size

re-estimation. To be conservative, the lower limit of the 95% CI around the proportion will be employed, of which some examples are given in Table 5.

Table 5 Number and proportion of subjects in PPS and 95% CIs for the proportion at the time of the sample size re-estimation

Number Randomized	Number in PPS	Proportion in PPS	95% CI*	
100	95	0.95	0.89	0.98
100	90	0.90	0.82	0.95
100	85	0.85	0.76	0.91
100	80	0.80	0.71	0.87

*Clopper-Pearson [Clopper 1934]. CI = confidence interval; PPS = Per-Protocol Set.

The number of subjects to be randomized will also take into account the need to collect sufficient exposure and safety data and is expected to be between 300 subjects and the originally planned 540 subjects.

12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timeliness 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.

Electronic CRF data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site staff 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 21 CFR Part 11).

Subject screening and enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

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. If a subject withdraws from the study, the reason must be noted on the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On documents (e.g., documents attached to SAE reports) submitted to Actelion and any external service providers, subjects must be identified only by number, and never by name or initials, hospital numbers, or any other 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 informed consent forms) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

Electronic CRFs will be used for all subjects. The investigator will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any timepoint 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 Actelion on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem 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 Actelion 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 event of health authority inquiries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples and ECG assessments will be processed through a central laboratory and central reader respectively and the results will be sent electronically to Actelion.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate SOP. After database closure, the investigator will receive the eCRFs of the

subjects of her/his site (including all data changes made) on electronic media or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion 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 research is conducted.

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB or IEC. Approval from the committee 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 subject information leaflet after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IRB/IEC 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 study staff member was present during a meeting, it must be clear that this person did not vote.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent(s) according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

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

Site staff authorized to participate to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on Actelion Delegation of Authority form. A study physician or advanced practice role, such as an advanced practice nurse or physician's assistant qualified by licensure, must always be involved in the consent process.

The subject and/or legal representative must sign, personally date, and time the ICF(s) before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF(s) must also be signed, personally dated, and timed by the authorized site staff listed on Actelion Delegation of Authority form.

A copy of the signed and dated ICF(s) is given to the subject and/or legal representative; the original is filed in the site documentation. The informed consent process must be fully documented in the subject's medical records. This must include the study reference, the subject number, the date and time when the subject was first introduced to the Actelion clinical study, the date and 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 family member), a copy of the signed ICF given to the subject / legal representative.

If that the site would like to recruit subjects who are considered vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure the subject's rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable), and the IRB/IEC must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IRB/IEC according to procedures, and before subjects are recruited.

13.4 Compensation to subjects and investigators

Actelion 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.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the 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 Actelion 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 GCP must be reported to the IRB/IEC and regulatory authorities according to Actelion or (overruling) local requirements.

13.6 Protocol amendments

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

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of 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 subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion'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 Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion 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 monitor has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the CRF 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 monitor 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 monitor. 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 subject's data. The printouts will be considered as the official clinical study records and must be filed either with the subject medical records or with the subject's printed eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor 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 monitor 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 Actelion's instructions. If it were not possible for the monitor 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.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The Principal Investigator (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 initiation visit.

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 monitor 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. Actelion 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 plan. 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 monitor. The required site personnel must be available during monitoring visits and allow adequate time to meet with the monitor to discuss study related issues.

The investigator agrees to cooperate with the monitor(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 database closure at the discretion of Actelion.

13.9 Investigator site file

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH E6 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 monitor 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. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from Actelion. 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 inform Actelion immediately.

If the PI will change, or if the site will relocate, the monitor must be notified as soon as possible.

13.10 Audit

Actelion's Global Quality Management 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 Actelion's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

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

13.11 Inspections

Health authorities and/or IRBs/IECs may also conduct an inspection of Actelion's clinical study (during the study or after its completion).

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

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

13.12 Reporting of study results and publication

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the Coordinating Investigator (or PI for single-center studies).

The Coordinating Investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Actelion will post results from the clinical study on Actelion's Clinical Trial Register and on external/national registries, as required by local law.

Actelion's Policy on Disclosure of Clinical Research Information can be found at:
http://www.actelion.com/documents/corporate/policies_charters/policy_clinical-research-information.pdf

In accordance with the Good Publication Practices and ethical practice, 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 publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors (ICMJE) 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 Actelion and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation. Upon review, Actelion 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.

Actelion's Policy on Scientific Publications can be found at:
http://www.actelion.com/documents/corporate/policies_charters/policy_scientific-publications.pdf

14 REFERENCES

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15 APPENDICES

Appendix 1 Marked laboratory abnormalities

Laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for "low", H for "high".

The term "marked abnormality" describes laboratory values above or below the thresholds, with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor in order to flag and/or communicate abnormal laboratory results from the central laboratory to the investigators, and for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events [CTCAE 2010] grading system.

PLEASE NOTE: Thresholds for abnormality of level L or H are not provided in this appendix but will be provided in the central laboratory manual. Parameters for which no threshold is defined in Table 6 below may be defined in the central laboratory manual.

Table 6 Threshold for marked laboratory abnormalities

Parameter	LL	LLL	HH	HHH	HHHH
Hematology					
Hemoglobin	< 100 g/L (< 10 g/dL; < 6.2 mm ol/L)	< 80 (< 8 g/dL; < 4.9 mmol/L;)	Increase in > 20 g/L above ULN or above baseline if baseline is above ULN	Increase in > 40 g/L above ULN or above baseline if baseline is above ULN	
Hematocrit	< 28% for females < 32% for males	< 20%	> 60% in men > 55% in women	> 65%	
Leukocytes	< 3.0×10^9/L (< 3000/mm^3)	< 2.0×10^9/L (<2000/mm^3)	> 20.0×10^9/L (> 20,000/mm^3)	> 100.0×10^9/L (> 100,000/mm^3)	
Platelet count	< 75×10^9/L (< 75,000/mm^3)	< 50×10^9/L (< 50,000/mm^3)	> 600×10^9/L	> 999×10^9/L	
Neutrophils	< 1.5 10^9/L (< 1500/mm^3)	< 1.0$10^9$/L (< 1000/mm^3)	NA	NA	
Eosinophils	NA	NA	> 5.0×10^9 or > 5% (> 5000 cells/mm^3)	NA	
Lymphocytes	< 0.8×10^9/L (< 800/mm^3)	< 0.5×10^9/L (< 500/mm^3)	> 4.0×10^9/L (> 4000/mm^3)	> 20×10^9/L (> 20,000/mm^3)	

Blood Chemistry					
AST (U/L)	NA	NA	> 3 × ULN	> 5 × ULN	> 8 × ULN
ALT (U/L)	NA	NA	> 3 × ULN	> 5 × ULN	> 8 × ULN
AP	NA	NA	> 2.5 × ULN	> 5 × ULN	
Bilirubin Total (µmol/L)	NA	NA	> 2 × ULN	> 5 × ULN	
Creatinine	NA	NA	> 1.5 × ULN or > 1.5 × baseline	> 3 × ULN or > 3 × baseline	
Creatinine clearance	< 60 (mL/min/1.73 m^2)	< 30 (mL/min/1.73 m^2)	NA	NA	
Glucose	< 3.0 mmol /L (< 55 mg/dL)	< 2.2 mmol /L (< 40 mg/ dL)	> 8.9 mmol /L (> 160 mg/dL)	> 13.9 mmol /L (> 250 mg/ dL)	
Sodium		< 130 mmol/L (< 130 mEq/L)	> 150 mmol/L (> 150 mEq/L)	> 155 mmol/L (> 155 mEq/L)	
Potassium	< 3.2(mmol/L)	< 3.0(mmol/L)	> 5.5(mmol/L)	> 6.0(mmol/L)	
Uric acid	NA	NA	> 0.59 mmol/L (> 10 mg/dL)	> 0.72(mmol/L) (> 12 mg/dL)	
Albumin	< 30 g/L (< 3.0 g/dL)	< 20(g/L (< 2.0 g/dL)	-	-	

Appendix 2 Central laboratory alert flags

On top of the flags described below, at a minimum, results above the upper limit or below the lower limit of the reference range for normal subjects will be flagged.

- **Exclusionary alert value – at Screening (Visit 1), and Visit 3:** The result is outside the study-specific defined limit for inclusion in the study.

  Hemoglobin < 100 g/L
  AST > 3 × ULN
  ALT > 3 × ULN
  Creatinine ≥ 2.26 mg/dl (200 µmol/L) or creatinine clearance <30 mL/min/1.73 m^2
  Serum pregnancy test positive.

- **Total bilirubin flag alert value – all visits except Screening (Visit 1):** In combination with ALT and/or AST ≥ 3 × ULN, study medication should be stopped if:

  Total bilirubin ≥ 2 × ULN.

- **Permanent discontinuation of study medication – all visits except Screening (Visit 1):** Please refer to the study protocol Section 5.1.11. Study medication must be stopped if:

  AST > 8 × ULN, ALT > 8 × ULN
  Serum pregnancy test positive
  Hemoglobin < 80 g/L
  Hemoglobin > 50 g/L decrease from baseline.

- **Repeat alert value – all visits after Randomization (Visit 4):** Repeat testing is needed (+ interrupt study medication if ALT and/or AST > 3 × ULN) if:

  AST ≥ 3 × ULN
  ALT ≥ 3 × ULN
  Hemoglobin > 20 g/L decrease from baseline

Appendix 3 Forbidden concomitant medication

A) Medication which may affect BP, such as:

- Drugs with vasopressor activity:
  - Anti-angiogenics, cyclosporine, tacrolimus, erythropoietin, sympathomimetics (any formulation of decongestants*), diet pills, ophthalmic preparation , cocaine (topical applications for local anesthesia excluded), amphetamine, herbal supplements (ephedra, ma huang), homeopathic compounds.

- All psychiatric drugs except SSRIs and anxiolytics [Kasper 2015].
- Drugs with effect on volemia:
  - Corticosteroids (topical/nasal applications excluded), CYP17A1 inhibitors, liquorice.

* Intermittent (not daily) use of topical decongestants is permitted, except within 3 days prior to a study visit.

B) Anti-hypertensive therapies, such as:

- Drugs that target the renin-angiotensin system
  - Angiotensin-converting enzyme inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindropril, quinapril, ramipril, trandolapril).
  - Angiotensin-receptor blockers (e.g., azilsartan, candesartan, eprosartan, ibresartan, losartan, olmesartan, telmisartan, valsartan).
  - Direct renin inhibitor (e.g., aliskiren)

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

- Calcium channel blockers
  - Dihydropyridines (e.g., amlodipine, felodipine, isradipine, nicardipine, nifedipine, nitrendipine, nisoldipine).
  - Non dihydropyridines (e.f., diltiazem,verapamil).

- Beta-blockers (e.g., acebutolol, alprenolol,atenolol, betaxolol, bisoprolol, carvedilol, labetolol, metoprolol/succinate, metoprolol/tartrate, nadolol, nebivolol, penbuterol, pindolol, propranolol, timolol).
- Alpha-adrenergic receptors blockers (e.g., doxazosin, phenoxybenzamine, phentholamine, prazosin, terazosin).
- Vasodilators (e.g., hydralazine, minoxidil).
- Central alpha-agenonits (e.g., clonidine, clonidine patch, guanfacine, methyldopa, rilmenidine).
- Adrenergic depleters (e.g., reserpine).

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

Appendix 4 Strong CYP3A4 inhibitors and inducers (FDA guidelines for drug interaction studies, February 2012)

Strong CYP3A4 inducers such as:

- Anticonvulsants, mood stabilizers
  - Phenytoin
  - Carbamazepine
- Barbiturates
  - Phenobarbital
- Bactericidal drugs
  - Rifampin
- St. John's wort

Strong cytochrome CYP3A4 inhibitors such as:

- Protease inhibitors
  - Boceprevir
  - Indinavir
  - Nelfinavir
  - Ritonavir / Lopinavir
  - Saquinavir
  - Telaprevir
- Macrolide antibiotics
  - Telithromycin
  - Clarithromycin
- Azole antifungals
  - Ketoconazole
  - Itraconazole
  - Posaconazole
  - Voriconazole
- Antidepressant
  - Nefazodone
- Vasopressin receptor antagonist
  - Conivaptan
- Constituent of grapefruit juice
  - Bergamottin

Source: [FDA 2012]