Statistical Analysis Plan

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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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

STUDY 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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LIST OF ABBEVIATIONS AND ACRONYMS

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
AIC	Akaike's Information Criterion
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BLQ	Below the limit of quantification
BMI	Body Mass Index
BOCF	Baseline observation carried forward
BP	Blood pressure
CI	Confidence interval
DB	Double-blind
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
E_{max}	Maximum effect
EOS	End-of-Study
EOT	End-of-Treatment
ET	Endothelin
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration (US)
HR	Heart rate
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
LSMeans	Least Squares Means
MAR	Missing at random
MCP-Mod	Multiple Comparison Procedure – Modeling
MCT	Multiple Contrast Test
MedDRA	Medical Dictionary for Regulatory Activities
o.d.	Once a day
OBPM	(automated) Office blood pressure measurement
OC	Observed cases

PD	Protocol deviation
PK	Pharmacokinetic
PPS	Per-Protocol Set
PR	Pulse rate
RIS	Run-in Set
RND	All Randomized Set
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SB	Single-blind
SBP	Systolic blood pressure
SCR	Screened Set
SD	Standard deviation
SiDBP	(Mean trough) sitting diastolic blood pressure
SiSBP	(Mean trough) sitting systolic blood pressure
SOC	System organ class
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
WD	Withdrawal
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses and data presentation for the Clinical Study Report of Study AC-080A201, the Phase 2 dose-finding trial with ACT-132577 in subjects with essential hypertension (grade 1 and 2).

This SAP is based on Version 3 of the protocol dated 30 May 2016 [D-16.063].

For the layouts of the tables Biostatistics Standards for Analysis Datasets and Outputs (Project Code: PR 070; version 3.0) will be used.

2 STUDY DESIGN AND FLOW

2.1 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 1000 subjects are enrolled into the study, in order to have at least 540 subjects randomized in the 6 following groups using 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 and lisinopril 20 mg. At least 420 subjects are expected to complete the trial. There are no stratification factors.

The study consists of the following study periods:

Screening

The screening period starts with the signature of the "study" informed consent form and lasts until Visit 1. During this period study assessments (e.g., laboratory test) are performed to determine whether the subject is eligible for the study.

Run-in period (Period I)

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

The run-in period lasts 4 weeks for anti-hypertensive treatment naïve subjects.

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

Treatment period (Period II)

Period II is a double-blind (DB) treatment period of 8 weeks which starts at Visit 4 with the first dose of DB study treatment and ends at Visit 7 at the first dose of SB withdrawal treatment.

Withdrawal period (Period III)

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

Follow-up period

The follow-up period, including follow-up telephone call, or follow-up visit only for women of childbearing potential to perform the pregnancy test at the site, starts after the last dose of SB WD study treatment (placebo) and ends at 30–33 days after the last dose of the DB treatment.

End-of-Study (EOS)

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 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 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.

2.2 Study visit and assessment schedule

Table 1 shows a schematic representation of the assessments 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 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.

3 OBJECTIVES

3.1 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.

3.2 Secondary objectives

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

3.3 Other objectives

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

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

4.1.1 Analysis sets

In addition to the analysis sets described in the section 11.1 of the protocol a 'Run-in Set' (RIS) and an 'All Randomized Set' (RND) are defined to be used in summaries of disposition and premature study discontinuation [see Section 7.1.2 and Section 7.1.3].

4.1.2 Analyses of the secondary efficacy variables

Where indicated, analyses based on analysis of covariance (ANCOVA) models, mixed models or logistic regression models planned in the protocol for the secondary variables, were supplemented by a Multiple Comparison Procedure – Modeling (MCP-Mod) analysis of the Least Squares Means (LSMeans) obtained from these models. MCP-Mod was qualified as an efficient statistical methodology for model-based design and analysis of Phase 2 dose finding studies [EMA 2014]. This approach replaces the Dunnett tests that were planned in the protocol for these endpoints.

In addition, a dose-response analysis was performed for the average change from baseline over time (Weeks 2, 4 and 8).

BP control rates. After completion of the protocol, the Canadian Hypertension Education Program (CHEP) issued guidelines proposing cut-offs of 85 mmHg for DBP and 135 mmHg for SBP, specifically focusing on measurement by automated office blood pressure measurement (OBPM) [Leung 2016]. These were added to the secondary endpoints.

Analysis data set for ABPM. ABPM is performed over a 24-h period with the ABPM device set to record DBP and SBP at a pre-defined inflation sequence over the 24-h period including three measurements per hour during the day and two per hour during the night. ABPM data are electronically transferred to [redacted] and subsequently to Actelion. The [redacted] supplements each ABPM reading with an indicator of whether the reading satisfied the quality control criteria agreed [redacted]

1. Start time of ABPM is between 06:00 and 11:00
2. Duration of ABPM is at least 24 hours
3. Percentage of valid readings in the period of duration is at least 75%
4. Number of required hours (i.e., hours with at least one reading) is at least 22
5. Number of exception hours (i.e., hours without a reading) is at most 2
6. No two consecutive exception hours

It should be noted that when an ABPM reading does not satisfy all 6 criteria this does not necessarily mean that this reading should be excluded from the analysis, as the ABPM analysis primarily focuses on the 24 hour means (according to [redacted] report dated [redacted] For the analysis of 24 hour means, criteria 3 and 6 are considered to be the most relevant ones by Actelion.

For this reason, the ABPM analyses will be based on the subset of subjects from the Per-Protocol Set (PPS) with baseline and Week 8 ABPM readings satisfying quality criteria 3 and 6 (i.e., ABPM readings having less than 75% valid readings and/or two consecutive exception hours will be excluded).

Trough to peak ratios based on ABPM. In the protocol it was assumed that trough to peak ratios of DBP and SBP measured by ABPM would be derived on a subject level. However, the definition of subject-specific trough to peak ratios [Omboni 1995] appears to be problematic because of individual ABPM variation over time. Based on clinical rationale and following the reasoning in recent FDA reviews such as FDA 2007, the trough to peak ratios of DBP (and SBP) were re-defined on a treatment group level based on the time course of the 24 hours ABPM. As a consequence, the analysis in the protocol (which assumed a definition on a subject level) was replaced by descriptive statistics [Section 10.7].

4.1.3 Safety analysis

As exploratory analyses, the change from baseline to Week 8 in hemoglobin and weight will be analyzed using the MCP-Mod approach [see Sections 10.9.4 and 10.9.5] to explore whether there is a dose-response relationship for these variables which are associated with the safety of ACT-132577.

4.2 Changes in the conduct of the study / data collection

A blinded sample size re-estimation was introduced in Version 3 of the protocol. This sample size re-estimation was based on the standard deviation (SD) of the primary endpoint, change from baseline to Week 8 in DBP as measured by OBPM in the PPS. As a consequence the number of randomized subjects was lowered to 490 (instead of the foreseen 540). The lower sample size did not affect the conduct of the study or the analysis of the data.

After database lock but before unblinding, it was noticed that one subject who had a Week 8 sitting diastolic blood pressure (SiDBP) outside of the analysis window was, however, included in the PPS (after accounting for the protocol deviations [PDs] present in the database). The decision was taken by management not to unlock the database and to maintain the PPS as it was. The subject remained in the PPS, with a missing value for the Week 8 SiDBP.

5 DEFINITIONS OF VARIABLES

Baseline assessments refer to the last available measurement before the start of double-blind treatment.

If date and time of the measurement are collected, baseline is the last one up to the start date and time of the double-blind treatment. If only the date is collected, baseline is the last one before the start date of the double-blind treatment. For ABPM baseline is the period from date/time of last run-in placebo intake up to the date/time of the first double-blind treatment intake, i.e., a maximum of 25 hours.

Screening assessments refer to last available measurement before or on run-in start date (Visit 1) before the start of placebo run-in medication.

5.1 Subjects disposition

Screened subjects: are all subjects who received a subject number.

Screening failures: are all subjects with answer 'NO' to the question 'Is the subject eligible for the Run-in period?' in the **Eligibility - Run-in Period** eCRF).

Reason for screening failure is collected in the same eCRF form.

Subjects who failed screening twice will only be counted once (and only the reason for the last screening failure will be tabulated).

Subjects in Run-in: are all subjects with answer 'YES' to the question 'Is the subject eligible for the Run-in period?' in the **Eligibility - Run-in Period** eCRF.

Run-in failures: are all subjects in Run-in with answer 'NO' to the question 'Was the subject randomized?' in the **Randomization** eCRF. Reason for run-in failure is collected in the same eCRF form.

Randomized subjects: are all subjects who received a randomization number from the Interactive Voice Response System (IVRS).

5.2 Subject characteristics

5.2.1 Demographics

Demographic variables are those collected at Screening on the **Demographics** eCRF pages 12–13 (or on page 14 in the event of Re-Screening):

- Sex
- Age
- Race (Black or African American; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Asian; White; Other)
- Ethnicity
- Country (derived from site number)

5.2.2 Baseline disease characteristics

Baseline disease characteristics include:

- Duration of essential hypertension (years) at Screening [see Section 11.8 for definition]
- Treatment for hypertension ongoing at Screening (Y/N), as collected in the **Treatment of Hypertension - Summary** eCRF.
- Mean trough sitting diastolic blood pressure (SiDBP) at Screening as measured by OBPM
- Mean trough sitting systolic blood pressure (SiSBP) at Screening as measured by OBPM

5.2.3 Other baseline characteristics

Other baseline characteristics, recorded on the **Height, Body Weight & BMI** eCRF page 22, at Screening and/or Re-Screening include:

- Height (cm) at Screening
- Body weight (kg) at Screening
- Body Mass Index (BMI; kg/m^2) at Screening

When necessary, height and body weight are converted into cm and kg, respectively [according to conversion rules detailed in Section 11.9]. BMI (kg/m^2), derived according to the formula in Section 11.10, is collected in the eCRF and will not be (re-) calculated.

In the event of re-screening, the last available measurement has to be considered in the analysis.

5.2.4 Medical history

Medical history includes previous and/or concomitant diseases or diagnoses collected on the **Medical History** eCRF page 15. Reported terms are coded using the MedDRA dictionary, Version 19.0.

Any disease or diagnosis is defined as previous if 'Ongoing at Screening' is not answered with 'Yes'; all other diseases/diagnoses are considered as concomitant.

5.2.5 Previous and concomitant therapies

Therapies are collected in the **Previous/Concomitant Medication** eCRF, and terms are coded using the WHO drug code dictionary and the anatomic therapeutic chemical (ATC) class code using the versions available at database lock

A previous therapy is any treatment for which the end date is prior to the start of study (i.e., signing of informed consent). If the end date is missing and the start date of therapy is prior to the date of informed consent, then the therapy is considered as previous if 'Ongoing at start of treatment?' is not ticked with 'Yes'.

A study-concomitant therapy 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 (Visit 8).

A double-blind treatment concomitant therapy 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.

Rules for handling partial or missing dates are detailed in Section 12.

Forbidden concomitant therapies

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 protocol synopsis Appendix A].

- Endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors.
- Strong inhibitors or inducers of cytochrome P450 3A4 isoenzyme [see protocol synopsis Appendix A].

These definitions will be used in the clinical review to identify potential PDs. Forbidden medication will not be tabulated as such.

Specific previous and concomitant therapies

Not applicable.

5.2.6 Other subject characteristics

Not applicable.

5.3 Study treatment duration and compliance

5.3.1 Study treatment duration

Double-blind treatment duration is defined as the number of days between the first dose of double-blind study treatment [see definition in Section 11.2] and the last dose of double-blind study treatment [see definition in Section 11.4] plus one day, without taking into account interruptions. For the purpose of tabulation treatment duration will also be expressed in weeks, calculated by dividing the above treatment duration (in days) by 7.

In addition, run-in treatment duration is defined as the number of days between the first dose and last dose of open-label placebo run-in treatment.

5.3.2 Compliance with study treatment

Double-blind treatment compliance is based on the **Study Drug Dispensing & Accountability** eCRF. Run-in treatment compliance is based on the same eCRF.

As per section 5.1.4.2 of the protocol, all subjects had to take 2 capsules o.d. every morning from the morning of Visit 4 / Randomization (i.e., Day 1, after completion of the baseline 24-hour ABPM recording) to the morning of Visit 7 / Part 1.

Compliance between Visit 4 and Visit 7 / Part 1 will be then calculated as follows:

Compliance =
[(number of capsules dispensed at Visit 4 – number of capsules returned at Visit 6 + number of capsules dispensed at Visit 6 – number of capsules returned at Visit 7)/ (Total number of capsules that should have been taken)] × 100.

The number of capsules that should have been taken during the double-blind period is the double-blind treatment duration (in days) as defined in Section 5.3.1, multiplied by 2.

Run-in compliance between Visit 1 and Visit 4 / Part 1 will be calculated similarly.

Here the expected number of capsules is the run-in treatment duration (in days) as defined in Section 5.3.1, multiplied by 2.

5.3.3 Study treatment discontinuation

A subject is considered to have prematurely discontinued double-blind study treatment if the 'reason for treatment end' in the **Study drug Log** eCRF is 'PREMATURE DISCONTINUATION' and the 'Study Period' is 'DB TREATMENT'. The reason for premature discontinuation will be taken from the **Premature Discontinuation of Study Treatment** eCRF and the study period is 'DB TREATMENT'.

Discontinuation from run-in study treatment is defined similarly and the reason will be taken from the same eCRF, but with study period = 'RUN-IN TREATMENT'. Discontinuation from withdrawal study treatment (listed only) is defined similarly with study period = 'SB WITHDRAWAL'. In those cases where a subject completed the double-blind treatment period, but did not start the withdrawal period, the reason for treatment discontinuation will be allocated to the withdrawal period.

5.3.4 Study treatment adjustments or interruptions

Study treatment interruptions in the double-blind period are recorded in the **Study drug Log** when 'Study Period' is 'DB TREATMENT'. A subject is considered to have had a study treatment interruption if the reason for treatment end is either 'Temporarily interrupted due to an AE' or 'Temporarily interrupted not due to an AE'.

5.4 Study discontinuation

Subjects who completed the study as per protocol are those with the question "Did the subject complete the study?" answered "Yes" in the **End-of-Study** eCRF.

On the other hand, a subject is considered to have prematurely discontinued the study if the answer to the question 'Did the subject complete the study?' in the **End-of-Study** eCRF is 'No'. The reason for study stop is derived from the same form. Reasons for study withdrawal are: Death, Lost to follow up, Subject decision, Physician decision, Sponsor decision.

5.5 Efficacy variables

All efficacy data are collected electronically and are transferred to Actelion by [redacted].

OBPM, SiDBP and SiSBP (mmHg) are measured at the study site by the BpTRU® device using six measurements per subject / visit. These measurements and their average (excluding the first measurement) are uploaded into the [redacted] database. The data

transfer from [redacted] to Actelion includes the separate measurements as well as the average which will be used as the subject's SiDBP or SiSBP value for that visit. The average will not be re-calculated by the sponsor. The sponsor will perform spot checks to confirm that the average was been correctly calculated [redacted]

ABPM is performed over a 24-h period with the ABPM device set to record DBP and SBP at a pre-defined inflation sequence over the 24-h period including three measurements per hour during the day and two per hour during the night. ABPM data are electronically transferred to [redacted] and subsequently to Actelion. The [redacted] supplements each ABPM reading with an indicator of whether the reading satisfied the quality control criteria agreed between [redacted] and Actelion [redacted]

1. Start time of ABPM is between 06:00 and 11:00
2. Duration of ABPM is at least 24 hours
3. Percentage of valid readings in the period of duration is at least 75%
4. Number of required hours (i.e., hours with at least one reading) is at least 22
5. Number of exception hours (i.e., hours without a reading) is at most 2
6. No two consecutive exception hours

In addition, there is an indicator (Y/N) for the overall quality of the ABPM reading. This is only set to Y if all six criteria are met.

It should be noted that when an ABPM reading does not satisfy all 6 criteria, this does not necessarily mean that this reading should be excluded from the analysis as the ABPM analysis primarily focuses on the 24 hour means [redacted]. For the analysis of 24 hour means, criteria 3 and 6 are considered to be the most relevant ones by Actelion.

For this reason, the ABPM analyses will be based on the subset of subjects from the PPS with baseline and Week 8 ABPM readings satisfying quality criteria 3 and 6 (i.e., ABPM readings having less than 75% valid readings and/or two consecutive exception hours will be excluded). As this subset is likely to be comprised of < 50% of subjects, formal dose-response analyses for the ABPM endpoints will be carried out as needed.

All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the time windows described in Section 11; reference to visits are to be intended as references to re-mapped visit, i.e., time window visits.

5.5.1 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 hours post-dose) SiDBP, measured by OBPM.

Baseline is defined as described in Section 5. Week 8 is the time window of Visit 7 [Section 11.1].

SiDBP is retrieved from the SDTM VS domain selecting VSTESTCD="DIABP" and VSSCAT ='Average'.

5.5.2 Secondary efficacy endpoints

- Change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiSBP, measured by OBPM and collected as described for SiDBP.
  - SiSBP is retrieved from the SDTM VS domain selecting VSTESTCD="SYSBP" and VSSCAT ='Average'.

- Control and response status at Week 8 of DB treatment period (Period II) based on trough SiDBP, measured by OBPM;
  - Controlled, if mean SiDBP < 90 mmHg;
  - Responder, if the reduction from baseline in mean SiDBP ≥ 10 mmHg;
  - Controlled according to CHEP guidelines [Leung 2016], if mean SiDBP < 85 mmHg.

- Control and response status at Week 8 of DB treatment period (Period II) based on trough SiSBP, measured by OBPM;
  - Controlled, if mean SiSBP < 140 mmHg;
  - Responder, if the reduction from baseline in mean SiSBP ≥ 20 mmHg;
  - Controlled according to CHEP guidelines [Leung 2016], if mean SiSBP < 135 mmHg.

- Change from baseline to Week 8 of DB treatment period (Period II) in 24-hour mean DBP, measured by ABPM;
  - ABPM will be measured before start of treatment (Day -1, Visit 4) and after the last dose (Day 55, Visit 7). At each visit the 24-hour mean DBP will be derived from the area under the DBP-time curve, divided by the time span. [See Figure 1 for clarification.] Time points later than 25 hours after the first time point will be excluded from the calculation. The change from baseline to Week 8 will be obtained as the difference in 24-hour mean DBP ABPM between Visit 7 and Visit 1.

- Change from baseline to Week 8 of DB treatment period (Period II) in 24-hour mean SBP, measured by ABPM;
  - The change from baseline to Week 8 will be obtained as the difference in 24-hour mean SBP ABPM between Visit 7 and Visit 1, where the 24-hour mean SBP ABPM is calculated similar to the 24-hour mean DBP ABPM.

- Trough to peak ratio for DBP based on ABPM.
  - The trough to peak ratio will be derived on treatment group level [FDA 2007] based on the time course of ABPM and will be corrected for baseline according to the following steps:
    - Patient level: for each visit (Visit 4 / Day -1 and Visit 7 / Part 1) the patient's ABPM-DBP will be averaged by hour after drug intake (0, 1, .., 24), applying a window of 30 minutes around each hour (lower limit excluded; upper limit included).
    - Group level: for each visit (Visit 4 / Day -1 and Visit 7 / Part 1) and hour after drug intake (0, 1, .., 24) the ABPM-DBP will be averaged by treatment group.
    - Group level: for each hour after drug intake (0, 1, .., 24) and the treatment group the difference in mean ABPM-DBP between Week 8 (Visit 7 Part 1) and baseline (Visit 4 Part 1) will be obtained.
    - Group level: the trough to peak ratio will be calculated as the average of the (five) differences at hours 20–24 (expected trough) divided by the average of the (five) differences at hours 2–6 (expected peak at 4 hours ± 2 hours) [See Appendix C for illustration.]

Baseline is defined as described in Section 5 and Week 8 is the time window of Visit 7 [Section 11.1].

In the evaluation of changes from baseline and control/response status, only subjects with both the baseline and the time point assessments available will be included.

5.5.3 Other efficacy endpoints

- Changes from baseline to time window Visit 5 (Week 2) and time window Visit 6 (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 daytime ABPM;
  - *Change from baseline in mean daytime DBP*. All ABPM measurements taken between 09:00 and 21:00 will be included in this calculation [O'Brien 2013]; there may be two parts of the daytime DBP-time curve to be considered for a subject at a given visit, one for each calendar day of Visits 4 and 7. At each visit the mean daytime DBP will be derived from the area under the DBP-time curve(s), divided by the time span(s) [see Appendix B for clarification]. The change from baseline to Week 8 will be obtained as the difference in mean daytime DBP ABPM between Visit 7 and Visit 4.
  - *Change from baseline in mean daytime SBP*. Similar to change from baseline in mean daytime DBP.

- Change from baseline to Week 8 of DB treatment period (Period II) in mean night time ABPM;
  - *Change from baseline in mean night time DBP*. All ABPM measurements taken between 01:00 and 06:00 will be included in this calculation [O'Brien 2013]; there should be one night time part of the DBP-time curve to be considered for each subject at a given visit; in the unlikely event that there are two, only the first one will be used). At each visit the mean night time DBP will be derived from the area under the DBP-time curve, divided by the time span [see Appendix B for further specification]. The change from baseline to Week 8 will be obtained as the difference in mean daytime DBP ABPM between Visit 7 and Visit 4.
  - *Change from baseline in mean night time SBP*. Similar to change from baseline in mean night time DBP.

- Trough to peak ratio for SBP based on ABPM;
  - The trough to peak ratio for SBP will be derived on treatment group level based on the time course of ABPM as similar to the trough to peak ratio for DBP.

- Changes from baseline to time window Visit 8 (Week 10 i.e., Week 2 of withdrawal period - Period III) in mean trough SiSBP and SiDBP (measured by OBPM);

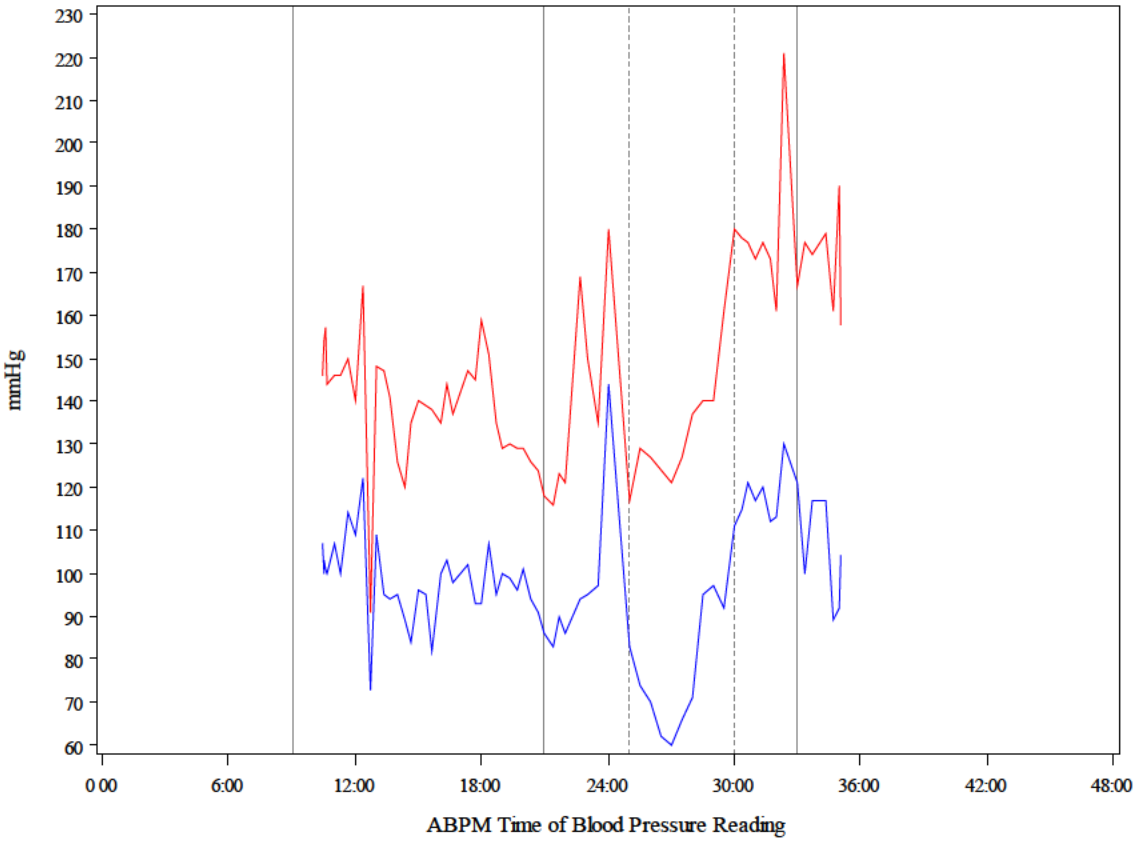
- Changes from Week 8 of Period II to time window Visit 8 (Week 10 i.e., Week 2 of withdrawal period - Period III) in mean trough SiSBP and SiDBP (measured by OBPM).

5.5.3.1 Illustration of derivation of ABPM endpoints

The derivation of the various endpoints based on ABPM is illustrated by means of an example. Figure 1 displays the DBP and SBP measured by ABPM in one subject at one visit. The data underlying this example figure are included in Appendix B.

Since ABPM measurements are obtained during 24 hours at two consecutive calendar days, the time on the horizontal axis runs from 0–48 hours, clock times 0:00–23:59 corresponding to the first day and times 24:00–48:00 to the second day The ABPM started on 10:29 on the first day and finished on 11:04 on the second day [35:04 in Appendix B].

Figure 1 Example DBP and SBP measured by ABPM



Example DBP (blue lines) and SBP (red lines) measured by ABPM in one subject at one visit. Vertical lines indicate inclusion of measurements in the calculation of daytime ABPM (solid) and night time ABPM (dotted).

The derivation of the 24-hour mean DBP (SBP), mean daytime DBP (SBP) and mean night time DBP (SBP) for these example data are as follows.

- The total duration of this ABPM (24 hours 35 minutes) was greater than 24 hours, but less than 25 hours, so all measurements were included in the calculation of 24-hours mean ABPM.
- The 24-hour mean DBP (SBP) is derived from the area under the DBP (SBP) curve, divided by the time span. The area under the curve is calculated by the trapezoidal rule. The implementation of this rule in SAS is given in Appendix B. For the example data the areas under the DBP and SBP curves are 8,640,870 and 12,956,970 mmHg sec, respectively. Dividing both areas by the time span of

88,500 sec gives a 24-hour means of 97.6 and 146.4 mmHg for DBP and SBP, respectively.
  - The trapezoidal rule will be applied up to the last measurement within 25 hours. If there is another measurement after 25 hours, there will be NO interpolation up to 25 hours exactly.
- The mean daytime DBP (SBP) is based on two periods: from 10:29 to 21:00 (limits included) on the first day and from 09:00 to 11:04 on the second day (limits included; 33:00 to 35:04 in Appendix B). The mean daytime DBP and SBP are 99.5 mmHg and 143.9 mmHg, respectively.
- The mean night time DBP (SBP) is based on the measurements between 01:00 and 06:00 on the second day (limits included; 25:00 to 30:00 in Appendix B). The mean night time DBP and SBP are 78.4 mmHg and 135.5 mmHg, respectively.
- Note that measurements between 21:00 on the first day and 01:00 on the second day (limits excluded) and between 06:00 and 09:00 on the second day (limits excluded) are only included in the calculation of the 24-hour means, but not in the calculation of the daytime or night time means.

5.6 Safety variables

All assessments are considered and re-assigned to the most appropriate visit according to the time windows described in Section 11; reference to visits are to be intended as references to re-mapped visit, i.e., time window visits.

The following safety variables will be evaluated:

- Treatment-emergent adverse events (AEs);
- AEs leading to premature discontinuation of study treatment;
- Treatment-emergent deaths;
- Treatment-emergent serious adverse events (SAEs);
- Treatment-emergent electrocardiogram (ECG) abnormalities;
- Treatment-emergent marked laboratory abnormalities;
- Changes from baseline to time window Visits 5, 6 and 7 (Weeks 2, 4 and 8, respectively) of DB treatment period (Period II) in laboratory parameters;
- Changes from baseline to time window Visits 6 and 7 (Week 4 and Week 8, respectively) of DB treatment period (Period II) in ECG parameters (pulse rate [PR], QRS, QT, QTcB, QTcF);
- Changes from baseline to time window Visits 5, 6 and 7 (Weeks 2, 4 and 8, respectively) of DB treatment period (Period II) in body weight and PR (BpTRU®).

5.6.1 Adverse events

An AE is defined as any term reported by the investigator in the **Adverse Event** eCRF. The original terms used by the investigators to describe AEs are assigned preferred terms for classification and tabulation using the MedDRA dictionary, Version 19.0.

5.6.1.1 Treatment-emergent adverse events

Double-blind treatment-emergent AEs are defined as those AEs with onset on or after the double-blind treatment start date [see definition in Section 11.2] up to the double-blind treatment end date [see definition in Section 11.4] plus 30 days (included). Run-in treatment-emergent AEs are AEs with onset dates between the start and end dates of the run-in placebo (or the start of double-blind treatment, if applicable; limits included).

5.6.1.2 Frequency of treatment-emergent adverse events

Except otherwise specified, the counting of treatment-emergent AEs in the summary table is handled as follows:

- Subjects who experienced the same AE more than once (as qualified by the same preferred term[s]) are counted only once.
- In the event that the reported AE is assigned to several preferred terms, subjects are counted for each individual preferred term.

5.6.1.3 Intensity of treatment-emergent adverse events

The intensity of an AE is determined by the investigator as 'mild', 'moderate' or 'severe'.

AEs reported more than once (as qualified by the same preferred term) for a subject within a specified time period but with different intensities are counted only once, with the worst reported intensity in the corresponding analysis. If intensity is missing, the event is considered severe.

5.6.1.4 Relationship of treatment-emergent adverse events

Relationship to study treatment is determined by the investigator as 'related' or 'not related'. An event is considered related if the response to the question 'Relationship to study treatment?' is answered 'Related'.

For AEs reported more than once (as qualified by the same preferred term) for a subject within a specified time period, the worst relationship reported is taken. AEs with missing relationship are considered in any analysis as 'Related'.

5.6.2 Deaths

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

The original terms used by the investigators to describe the primary death cause are assigned preferred terms for classification and tabulation using the MedDRA dictionary.

Double-blind treatment-emergent deaths are those with occurrence on or after the double-blind treatment start date [see definition in Section 11.2] up to the double-blind treatment end date [see definition in Section 11.4] plus 30 days (included). Run-in

treatment-emergent deaths are deaths that occur between the start and end of the run-in placebo (or the start of double-blind treatment, if applicable; limits included).

5.6.3 Serious adverse events

An SAE is defined as an AE with "Serious?" = "Yes" on the **Adverse Events** eCRF.

Double-blind treatment-emergent SAEs are all SAEs with onset on or after the double-blind treatment start date [see definition in Section 11.2] up to the double-blind treatment end date [see definition in Section 11.4] plus 30 days (included). Run-in treatment-emergent SAEs are SAEs with onset date between the start and end dates of the run-in placebo (or the start of double-blind treatment, if applicable; limits included).

5.6.4 Adverse events leading to discontinuation of study treatment

These are AEs with 'Action taken with study drug' recorded as 'permanently discontinued' on the **Adverse Event** eCRF.

5.6.5 Other adverse events

Not applicable.

5.6.6 Physical examination, vital signs and body weight

Vital signs include PR measured by BpTRU® (simultaneously with BP; the mean is provided in the same way, i.e., based on the last 5 of 6 measurements) and body weight (DBP and SBP are evaluated as efficacy endpoints). For PR, the value is retrieved from the SDTM VS domain by selecting VSTESTCD = "HR" and VSSCAT = 'Average'.

All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the time windows described in Section 12.

5.6.7 Electrocardiogram

A standard 12-lead ECG is performed as defined in the 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. All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the rules described in Section 11.1.

The following variables will be evaluated: heart rate (HR; bpm), PR (ms), QRS (ms), QT (ms), QTc (ms). In addition, the percentage of subjects with any ECG findings will be evaluated.

QTc (ms) will be calculated according to Fridericia's formula $QTcF = QT/(RR)^{1/3}$.

ECG data will be electronically transferred from the ECG laboratory database to Actelion and will not be (re-)calculated. Note that ECG HR will be evaluated only in the context of the ECG. For vital signs, PR will be used based on BpTRU®.

5.6.7.1 Treatment-emergent ECG abnormalities

Double-blind treatment-emergent ECG abnormalities are defined as follows:

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

In addition, each of the six combinations of maximum QTcF and increase in QTcF will be considered.

Note that, in order to allow appropriate interpretation of overall incidence of abnormalities > 450 ms, the marked abnormalities are presented cumulatively, e.g., a QTc value of 501 ms is reported in > 450 ms (H), > 480 ms (HH) and > 500 ms (HHH) categories; the same holds for abnormalities related to changes from baseline (i.e., they are presented cumulatively).

Treatment-emergent ECG abnormalities are defined as those abnormalities with onset on or after the double-blind treatment start date [see definition in Section 11.2] up to the double-blind treatment end date [see definition in Section 11.4] plus 30 days (included): i.e., the highest QTc absolute value and the highest QTc change value at any post-baseline time point of assessment up to 30 days after study treatment discontinuation are considered in the evaluation of the categories, as defined above.

5.6.8 Laboratory

Laboratory data are evaluated in standard international units as provided by the central laboratory. The following tests are considered:

- Hematology: hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential counts, platelet count.
- Chemistry: aminotransferases (aspartate aminotransferase [AST] / alanine aminotransferase [ALT]), alkaline phosphatase [AP], total and direct bilirubin, lactate hehydrogenase, creatinine, creatinine clearance, uric acid, glucose, sodium, potassium, total protein, albumin, thyroid hormones (triiodothyronine [free T3], thyroxine [free T4]) and thyroid-stimulating hormone.
- Urinalysis: Urine albumin-to-creatinine ratio (UACR).

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

Results of local laboratory tests (collected on the **Local Laboratory** eCRF) may be used to identify marked abnormalities, but only if no central laboratory test has been performed in the same time window. Local laboratory test results will not be used in summaries, but will still be listed.

5.6.8.1 Treatment-emergent marked laboratory abnormalities

The marked laboratory abnormalities are given in Table 2, copied from appendix 1 of the protocol.

Table 2 Thresholds for marked laboratory abnormalities

Parameter	LL	LLL	HH	HHH	HHHH
Hematology					
Hemoglobin	< 100 g/L (< 10 g/dL; < 6.2 mmol/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)	

Parameter	LL	LLL	HH	HHH	HHHH
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	< 30 mL/min	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	> 590 (umol/L) (> 10 mg/dL)	> 720 (umol/L) (> 12 mg/dL)	
Albumin	< 30 g/L (< 3.0 g/dL)	< 20(g/L (< 2.0 g/dL)	-	-	

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; NA = not applicable; ULN = upper limit of normal.

Treatment-emergent marked laboratory abnormalities are those marked abnormalities with onset date after the double-blind treatment start date [see definition in Section 11.2] and before or on double-blind treatment end date [see definition in Section 11.4] plus 30 days (included), that were not present at baseline.

Baseline for laboratory data is defined in Section 5. Each condition is triggered at any post-baseline time point of measurement up to the double-blind treatment end date plus 30 days (included). When determining double-blind treatment-emergent marked laboratory abnormalities, all assessments (including the unscheduled ones) are considered.

5.6.9 Other safety variables

Not applicable.

5.7 Quality of life variables

Not applicable.

5.8 Pharmacoeconomic variables

Not applicable.

5.9 Pharmacodynamic variables

Trough plasma concentrations of ET-1, measured at steady state at Weeks 2, 4 and 8 in DB treatment period (Period II).Trough is defined as a sample taken in the morning of the visit prior to study treatment administration of that visit.

5.10 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) [redacted]

6 DEFINITION OF PROTOCOL DEVIATIONS

PDs include deviations from inclusion and/or exclusion criteria and deviations from the protocol during the conduct of the study, classified as per latest version of PD code list. Each PD is reported in the SDTM DV domain and categorized according to time period:

1. PD at Screening
2. PD during Run-in period
3. PD at Visit 4 / Pre-randomization

4. PD during DB treatment period
5. PD during withdrawal period and follow-up

Each PD is classified as important or not. Only important PDs during time periods 3, 4 and 5 will be summarized by treatment group for the RND set. (All PDs will be listed.)

Note that an important PD does not necessarily lead to exclusion from the PPS [see Section 7.1.6], whereas an unimportant PD may lead to exclusion from the PPS. The subset of PDs *leading to exclusion* from the PPS are:

1. Double-blind treatment duration less than 49 days: PV_PP.535.
2. No or no valid Week 8 SiDBP (hence, no primary endpoint): PV_PP.501 and PV_MM.501.
3. Anti-hypertensive treatment still ongoing at randomization: PV_MM.307.
4. Taking medication during the double-blind treatment interfering with the primary efficacy parameter (SiDBP): PV_MM.503, PV_MM.504, PV_MM.506, PV_MM.507, PV_MM.508, PV_MM.509, PV_MM.534.
5. Compliance with double-blind treatment < 80% or > 120% or treatment not taken as per protocol: PV_PP.502 and PV_MM.515.

Note that exclusion will be done on a subject basis (rather than on subject / visit basis). In this particular study this approach is not unreasonable since PDs 1–5 are related to the 8 week DB treatment period and the primary efficacy endpoint is measured at the end of that period.

The one PD *leading to exclusion* from the Pharmacokinetic (PK) Set [see Section 7.1.6] is that the PK sample for that subject/visit was not taken at trough: PV_MM.512.

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Screened Set

The Screened Set (SCR) includes all subjects who received a subject number.

7.1.2 Run-in Set

The RIS includes all subjects who received at least one dose of SB placebo in Period I.

7.1.3 All Randomized Set

The RND includes all subjects who received a randomization number from the IVRS.

7.1.4 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects in the RND Set 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).

7.1.5 Per-Protocol Set

The PPS includes all subjects from the FAS who have a mean trough SiDBP at Week 8 of Period II and do not have any important PD as defined in Section 6. Subjects are evaluated according to the study treatment they have been assigned to.

7.1.6 Safety Set

The Safety Set (SAF) 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.

7.1.7 Pharmacokinetic Set

The PK Set includes all subjects from the PPS who had at least one evaluable PK trough sample. Subjects are evaluated according to the study treatment they have received.

8 DEFINITION OF SUBGROUPS

All subgroup analyses will be performed to investigate the consistency of the treatment across subgroups defined by:

Age	< 65 versus ≥ 65 years
	18–64, 65–84 and ≥ 85 years; for European Clinical Trials (EudraCT) Database purposes only
Sex	Female, male
Race	Black or African American; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Asian; White; Other. Categories containing less than 5% of randomized subjects will be considered in the category 'Other' for purpose of analysis.
Country	United States (including Puerto Rico, USA); Canada (CAN); Israel (ISR)

9 GENERAL STATISTICAL METHODOLOGY

This section describes the general statistical methodology, independent of which analysis data set is used. These aspects will be addressed in Section 10. SAS and R programming statements are provided to specify the details of the analyses.

9.1 Missing data

All analyses based on the PPS will be based on observed cases (OC). It is acknowledged that the PPS analyses are based on a selected subset of patients who completed the 8 weeks of DB treatment with sufficient compliance and who have no missing data at Week 8. For the assessment of dose-response reliance on this subset was deemed appropriate.

In analyses based on the FAS missing data will be imputed using last observation carried forward (LOCF). This may be justified as a conservative analysis since in this study the majority of patients are expected to improve over time [EMA 2010].

Baseline observation carried forward (BOCF) will be used as a sensitivity analyses for missing data imputation. Another sensitivity analysis is provided by a mixed model which does not impute the missing data and, in that sense, can be seen as a OC analysis. Mixed models are based on the missing at random (MAR) assumption, i.e.: missing data can be fully accounted for by baseline covariates and prior measurements. The MAR assumption is not unreasonable in the hypertension context, although it cannot be proven.

9.2 Dose-response analysis for the primary endpoint

Dose-response data include changes from baseline to Week 8 of DB treatment period in mean trough SiDBP (primary endpoint) and mean trough SiSBP (secondary endpoint). These data will be analyzed using the MCP-Mod approach [Bretz 2005, Pinheiro 2006]. In brief, this methodology consists of two steps:

1. MCPs step to establish a dose-response signal (i.e., the dose-response curve is not flat) using MCPs.
2. Modeling (Mod) step to estimate the dose-response curve and target doses using modeling techniques.

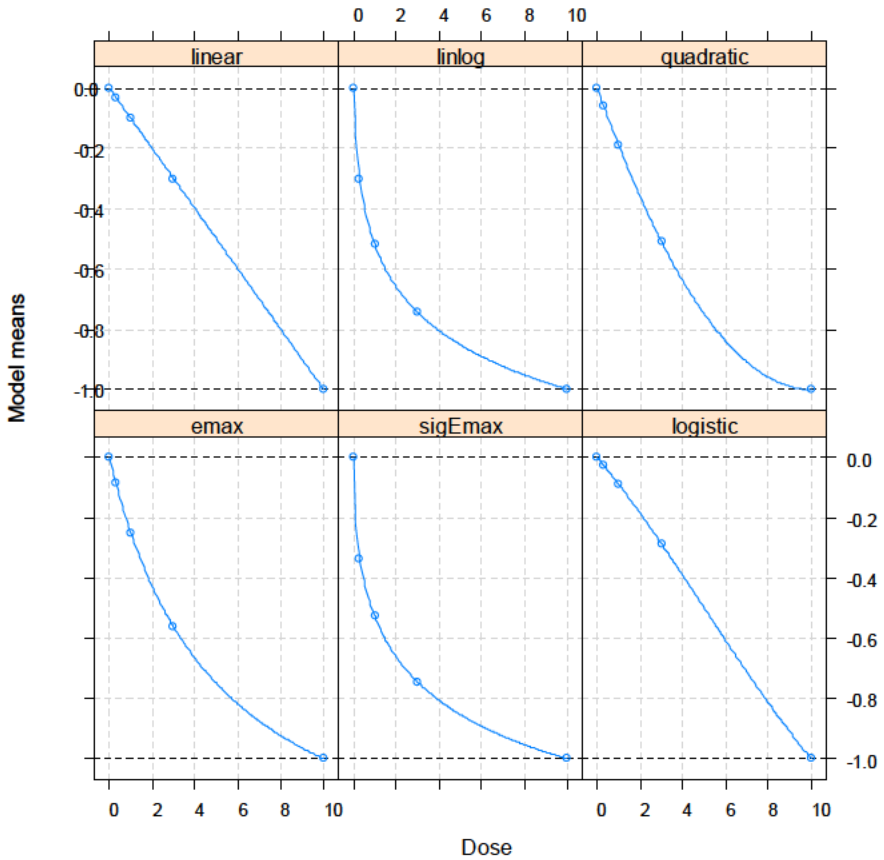
In this study six models have been pre-specified in the protocol for consideration in all MCP-Mod analyses: linear, linear in log (linlog), quadratic, maximum effect (E_{max}), sigmoidal E_{max} and logistic. See Table 3 for the parameterization of the dose-response models and Figure 2 as an illustration of their basic shapes. The initial values for the parameters are needed in the MCP step of the procedure. They will be estimated in the Mod step based on the actual data.

Table 3 Parameterization of models considered in MCP-Mod analyses

Model	**Response***	**Initial value(s) for parameters**
Linear	E0 + delta • *dose*	NA*
Linear in log	E0 + delta • log(*dose* + 0.5)	NA*
Quadratic	E0 + beta1 • *dose* + beta2 • *dose*^2	beta2/beta1 = -0.005
E_{max}	E0 + E_{max} • *dose*/(ED50 + *dose*)	ED50 = 50
Sigmoidal E_{max}	E0 + E_{max} • *dose*^h/(ED50^h + *dose*^h)	ED50 = 50, h = 0.5
Logistic	E0 + E_{max}/(1 + exp[{ED50 - *dose*}/delta])	ED50 = 50, delta = 50

Dose = 0, 5, 10, 25 and 50 mg of ACT-132577;
*Not applicable for E0, delta (in linear and linlog models), and E_{max}

Figure 2 Dose-response curves considered in MCP-Mod procedure



The Lisinopril group will be excluded from all analyses of the dose-response. Note that the 'Model means' on the vertical axis are plotted on a scale from 0 to -1 for illustrative purposes. The actual scale will depend on the endpoint analyzed.

The null hypothesis of 'no dose-response' will be rejected if at least one of the six Multiple Contrast Tests (MCTs) has a multiplicity adjusted p-value < 0.05. All statistically significant models (i.e., with an adjusted p-value < 0.05) are fitted in the Mod step and for each model Akaike's Information Criterion (AIC) is calculated. The smaller the value of AIC (= model deviance + 2 times the number of model parameters), the better the fit. The analysis will be performed using the R-package *DoseFinding* [Bornkamp 2016]. The basic R-code is:

```
library(DoseFinding)
doses <- c(0, 5, 10, 25, 50)
candMod <- Mods(linear = NULL, linlog = NULL, quadratic = -0.005, emax = 50,
                sigEmax = c(50, 0.5), logistic = c(50, 50), doses = doses,
                direction="decreasing")
MMfit <- MCPMod(dose=dose, resp=resp, data=DF, addCovars=~base, models =
candMod, Delta=3)
```

In the Mods function call the candidate models are specified, together with the assumed direction of the effect (decreasing for change from baseline in blood pressure). In the call to the MCPMod function, DF is a data frame with objects dose, resp (for response), and base (for the baseline value) and Delta is a target difference vs placebo (Delta=3 for DBP; Delta=5 for SBP). The object *MMfit* will be summarized to obtain the MCP test, parameter estimates, target dose and AIC. These elements will go in a summary table. The object will be plotted to display the fitted dose-response curves.

Subgroup analyses based on MCP-Mod can be performed by fitting the selected model by subgroup using the *fitMod* function for which the basic R-code is:

```
MMfit1 <- fitMod(dose=dose, resp=resp, data=DF[DF$subg==1,], addCovars=~base,
model=MMfit$selMod)
MMfit2 <- fitMod(dose=dose, resp=resp, data=DF[DF$subg==2,], addCovars=~base,
model=MMfit$selMod)
```

As a supportive analysis to MCP-Mod, change from baseline to Week 8 in DBP and SBP will also be analyzed in an ANCOVA model using the Dunnett test.

```
proc mixed data=dset;
  class treat;
  model outcome=treat base;
  lsmeans treat/ adjust=Dunnett diff=control('0') cl;
  where week=8 and treat in (0,1,2,3,4);
run;
```

9.3 Dose-response analyses for continuous data

Changes from baseline to Week 8 for other continuous OBPM endpoints will be analyzed using the general MCP-Mod approach which consists of two steps.

First an ANCOVA model is fitted with a factor for treatment group and a covariate for the baseline value. The SAS statements (using mock variable names and values) for this model are:

```
ods output lsmeans=lsm; * export data set lsm as xpt file;
proc mixed data=dset;
  class treat;
  model outcome=treat base;
  lsmeans treat/ cov;
  where week=8 and treat in (0,1,2,3,4);
run;
```

Here, treat=0, 1, 2, 3, and 4 for placebo, 5 mg, 10 mg, 25 mg and 50 mg of ACT-132577, respectively. Note that the active comparator (treat=5) is excluded from this analysis.

Then the LSMeans from this model will be analyzed using the general MCP-Mod approach. The R statements for this analysis are (Delta=3 for DBP; Delta=5 for SBP):

```
# read data frame lsm from xpt file
est <- lsm$ESTIMATE # LSMeans
C <- lsm[,c("COV1","COV2","COV3","COV4","COV5")] # covariance matrix
doses <- c(0,5,10,25,50)
MMfit <- MCPMod(type="general", dose=doses, resp=est, S=as.matrix(C),
models=candMod, Delta=3, alpha=0.05)
```

Repeated measurements (e.g., changes from baseline to Weeks 2, 4 and 8) will be analyzed in two ways: focusing on the last time point (e.g., Week 8 and using Week 2 and Week 4 only to predict missing data, if needed) and estimating the average effect over time. In both cases the general MCP-Mod approach was used.

Last time point. First a mixed model is fitted with factors for treatment group, time and treatment by time interaction and covariates for the baseline value and the interaction between baseline and time. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. The SAS statements for this model are:

```
ods output lsmeans=lsml (where=(week=8)); * export data set lsml as xpt file;
proc mixed data=dset noclprint=6;
  class treat week subjid;
  model outcome=treat week treat*week base base*week;
  repeated week/ subject=subjid type=un;
  lsmeans treat*week/ cov;
  where treat in (0,1,2,3,4);
run;
```

The LSMeans at Week 8 will then be analyzed using the general MCP-Mod approach. The R statements for this analysis are the same as above, except for:

```
C <- lsm[,c("COV3","COV6","COV9","COV12","COV15")] # covariance matrix
```

Average over time. First the same mixed model is fitted, but without the treatment by time interaction. The SAS statements for this model are:

```
ods output lsmeans=lsm2; * export data set lsm2 as xpt file;
proc mixed data=dset noclprint=6;
  class treat week subjid;
  model outcome=treat week base base*week;
  repeated week/ subject=subjid type=un;
  lsmeans treat/ cov;
  where treat in (0,1,2,3,4);
run;
```

Then the LSMeans (averages over time) will be analyzed using the same R statements as above with:

```
C <- lsm[,c("COV1","COV2","COV3","COV4","COV5")] # covariance matrix
```

9.4 Dose-response analyses for binary data

Binary outcomes include the control and response status for DBP (or SBP) at a fixed time point and will also be analyzed using the general MCP-Mod approach. First a logistic regression model is fitted with a factor for treatment group and a covariate for the baseline value of DBP (or SBP). The SAS statements (using mock variable names and values) for this model are:

```
ods output lsmeans=lsm; * export data set lsm as xpt file;
proc logistic data=dset descending;
  class treat/param=glm;
  model resp=treat base;
  lsmeans trt01pn/ ilink cov;
  where week=8 and treat in (0,1,2,3,4);
run;
```

Then the estimated differences vs placebo (in data set diff) will be analyzed using the general MCP-Mod approach [Pinheiro 2014].

```
# read data frame lsm from xpt file
est <- lsm$MU #LSMeans
C <- diag(lsm$STDERRMU^2)
candMod <- Mods(linear = NULL, linlog = NULL, quadratic = -0.005, emax = 50,
```

```
                sigEmax = c(50, 0.5), logistic = c(50, 50), doses = doses,
                direction="increasing")
MMfit <- MCPMod(type="general", dose=doses, resp=est, S=as.matrix(C),
models=candMod, Delta=0.1, alpha=0.05)
```

Since control and response statuses are not expected to change much over time (i.e., from Week 2 to 8) a repeated measures analysis of these binary endpoints was omitted.

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

All statistical testing will be performed at a two-sided significance level of 0.05 using 95% confidence intervals (CIs).

In the main analysis of the primary endpoint in the PPS the type I error is controlled by the MCT part of the MCP-Mod methodology. The primary objective of the trial will be evaluated based on this analysis.

The type I error of the MCP-Mod analysis in the FAS is similarly protected. In the other supportive analysis of the primary endpoint Dunnett's test will be used to correct for testing multiple doses vs placebo. The alpha is formally controlled only for the main analysis; all other analyses are considered exploratory.

In all analyses of secondary and other efficacy variables, no correction will be made for multiple testing.

10.2 General rules for data presentations

This section describes the general rules applied for all data displays.

SAS version 9.3 is used for the statistical analyses except for the primary endpoint (dose-response analysis) that is analyzed by means of the R package.

Unless otherwise specified in this document:

- All listings are sorted by randomized treatment, subject number and, when appropriate, by visit / date of assessment. If a listing includes non-randomized subjects, these will appear after the randomized subjects. All data collected are displayed, including unscheduled visits (if any).
- In summary tables and graphical representations, subjects are grouped by randomized treatment group, except for the SAF for which the actual treatment is used.
- In summary tables based on the RND, FAS, PPS and SAF, the order of the treatment groups is: placebo, ACT-132577 5 mg , ACT-132577 10 mg, ACT-132577 25 mg, ACT-132577 50 mg and Lisionpril 20 mg, followed by Total (if required). In summary tables based on the RIS or SCR, only a total column will be given.

- The absolute change from baseline to Visit X is defined as the difference between the post-baseline Visit X value and the baseline value.
- In order to analyze the data at the relevant planned (scheduled) visits, all recorded assessments for each subject up to the Week 10 visit are reassigned to the most appropriate visit according to the time window for that visit. The windows are consecutive (i.e., there are no gaps) and are based on the study day corresponding to the date of assessment. Any unscheduled visit is also mapped to a time window. Details of the visit mapping are given in Section 11.1.
- According to section 11.3.2.2 of the protocol, imputation rules for missing data are defined for the evaluation of efficacy endpoints at Week 8. Subjects without a value in the defined Week 8 time window are included in the analysis according to the rules highlighted in Section 9.

10.3 Display of subject disposition, protocol deviations and analysis sets

10.3.1 Subject disposition

Summary tables are provided, on the SCR, RIS and RND sets [see Section 7 for terminology], by treatment group (where applicable) and overall, to display the following information:

- Disposition of subjects (screened, entered in run-in, randomized, treated i.e., who received at least one dose of study treatment, who completed treatment - see Section 5.3.3 for definition, who completed study - see Section 5.4 for details). This summary table is also provided by site.
- Reasons for screening failures [see definition in Section 5.1, overall only].
- Reasons for run-in failures [see definition in Section 5.1, overall only].

Percentages are calculated based on screened subjects [see definition in Section 5.1] or run-in subjects where appropriate. A listing of screening failures is provided for the SCR and a listing of run-in failures for the RIS. Randomization scheme and codes and code break or subject unblinding (if any) are provided in separate listings on the RND set.

10.3.2 Protocol deviations

All important PDs (as defined by the PD list) will be summarized on the FAS by categories, displaying counts and percentages of subjects with at least a PD, by treatment group and overall. This summary table is sorted, within each PD temporal category, by overall frequency, in descending order; if a tie occurs, the tied characteristics will be sorted alphabetically.

All reported PDs will be reported in a subject listing on the SCR set. Important PDs will be flagged accordingly.

10.3.3 Analysis sets

A summary table is provided on the RND set to display the composition of FAS, PPS and SAF analysis sets, by treatment group and overall. A listing of subject participation in the different analysis sets is also provided.

A separate summary table is provided on the RND set to display the reasons for exclusion from the above analysis sets, by treatment group and overall. In addition, the same table is provided by site.

10.4 Analyses of subject characteristics

10.4.1 Demographics

All data [see definition in Section 5.2.1] will be reported in a subject listing based on the RND. The listing will include the other baseline characteristics defined in Section 5.2.3.

Demographic characteristics will be summarized using descriptive statistics by treatment group as well as overall for the FAS and PPS.

Note that age will be summarized as a continuous variable as well as a categorical variable (< 65, ≥ 65 years). Age as per EudraCT categories (18–64, 65–84, ≥ 85 years) will be tabulated separately based on the FAS.

10.4.2 Baseline disease characteristics

All data [see definition in Section 5.2.2] will be reported in a subject listing based on the SCR. Baseline disease characteristics will be summarized by treatment group as well as overall for the FAS and PPS.

10.4.3 Other baseline characteristics.

Other baseline disease characteristics [see definition in Section 5.2.3] will be summarized by treatment group and overall using descriptive statistics for the FAS and PPS.

10.4.4 Medical history

All previous or ongoing diseases / diagnoses [see definition in Section 5.2.4] will be reported in a subject listing. Ongoing diseases / diagnoses will be flagged accordingly. Previous and ongoing diseases / diagnoses will be summarized in separate tables. This will be done for the FAS and PPS.

Previous or ongoing diseases / diagnoses will be summarized by treatment group and overall, together displaying counts and percentages of subjects having experienced at least one disease. Counts and percentages of subjects having experienced at least one disease are presented by system organ class (SOC) and individual preferred term within each SOC. The summary table is presented in descending order according to the

incidence in the highest-dose of active test treatment (e.g., SOC and individual preferred term within each SOC with the highest number of occurrences appears first). Equal frequency of different SOC / individual preferred terms is sorted in alphabetical order of the SOC / individual preferred term.

The counting of the diseases is handled as follows:

- Subjects with two or more occurrences of the same disease (as qualified by the same preferred term[s]) are counted only once.
- In the event that the reported disease is assigned to several preferred terms, subjects are counted for each individual preferred term.

10.4.5 Previous and concomitant therapies

For study reporting purposes, all previous and/or concomitant therapies will be reported in a subject listing.

Counts and percentages of subjects having taken at least one previous, study concomitant and double-blind treatment concomitant therapy [see definition in Section 5.2.5] are presented by treatment group, by ATC class and individual preferred term within each ATC class, separately.

The summary tables are presented in descending order according to the incidence in the highest-dose of active test treatment (e.g., ATC and individual preferred term within each ATC with the highest number of occurrences appear first). Equal frequency of different ATC / individual preferred terms is sorted in alphabetical order of the ATC / individual preferred term.

The counting of the therapies is handled as follows:

- Subjects who took the same therapy more than once (as qualified by the same preferred term[s]) are counted only once.
- In the event of the reported medication being assigned to several preferred terms, subjects are counted for each individual preferred term.

For each preferred term the class are allocated using the 3 digits of the ATC code.

Specific previous and concomitant therapies will be displayed separately as described above.

10.4.6 Other subject characteristics

Not applicable.

10.5 Analysis of study treatment duration and compliance

10.5.1 Study treatment duration

The duration of double-blind study treatment [see definition in Section 5.3.1] will be summarized on the PPS and SAF using descriptive statistics. Additionally, double-blind study treatment will be summarized as categorical variable, presenting the cumulative distribution by class interval categorized as 0–2, > 2–4, > 4–8 and > 8 weeks and displaying counts and percentages of subjects in each class interval.

In addition, run-in study treatment duration will be summarized for the RIS.

10.5.2 Compliance with study treatment

Double-blind treatment compliance [see definition in Section 5.3.2] will be summarized on the FAS and PPS displaying counts and percentages of subjects with compliance categorized as: < 80%, 80–120%, and > 120%. Run-in treatment compliance will be summarized similarly for the RIS.

10.5.3 Study treatment discontinuation

A summary table is provided for the SAF to display counts and percentages of subjects who prematurely discontinued double-blind study treatment, as well as the associated reasons [see definition in Section 5.3.3], by treatment group and overall.

Note that premature double-blind study treatment discontinuation does not necessarily imply study withdrawal.

In addition, premature run-in treatment discontinuation will be summarized for the RIS.

10.5.4 Study treatment adjustments or interruptions

The number and percentage of subjects with DB study treatment interruptions will be provided for the SAF. The associated reasons will be summarized similarly.

10.5.5 Study withdrawal

A summary table is provided for the RND to display counts and percentages of subjects who prematurely discontinued the study after randomization, as well as the associated reasons by treatment group and overall. A listing of discontinued subjects is provided on the RND set. A similar table and listing based on the RIS will be provided for premature study discontinuation during run-in.

10.6 Analysis of the primary efficacy variable(s)

The primary efficacy variable (change from baseline to Week 8 of DB treatment in mean trough SiDBP, measured by OBPM) will be analyzed in the PPS and the FAS. The PPS analysis is the primary analysis, the analysis in the FAS is supportive.

The primary efficacy variable will be summarized by treatment group using descriptive statistics for the PPS and FAS.

10.6.1 Hypothesis and statistical model

The null hypothesis associated with the primary endpoint is that there is no dose-response relationship.

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.

10.6.2 Handling of missing data

In the PPS there will be no missing data from the primary endpoint given the definition of PPS. For the handling of missing data in the FAS, refer to Section 9.1.

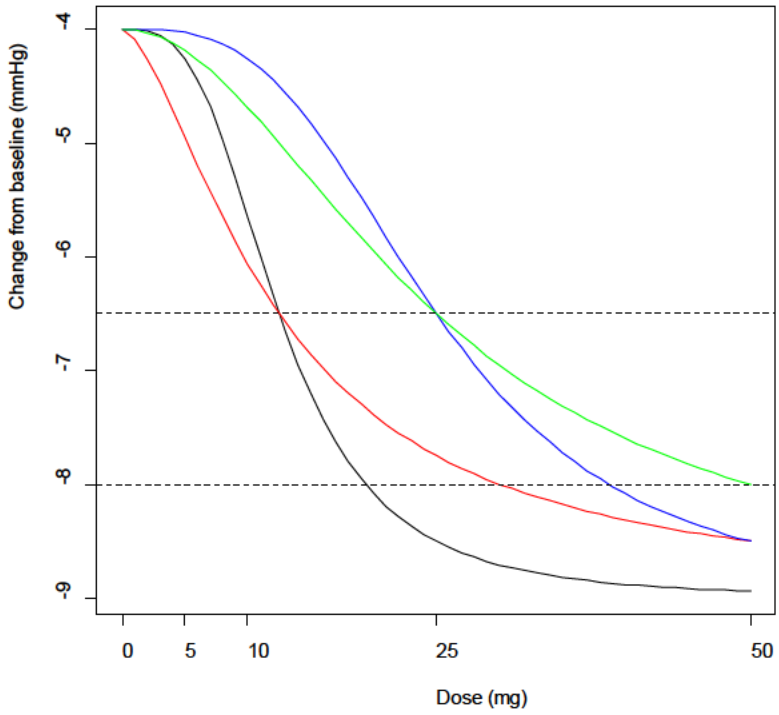
10.6.3 Main analysis

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] described in Section 9.1.

A placebo-corrected mean reduction from baseline of at least 4 mmHg is considered clinically relevant.

Some examples of E_{max} dose-response relationships are given in Figure 3, where it is assumed that the minimum response will be obtained with placebo (mean change from baseline -4 mmHg) and the maximum response (change from baseline -8 or -9 mmHg) will be reached at the highest dose of ACT-132577 (50 mg).

Figure 3 Examples of E_{max} dose-response relationships



Six candidate dose-response models were pre-specified in the protocol: linear, linear in log-dose, quadratic, E_{max}, sigmoidal E_{max} and logistic. The analysis will be performed using the R-package *DoseFinding* [Bornkamp 2016]. 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 will be selected based on AIC. That model 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.

10.6.4 Supportive/sensitivity analyses

Supportive analyses. The analysis of the primary endpoint in the FAS using LOCF to impute missing Week 8 data will be performed as described in the previous section.

In the PPS as well as the FAS (with LOCF), change from baseline to Week 8 of DB treatment period (Period II) in mean trough SiDBP will be analyzed using an 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. In the FAS missing data will be imputed by LOCF.

Sensitivity analysis. As a sensitivity analysis for missing data imputation by LOCF an MCP-Mod analysis based on BOCF will be performed in the FAS.

Also in the FAS, changes from baseline to time window Visit 5 (Week 2), time window Visit 4 (Week 4) and Week 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. This can be seen as an OC analysis. The treatment group LSMeans obtained from this model will be analyzed using the general MCP-Mod approach [Pinheiro 2014].

Average effect over time. In order to investigate the dose-response on the average treatment effect over time, the same mixed model will be used, but without the treatment by time interaction. Treatment group LSMeans will be analyzed using the general MCP-Mod approach.

10.6.5 Subgroup analyses

Subgroup analyses will be performed on the PPS by age (< 65 versus ≥ 65 years), sex, race and country.

In the absence of a published, consolidated approach for subgroup analyses for dose-response, subgroup analyses will be performed by fitting the 'best' model from the overall analysis [see Section 10.6.3] in each of the subgroups. The fitted dose-response curves will be compared visually between subgroups. Dose-response by subgroup interaction may be investigated in an ad hoc fashion based on AIC.

10.7 Analysis of the secondary efficacy variables

Secondary efficacy variables will be analyzed for the PPS at $\alpha = 0.05$ (two-sided) using 95% CIs. Additionally, change from baseline to Week 8 in mean trough SiSBP will be analyzed for the FAS. 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 models described above. The correlation between the changes from baseline in SiDBP and SiSBP will be displayed in a scatter plot for each post-baseline time point.

Control (< 90 mmHg and < 85 mmHg, separately) and response (Y/N) 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 status 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-hour mean DBP based on ABPM will be analyzed using an ANCOVA with a factor for treatment group and a covariate for baseline 24-hour mean DBP. Change from baseline to Week 8 of DB treatment period (Period II) in 24-hour mean SBP based on ABPM will be analyzed similarly.

The baseline and Week 8 average ABPM-DBP curves over time (by hour) will be plotted by treatment group [averaging as described in Section 5.5.2]. Additionally, the Week 8 minus baseline difference will be plotted vs time. Trough to peak ratios for DBP will be calculated by treatment group as described in Section 5.5.2.

10.8 Analysis of other efficacy variables

Other efficacy analyses will be performed on the PPS.

Changes from baseline to Week 2 (time window Visit 5) and Week 4 (time window Visit 6) of DB treatment period (Period II) in mean trough SiSBP and SiDBP (OBPM) will be obtained from the repeated measurements model as described in Section 10.6.4 under *sensitivity analysis*.

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

ABPM-SBP curves will be plotted and trough to peak ratios for SBP will be calculated as described for DBP based on ABPM.

Changes from baseline to Week 10 (time window Visit 8; 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 10.6.4 with an additional time point for time window Visit 8 (Week 10 i.e., Week 2 of withdrawal period - Period III).

Changes from Week 8 of Period II to time Week 10 (time window Visit 8; Week 2 of withdrawal period - Period III) in mean trough SiSBP and SiDBP (OBPM) will be obtained from the same model using appropriate treatment and time contrasts.

All efficacy analyses are summarized in Table 4.

Table 4 Summary of efficacy analyses

Efficacy analysis	Endpoint	Measure	Week	Model	Dataset(imputation)	
Primary	SiDBP	OBPM	8	MCP-Mod	PPS	
- Supportive	SiDBP	OBPM	8	MCP-Mod		FAS (LOCF)
	SiDBP	OBPM	8	ANCOVA (Dunnett)	PPS	FAS (LOCF)
- Sensitivity	SiDBP	OBPM	8	MCP-Mod		FAS (BOCF)
	SiDBP	OBPM	8	MCP-Mod based on mixed model[a]		FAS (OC)
- Average over time	SiDBP	OBPM	2,4,8	MCP-Mod based on mixed model[b]	PPS	FAS (OC)
- Subgroup	SiDBP	OBPM	8	MCP-Mod by subgroup	PPS	
Secondary	SiSBP	OBPM	8	MCP-Mod	PPS	FAS (LOCF)
	SiSBP	OBPM	8	ANCOVA (Dunnett)	PPS	FAS (LOCF)
	SiSBP	OBPM	8	MCP-Mod based on mixed model[a]		FAS (OC)
	Average SiSBP over time	OBPM	2,4,8	MCP-Mod based on mixed model[b]	PPS	FAS (OC)
	Subgroup SiSBP	OBPM	8	MCP-Mod	PPS	
	Control/ response of SiDBP	OBPM	8	MCP-Mod based on logistic regression	PPS	
	Control/ response of SiSBP	OBPM	8	MCP-Mod based on logistic regression	PPS	
	24-hour mean DBP	ABPM	8	ANCOVA	PPS[c]	
	24-hour mean SBP	ABPM	8	ANCOVA	PPS[c]	
	Trough to peak ratio DBP	ABPM	8	Descriptive statistics	PPS[c]	
Other	Mean daytime DBP	ABPM	8	ANCOVA	PPS[c]	

Efficacy analysis	Endpoint	Measure	Week	Model	Dataset(imputation)	
	Mean night time DBP	ABPM	8	ANCOVA	PPS[c]	
	Mean daytime SBP	ABPM	8	ANCOVA	PPS[c]	
	Mean night time SBP	ABPM	8	ANCOVA	PPS[c]	
	Trough to peak ratio SBP	ABPM	8	Descriptive statistics	PPS[c]	
	SiDBP	OBPM	8,10	ANCOVA	PPS	
	SiSBP	OBPM	8,10	ANCOVA	PPS	

* If applicable. In the PPS all analyses are based on OC.

[a] Also including Week 2 and 4 data, but only to predict missing Week 8 data.

[b] Including Week 2, 4 and 8 data to estimate the average effect of time.

[c] ABPM analyses are based on the subset of the PPS described in Section 5.5.

ABPM = ambulatory blood pressure monitoring; ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; DBP = diastolic blood pressure; FAS = Full Analysis Set; LOCF = last observation carried forward; MCP-Mod = Multiple Comparison Procedure – Modeling; OBPM = automated office blood pressure measurement; OC = observed cases; PPS = Per-Protocol Set; SBP = systolic blood pressure; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.

MCP-Mod based on mixed model (logistic regression, ANCOVA) implies that first the mixed model (logistic regression, ANCOVA) is performed and then the estimated differences vs placebo are analyzed using the general MCP-Mod approach [Pinheiro 2014].

10.9 Analysis of safety variables

All safety analyses described below will be performed on the SAF. All safety data will be listed, with flags for abnormalities, when applicable.

10.9.1 Adverse events

All reported AEs will be listed, together with the assigned preferred term/SOC. The listings will indicate the period of onset of the AE (run-in, DB treatment or placebo WD).

Treatment-emergent AEs [see definition in Section 5.6.1.1] will be summarized displaying, for each treatment group, counts and percentages of subjects having experienced at least one treatment-emergent AE. Counts and percentages of subjects having experienced at least one treatment-emergent AE are presented by SOC and individual preferred term within each SOC. The summary tables are presented in descending order according to the incidence in the highest-dose of active test treatment (e.g., SOC and individual preferred term within each SOC with the highest number of

occurrences appears first). Equal frequency of different SOC/individual preferred terms is sorted in alphabetical order of the SOC/individual preferred term.

Treatment-emergent AEs related to study treatment, treatment-emergent AEs leading to premature discontinuation of study treatment and treatment-emergent AEs with fatal outcome will be summarized, separately, by SOC and individual preferred term.

Treatment-emergent AEs, treatment-emergent AEs leading to premature discontinuation of study treatment and treatment-emergent AEs with fatal outcome will be summarized also by preferred term only. Treatment-emergent AEs are also summarized by maximum intensity.

For the disclosure of the results to EudraCT and ClinicalTrials.gov (rather than for the purpose of the clinical study report), a summary table with an overview of treatment-emergent AEs is provided displaying, for each treatment group, counts and percentages of subjects having experienced at least a treatment-emergent AE, a severe AE, a study-treatment related AE, an AE leading to study treatment discontinuation, a non-serious frequent AE, a serious AE, a study-treatment related serious AE, a fatal SAE.

The occurrence of non-serious, frequent (i.e., the percentage of subjects in at least one of the treatment groups equals or exceeds five percent) treatment-emergent AEs will be tabulated by SOC and individual preferred term within each SOC.

10.9.2 Deaths, other serious adverse events

10.9.2.1 Deaths

The primary cause of death coded according to MedDRA dictionary [see Section 5.6.2] will be summarized displaying, for each treatment group, counts and percentages of subjects by class and individual preferred term within each class; the summary table is presented in descending order according to the incidence in the highest-dose of active test treatment (equal frequencies are sorted in alphabetical order).

All deaths will be listed. The listings will indicate the period in which the death occurred (run-in, DB treatment, placebo WD).

10.9.2.2 Serious adverse events

All reported SAEs will be listed and tabulated as described above for AEs.

The occurrence of treatment-emergent serious AEs will be summarized by SOC and individual preferred term within each SOC. The table is presented in descending order according to the incidence in the highest-dose of active test treatment (i.e., SOC and individual preferred term within each SOC with the highest number of occurrences appears first). Ties are sorted in alphabetical order.

Treatment-emergent SAEs will also be summarized by preferred term only.

For the disclosure of the results to EudraCT and ClinicalTrials.gov (rather than for the purpose of the clinical study report), treatment-emergent SAEs will be summarized displaying, for each treatment group, counts and percentages of subjects with at least a treatment-emergent SAE plus the number of events (counted exactly the number of times they occurred also within a subject) by SOC and individual preferred term. The summary table is presented in descending order according to the incidence in the highest-dose of active test treatment (i.e., SOC and individual preferred term within each SOC with the highest number of occurrences appears first). Equal frequency of different individual preferred terms is sorted in alphabetical order of the individual preferred term. Similarly, a separate summary is presented for treatment-emergent SAEs related to study treatment. In addition, treatment-emergent SAEs with fatal outcome and treatment-emergent SAEs with fatal outcome related to study treatment will be summarized separately, similarly to treatment-emergent SAEs.

10.9.2.3 Adverse events leading to study treatment discontinuations

A separate subject listing is provided with treatment-emergent AEs leading to study treatment discontinuation. Treatment-emergent AEs leading to premature study treatment discontinuation will be summarized by SOC and preferred term as well as by preferred term only.

10.9.2.4 Other adverse events

Not applicable.

10.9.3 Electrocardiography (ECG)

Double-blind treatment-emergent ECG abnormalities [see definition in Section 5.6.7.1] will be summarized, by treatment group, displaying counts and percentages of subjects (and 95% confidence limits according to the Clopper-Pearson method) with at least one treatment-emergent ECG abnormality. Values from unscheduled visits are included. Subjects may be included in more than one category as the marked abnormality are presented cumulatively.

ECG variables are displayed in a subject listing on the SCR set; a separate listing is provided of all ECG variables, restricted to subjects with at least one abnormality [see Section 5.6.7 for details].

10.9.4 Laboratory tests

All hematology and chemistry parameters provided by the central and local laboratory are displayed in a subject listing. Marked laboratory abnormalities will be flagged

accordingly. Laboratory values below the limit of detection (i.e., preceded by '<') will be replaced by half that limit in calculations as well as in determining abnormalities.

Hematology, chemistry and urine parameters UACR will be summarized by treatment group for each time window visit. Changes from baseline in these parameters will be summarized for each post-baseline assessment, displaying:

- observed values at baseline and at the post-baseline visit window
- absolute change from baseline to post-baseline visit window

In each evaluation only subjects who had both the assessments at baseline and the considered post-baseline time point are included.

10.9.4.1 Treatment-emergent marked laboratory abnormalities

For each category (i.e., LL, LLL, HH, HHH, HHHH), treatment-emergent marked laboratory abnormalities [see definition in Section 5.6.8.1] will be summarized by treatment group, displaying counts and percentages of subjects with at least a treatment-emergent marked laboratory abnormality for each parameter for which the marked abnormality is defined. Values from unscheduled visits are included. Subjects may be included in more than one category for the same parameter.

In addition, the number of patients with ALT > 3 × upper limit of normal (ULN) and bilirubin > 2 × ULN will be tabulated by treatment group and time point (baseline, Week 8).

Percentages are calculated as number of subjects with at least one abnormality for the parameter under consideration divided by the number of subjects with any post-baseline laboratory measurement.

The distribution of the changes from baseline in hemoglobin will be plotted for each post-baseline visit. As an exploratory analysis, dose trends in the change from baseline to Week 8 in hemoglobin will be analyzed using the MCP-Mod approach. The active comparator will be excluded from these analyses.

10.9.5 Physical examination, vital signs and body weight

Physical examination data performed during the course of the study will be reported in a subject listing. Pulse rate and body weight measurements will be reported in a subject listing and summarized by time window visit.

Furthermore, for each post-baseline assessment, average PR (from BpTRU®) and body weight will be summarized displaying, for each treatment group, descriptive statistics for:

- observed values at baseline and at the post-baseline visit window
- absolute change from baseline to post-baseline visit window

In each evaluation only subjects who had both the assessment at baseline and the considered post-baseline assessment are included. Only measurements obtained in sitting position will be taken into account.

The density of the changes from baseline in body weight will be plotted for each post-baseline visit. As an exploratory analysis, dose trends in the change from baseline to Week 8 in body weight ([kg]) will be analyzed using the MCP-Mod approach. The active comparator will be excluded from these analyses.

10.9.6 Other safety variables

Not applicable.

10.10 Analysis of quality of life variables (TSQM vII)

Not applicable.

10.11 Analysis of pharmacoeconomic variables

Not applicable.

10.12 Analysis of epidemiological measures and risk-benefit evaluations

Not applicable.

10.13 Analysis of pharmacodynamic variables

For the analysis of ET-1 the PK set will be used. ET-1 plasma concentrations will be summarized by active treatment and visit by arithmetic mean, SD of the mean, minimum, maximum, median, coefficient of variation of the arithmetic mean (CV%), and number of observations. A subject listing presenting ET-1 data will also be provided. Data presentations will follow the general rules as described in Section 10.2.

10.14 Analysis of pharmacokinetic variables

ACT-132577 plasma concentrations and, if applicable, [redacted], will be summarized for ACT-132577 treated groups only.

The data will be summarized by active treatment and visit by arithmetic mean, SD of the mean, minimum, maximum, median, coefficient of variation of the arithmetic mean (CV%), and number of observations. For mean value calculations, all values below the limit of quantification (BLQ values) will be set to zero. If $\leq 50\%$ of the values at a given time point are BLQ, these values will be set to zero for calculation of the mean value. If $\geq 50\%$ of the values at a given time point are BLQ, no mean value will be calculated. Additionally, summaries will be created by sex, race and age.

A subject listing presenting ACT-132577 data will also be provided. Data presentations will follow the general rules as described in Section 10.2.

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Time windows

To allow analysis of data at the relevant planned (scheduled) visits, all recorded assessments, including unscheduled ones, are re-assigned to the most appropriate visit according to the best fitting time window for that visit [see Table 5]. Note that there are no 'gaps' between the visit windows in order to keep all values in the analysis.

Table 5 Visit time windows

Visit	Target day*	Min. day	Max. day
1	–42	-	–35
2	–28	–34	–18
3	–7	–17	–4
4	1	–3	1
5	14	1	21
6	28	22	42
7 - I	55	43	EOT***
7 - II**	56	EOT + 01 m	EOT + 25 h
8	70	EOT + 25 h 01 m	No limit

* Number of days from start of double-blind treatment.
** Only for ABPM.
*** For OBPM use EOT + 05 m (for the time of the average SiDBP)
ABPM = ambulatory blood pressure monitoring; EOT = End-of-Treatment; OBPM = office blood pressure measurement; SiDBP = sitting diastolic blood pressure.

For assessments for which time is collected, please use the following rules:

- Target day = Target day and time 12:00
- Min. day = Min. day and time 0:00
- Max. day = Max. day and time 23:59

Visit 4 / Day 1

- Target day 1 = Start date/time of DB treatment
- Max. day1 = Start date/time of DB treatment

Visit 5 / Day 1

- Min. day 1 = Start date/time of DB treatment + 1 minute

Visit 7 - I / EOT

- Max. day = End date/time of DB treatment

Visit 7 - II / EOT

- Min. day = End date/time of DB treatment + 1 minute

In the event that there is more than one value within the same time window, the value closest to the planned assessment date will be taken. In the event of equidistant values from the planned time point, the last assessment will be considered for the analyses. Where multiple assessments fall on the same day the latest is then used.

11.2 Run-in treatment start date/time

The run-in treatment start date is the first day of intake of study treatment during the run-in period. It is derived from the first treatment start date (in chronological order) in the **Study Drug Log** eCRF where the 'Study Period' is ' SB RUN-IN'. If the start time of the run-in period is missing, it will be set to 00:00.

11.3 Run-in treatment end date/time

The run-in treatment end date is the last day of intake of run-in study treatment. It is derived from the last DB treatment end date (in chronological order) in the **Study Drug Log** eCRF where the 'Study Period' is 'SB RUN-IN'. If the end time of the run-in period is missing, it will be set to the start time of the DB period minus 1 minute, in the event that the DB period is missing it will be set to 23:59.

11.4 Randomization date/time

The randomization date/time is taken from IVRS.

11.5 Double-blind treatment start date/time

It is the first day of intake of study treatment during the double-blind period. It is derived from the first treatment start date (in chronological order) in the **Study Drug Log** eCRF where the 'Study Period' is 'DB TREATMENT'.

If the date is missing the randomization date (see definition below) is used. If the subject is listed as run-in failure [see definition in Section 5.1] the date is set to 'missing'. If the start time of the double-blind treatment is missing and the start date of DB period corresponds to the date of Randomization, the Randomization time will be used. In other cases the start time of DB will be set to 00:00.

11.6 Double-blind treatment end date/time

The double-blind treatment end date is the last day of intake of DB study treatment. It is derived from the last DB treatment end date (in chronological order) in the **Study Drug Log** eCRF where the 'Study Period' is 'DB TREATMENT' and the reason for treatment end is ≠ "TEMPORARILY INTERRUPTED DUE TO AN AE" or "TEMPORARILY INTERRUPTED NOT DUE TO AN AE".

If the study treatment end date is still missing after this derivation, the earliest of the date of Visit 7 - Week 8 / EOT /Part 1 and the date of death (if any) is to be imputed. If the end date is still missing, the EOS date as defined in the Section 2.1 will be used. If the end time of double-blind treatment is missing and DB end date corresponds to the date of the first assessment of ABPM at Visit 7, the time of the first ABPM assessment will be used, otherwise, it will be set to 23:59.

11.7 Withdrawal period start date/time

The withdrawal period start date is the first day of intake of placebo during the withdrawal period. It is derived from the first treatment start date (in chronological order) in the **Study Drug Log** eCRF where the 'Study Period' is 'SB WITHDRAWAL'. If the time of the WD period is missing the time of last assessment of ABPM at Visit 7 will be used, otherwise it will be set to 23:59.

11.8 Withdrawal period end date/time

The withdrawal period end date is the date of Visit 8, collected in the **Visit Date** eCRF. If the time is missing it will be set to 23:59.

11.9 Study day

The study day is the number of days elapsed since the day of first DB treatment plus 1 (start of DB treatment is considered Day 1). For dates prior to Day 1, study day is the negative number of days between the date under consideration and the date of first DB treatment. Therefore, the study day is always different from zero.

11.10 Duration of essential hypertension (years)

Duration of essential hypertension (years) = (date of Visit 1 – date of diagnosis)/365.25 with the date of diagnosis collected in the **Essential Hypertension Relevant Disease History** form of the eCRF.

11.11 Unit conversion rules

Height (cm) = height (in) × 2.54

Weight (kg) = weight (lbs) × 0.4536

11.12 Body Mass Index (BMI)

BMI (kg/m^2) = weight (kg) / (height [cm] / 100)^2

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

All dates and times used in the analyses are supposed to be complete, apart from the types included in the table below.

The dates in these types that are missing or incomplete are derived as follows:

1 Dates are split in 3 parts: year, month and day. Year is the top-level, month is the medium level and day is the low level. If a part expected to contain a number is numeric but the value is outside a valid range, the complete date is handled as missing. For example, if date = 44Nov2000 the whole date is considered to be missing.
2 If a part is expected to contain a number is not numeric, i.e., contains values, for example, ND, NA, --, ??, 2?, it is considered as missing.
3 If a part is missing, all lower level parts are considered to be missing. This means that a ddmmyy date '21ND99' is considered as '----99'.
4 Missing parts are changed into acceptable non-missing values in a way depending on the type of date to be replaced.

In the following, 'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. The earliest and the latest of different dates refer to the first or last date, respectively, when ordered in sequence.

Type of date	Date is incomplete	Date is missing
AE resolution date	The upper limit.	No replacement, the AE is considered as ongoing in the analysis.

Type of date	Date is incomplete	Date is missing
AE onset date	If the end date of the AE is not before the start of double-blind treatment, and if the study treatment start falls in the range of possible dates, the study treatment start date is used. In all the other cases the lower limit is used.	Whichever is the earlier of the date of resolution of the AE and the study treatment start date.
Medical history end date	The upper limit.	No replacement.
Medical history start date	The lower limit.	No replacement.
Concomitant medication end date	If the answer to the question 'Ongoing at start of treatment?' in the **Previous/Concomitant Medication** eCRF is answered 'No' or if the study treatment start date-1 falls in the range of possible dates, the study treatment start date-1 is used. In all the other cases the upper limit is used.	No replacement. If the answer to the question 'Ongoing at start of treatment?' in the **Previous/Concomitant Medication** eCRF is answered 'Yes' the therapy is considered to have finished after the start of treatment.
Concomitant medication start date	If the end date of the medication is not before the informed consent signature date and if the informed consent date falls in the range of possible dates, the informed consent date is used. If the end date of the medication is not before the study treatment start date and if the study treatment start date falls in the range of possible dates, the study treatment start date is used. In all the other cases the lower limit is used.	No replacement. The medication is considered to have started before the date of consent.

Type of date	Date is incomplete	Date is missing
Hospitalization discharge date	The upper limit is used.	No replacement. The hospitalization is considered as ongoing in the analysis.
Hospitalization admission date	If the onset date of the AE leading to hospitalization falls in the range of possible dates, the onset date of the AE is used. In all the other cases the lower limit is used.	The onset date of the AE leading to hospitalization is used.

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

The table, listing, and figure naming conventions have three components: ***Display*** (T, L, F), ***Name*** (free text, in general not more than eight characters, but if required to maintain uniqueness up to a maximum of ten characters), ***Suffix*** (for example, for analysis sets, or subgroups, not longer than four characters). Multiple suffixes can be added; components/suffixes are separated by '_'. Example: *T_TEAE _SAF, summary table (T) of treatment-emergent adverse events (TEAE) on the SAF*.

The mock layout column refers to the BST standard Outputs Version 3.0 as of March 31, 2016.

A number of outputs have been identified as key outputs based on which an initial assessment of the dose-response relationship can be made. These are indicated with a 'Yes' in the 'Key' columns of the tables below.

13.1 Subject disposition

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DISP	T	Disposition of subjects	SCR	Yes	LAYDISP001
DISP_SITE	T	Disposition of subjects by site	SCR		LAYDISP001
SCRFAIL	T	Reasons for screening failure	SCR		LAYDISP002
SCRFAIL	L	Listing of reasons for screening failure	SCR		LSTCSR011
RUNFAIL	T	Reasons for run-in failure	RIS		LAYDISP002
RUNFAIL	L	Listing of run-in failures	RIS		LSTCSR011
ANSETOV	T	Overview of FAS, PPS, SAF and PK analysis sets	RND	Yes	LAYDISP001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
ANSET	L	Listing of subject participation in the different analysis sets	RND		LSTCSR031
RAND	L	Randomization scheme and codes	RND		LSTRAN
UNBLIND	L	Listing of code break or subject unblinding	RND		LSTCSR032

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; PK = Pharmacokinetic; PPS = Per-Protocol Set; RIS = Run-in Set; RND = All Randomized Set; SAF = Safety Set; SCR = Screened Set.

13.2 Protocol deviations

Output name	Display *	Title (Description)	Analysis set(s)**	Key	Mock layout
PRDEVA	T	Important protocol deviations during the double-blind period	FAS		LAYPD001
PRDEVI	T	Protocol deviations leading to exclusion from PPS	FAS	Yes	LAYPD002
PRDEVA	T	Important protocol deviations during run-in period	RIS		LAYPD001
PRDEV	L	Listing of protocol deviations	SCR		LSTCSR021

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; PPS = Per-Protocol Set; RIS = Run-in Set; SCR = Screened Set.

13.3 Subject characteristics

13.3.1 Demographics

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DEMOG	T	Demographic characteristics	FAS, PPS, PK	Yes	LAYDEM001
DEMOG	L	Listing of demographic characteristics	RIS		LSTCSR041
AGECATEU	T	EudraCT age categories	FAS		LAYDEM004

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; PK = Pharmacokinetic; PPS = Per-Protocol Set; RIS = Run-in Set.

13.3.2 Baseline disease characteristics

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
BASDC	T	Essential hypertension at Screening	FAS, PPS		LAYMIX001
BASDC	L	Listing of essential hypertension at Screening	SCR		LSTCSR091

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; PPS = Per-Protocol Set; SCR = Screened Set.

13.3.3 Other baseline characteristics

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
OBASDC	T	Height at Screening, weight and BMI at baseline	FAS, PPS, PK		LAYDEM001

* T = Summary Table; L = Listing.
BMI = body mass index; FAS = Full Analysis Set; PK = Pharmacokinetic; PPS = Per-Protocol Set;

13.3.4 Medical history

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
MHSCPR	T	Medical history by primary system organ class (SOC) and preferred term	FAS		LAYMH001
CDSCPR	T	Concomitant disease by primary system organ class (SOC) and preferred term	FAS		LAYMH001
PCMHIST	L	Listing of subjects with previous and concomitant medical history	SCR		LSTCSR043

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; SCR = Screened Set; SOC = system organ class.

13.3.5 Previous and concomitant therapies

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
PTATCPR	T	Previous therapies by anatomical therapeutic chemical (ATC) class and preferred term	FAS		LAYCONMED001
DBCATCPR	T	Double-blind treatment concomitant therapies by anatomical therapeutic chemical (ATC) class and preferred term	FAS		LAYCONMED001

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
STCATCPR	T	Study-concomitant therapies by anatomical therapeutic chemical (ATC) class and preferred term	FAS		LAYCONMED001
PCTHER	L	Listing of subjects with previous and concomitant therapies	RIS		LSTCSR044

* T = Summary Table; L = Listing.
ATC = anatomical therapeutic chemical; FAS = Full Analysis Set; RIS = Run-in Set.

13.3.6 Specific previous and concomitant therapies

Not applicable.

13.3.7 Other subject characteristics

Not applicable.

13.4 Study treatment duration and compliance

13.4.1 Study treatment duration

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
TREXP	T	Double-blind treatment duration	FAS, PPS, SAF	Yes	LAYEX001
TREXP	T	Run-in treatment duration	RIS		LAYEX001
TREXP	L	Listing of run-in and double-blind treatment duration	RIS		LSTCSR052

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; PPS = Per-Protocol Set; RIS = Run-in Set; SAF = Safety Set.

13.4.2 Compliance with study treatment

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
COMPA	T	Compliance with double-blind study treatment	PPS, FAS		LAYCAT001
COMPA	T	Compliance with run-in study treatment	RIS		LAYCAT001
COMPA	L	Listing of compliance with double-blind study treatment	SAF		LSTCSR051a

* T = Summary Table; L = Listing.
FAS = Full Analysis Set; PPS = Per-Protocol Set; RIS = Run-in Set; SAF = Safety Set.

13.4.3 Study treatment discontinuation

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
PDISCTR	T	Reasons for premature discontinuation of double-blind study treatment	SAF	Yes	LAYDISP003b
PDISCTR	T	Reasons for premature discontinuation of run-in treatment	RIS		LAYDISP003b
PDISCTR	L	Listing of subjects who discontinued treatment	RIS		LSTCSR012

* T = Summary Table; L = Listing.
RIS = Run-in Set; SAF = Safety Set.

13.4.4 Study treatment adjustments or interruptions

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
TREINT	T	Reasons for double-blind treatment interruptions	SAF		LAYMIX001
TREINT	L	Listing of subjects with double-blind treatment interruptions	SAF		L_TREINT

* T = Summary Table; L = Listing.
SAF = Safety Set.

13.5 Study withdrawal

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
PDISCST	T	Reasons for premature study discontinuation after randomization	RND		LAYDISP004b
PDISCST	T	Reasons for premature study discontinuation before randomization	RIS		LAYDISP004b
PDISC	L	Listing of subjects who discontinued the study prematurely	RIS		LSTCSR012

* T = Summary Table; L = Listing.
RIS = Run-in Set; RND = All Randomized Set.

13.6 Primary efficacy analyses

13.6.1 Main analysis

All outputs for the main analysis will be based on the PPS. Some outputs will also be generated for the FAS. These are listed in 13.6.2.

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_VIS	T	Mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by visit and treatment group	PPS		LAYCON001
DBP_CHG	T	Change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group	PPS	Yes	LAYBASE001
DBP_MCHG	F	Mean change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group	PPS	Yes	LAYTIME
DBP_CHG	F	Density of change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group	PPS		LAYDENS
DBP_MCPMOD1	T	MCP-Mod test for dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)	PPS	Yes	LAYMCP1

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_MCPMOD2	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)	PPS	Yes	LAYMCP2
DBP_MCPMOD	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)	PPS		LAYMCP3
DBP_MCPMOD_SEL	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - Best fitting model	PPS	Yes	LAYMCP4
DBP_MCPMOD_SEL	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - Best fitting model	PPS		LAYMCP5

* T = Summary Table; F = Figure.
PPS = Per-Protocol Set; MCP-Mod = Multiple Comparison Procedure – Modeling; OBPM = automated office blood pressure measurement; SiDBP = sitting diastolic blood pressure.

13.6.2 Supportive/sensitivity analyses

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_VIS	T	Mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by visit and treatment group	FAS		LAYCON001
DBP_CHG	T	Change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group	FAS	Yes	LAYBASE001
DBP_MCHG	F	Mean change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group	PPS	Yes	LAYTIME
DBP_CHG	F	Density of change from baseline to post-baseline visits in mean trough sitting diastolic blood pressure (SiDBP) as measured by OBPM by treatment group	FAS		LAYDENS
DBP_MCPMOD1	T	MCP-Mod test for dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)	FAS	Yes	LAYMCP1

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_MCPMOD2	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)	FAS	Yes	LAYMCP2
DBP_MCPMOD	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP)	FAS		LAYMCP3
DBP_MCPMOD_SEL	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - Best fitting model	FAS	Yes	LAYMCP4
DBP_MCPMOD_SEL	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - Best fitting model	FAS		LAYMCP5
DBP_ANCOVA	T	ANCOVA for change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - ACT-132577 vs placebo	PPS, FAS	Yes	LAYBETW001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_ANCOVA	F	ANCOVA for change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - ACT-132577 vs placebo	PPS, FAS	Yes	LAYFOR
DBP_ANCOVA_L	T	ANCOVA for change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) - Lisinopril vs placebo	PPS, FAS	Yes	LAYBETW001
DBP_MCPMBOCF1	T	MCP-Mod test for dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP, BOCF)	FAS		LAYMCP1
DBP_MCPMBOCF2	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP, BOCF)	FAS		LAYMCP2
DBP_MCPMBOCF	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP, BOCF)	FAS		LAYMCP3

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_MIXED_W2_W4_W8	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - ACT-132577 vs placebo	FAS		LAYBETW001
DBP_MIXED_W2_W4_W8_MCP1		Mixed Model for changes from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - MCP-Mod test for dose-response at Week 8	FAS		LAYMCP1
DBP_MIXED_W2_W4_W8_MCP2		Mixed Model for changes from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - MCP-Mod estimation of dose-response at Week 8	FAS		LAYMCP2
DBP_MIXED_W2_W4_W8_L	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - Lisinopril vs placebo	FAS		LAYBETW001
DBP_MIXED_AVER8	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - ACT-132577 vs placebo	PPS, FAS		LAYBETW001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_MIXED_AVER8_MCP1	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - MCP-Mod test for dose-response	PPS, FAS		LAYMCP1
DBP_MIXED_AVER8_MCP2	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - MCP-Mod estimation of dose-response	PPS, FAS		LAYMCP2
DBP_MIXED_AVER8_L	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in mean trough sitting diastolic blood pressure (SiDBP, OC) - Lisinopril vs placebo	PPS, FAS		LAYBETW001

* T = Summary Table; L = Listing; F = Figure.
ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; FAS = Full Analysis Set; MCP-Mod = Multiple Comparison Procedure – Modeling; OBPM = automated office blood pressure measurement; PPS = Per-Protocol Set; SiDBP = sitting diastolic blood pressure.

13.6.3 Subgroup analyses

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_MCPMOD_AGE	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) by Age	PPS		LAYMCP2

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DBP_MCPMOD_AGE	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) by Age	PPS		LAYMCP6
DBP_MCPMOD_SEX	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) by Sex	PPS		LAYMCP2
DBP_MCPMOD_SEX	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) by Sex	PPS		LAYMCP6
DBP_MCPMOD_RACE	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) by Race	PPS		LAYMCP2
DBP_MCPMOD_RACE	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting diastolic blood pressure (SiDBP) by Race	PPS		LAYMCP6

* T = Summary Table; F = Figure.
MCP-Mod = Multiple Comparison Procedure – Modeling; PPS = Per-Protocol Set; SiDBP = sitting diastolic blood pressure. Age category: < 65 vs ≥ 65 years.

13.7 Secondary efficacy analyses

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
SBP_VIS	T	Mean trough sitting systolic blood pressure (SiSBP) as measured by OBPM by visit and treatment group	PPS, FAS		LAYCON001
SBP_CHG	T	Change from baseline to post-baseline visits in mean trough sitting systolic blood pressure (SiSBP) as measured by OBPM by treatment group	PPS, FAS	Yes	LAYBASE001
SBP_MCHG	F	Mean change from baseline to post-baseline visits in mean trough sitting systolic blood pressure (SiSBP) as measured by OBPM by treatment group	PPS, FAS	Yes	LAYTIME
SBP_CHG	F	Density of change from baseline to post-baseline visits in mean trough sitting systolic blood pressure (SiSBP) as measured by OBPM by treatment group	PPS, FAS		LAYDENS
SBP_MCPMOD1	T	MCP-Mod test for dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP)	PPS, FAS	Yes	LAYMCP1
SBP_MCPMOD2	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in sitting systolic blood pressure (SiSBP)	PPS, FAS	Yes	LAYMCP2

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
SBP_MCPMOD	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in sitting systolic blood pressure (SiSBP)	PPS, FAS		LAYMCP3
SBP_MCPMOD_SEL	F	MCP-Mod estimation of response at study doses in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) - Best fitting model	PPS, FAS	Yes	LAYMCP4
SBP_MCPMOD_SEL	F	MCP-Mod estimation of response at study doses in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) - Best fitting model	PPS, FAS		LAYMCP5
SBP_ANCOVA	T	ANCOVA for change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) - ACT-132577 vs placebo	PPS, FAS	Yes	LAYBETW001
SBP_ANCOVA	F	ANCOVA for change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) - ACT-132577 vs placebo	PPS, FAS	Yes	LAYFOR
SBP_ANCOVA_L	T	ANCOVA for change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) - Lisinopril vs placebo	PPS, FAS	Yes	LAYBETW001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
SBP_MIXED_W2_W4_W8	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in sitting systolic blood pressure (SiSBP, OC) - ACT-132577 vs placebo	FAS		LAYBETW001
SBP_MIXED_W2_W4_W8_MCP1	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in sitting systolic blood pressure (SiSBP, OC) - MCP-Mod test for dose-response at Week 8	FAS		LAYMCP1
SBP_MIXED_W2_W4_W8_MCP2	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in sitting systolic blood pressure (SiSBP, OC) - MCP-Mod estimation of dose-response at Week 8	FAS		LAYMCP2
SBP_MIXED_W2_W4_W8_L	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in mean trough sitting systolic blood pressure (SiSBP, OC) - Lisinopril vs placebo	FAS		LAYBETW001
SBP_MIXED_AVER8	T	Mixed Model for changes from baseline to Weeks 2, 4 and 8 in sitting systolic blood pressure (SiSBP, OC) - ACT-132577 vs placebo	PPS, FAS		LAYBETW001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
SBP_MIXED_AVER8_MCP1	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in sitting systolic blood pressure (SiSBP, OC) - MCP-Mod test for dose-response	PPS, FAS		LAYMCP1
SBP_MIXED_AVER8_MCP2	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in sitting systolic blood pressure (SiSBP, OC) - MCP-Mod estimation of dose-response	PPS, FAS		LAYMCP2
SBP_MIXED_AVER8_L	T	Mixed Model for average change from baseline to Weeks 2, 4 and 8 in mean trough sitting systolic blood pressure (SiSBP, OC) - Lisinopril vs placebo	PPS, FAS		LAYBETW001
SBP_MCPMOD_AGE	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) by Age	PPS		LAYMCP2
SBP_MCPMOD_AGE	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) by Age	PPS		LAYMCP6
SBP_MCPMOD_SEX	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) by Sex	PPS		LAYMCP2

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
SBP_MCPMOD_SEX	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) by Sex	PPS		LAYMCP6
SBP_MCPMOD_RACE	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) by Race	PPS		LAYMCP2
SBP_MCPMOD_RACE	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in mean trough sitting systolic blood pressure (SiSBP) by Race	PPS		LAYMCP6
COR_DBP_SBP	F	Correlation between change from baseline in Diastolic and Systolic Blood Pressure by Visit and Treatment Group	PPS		LAYCORR
CRR_DBP	T	Control and response rates at Week 8 for sitting diastolic blood pressure (SiDBP) as measured by OBPM	PPS		LAYCAT002
CR_DBP_LOGREG1	T	Logistic regression for control rates at Week 8 for sitting diastolic blood pressure (SiDBP) as measured by OBPM < 90 mmHg	PPS		LAYLOGR

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
CR_DBP_LOGREG2	T	Logistic regression for control rates at Week 8 for sitting diastolic blood pressure (SiDBP) as measured by OBPM < 85 mmHg	PPS		LAYLOGR
CR_DBP_LOGREG_MCP1	T	Logistic regression for control rates at Week 8 for sitting diastolic blood pressure (SiDBP) as measured by OBPM < 90 mmHg - MCP-Mod test for dose-response	PPS		LAYMCP1
CR_DBP_LOGREG_MCP2	T	Logistic regression for control rates at Week 8 for sitting diastolic blood pressure (SiDBP) as measured by OBPM < 90 mmHg - MCP-Mod estimation of dose-response	PPS		LAYMCP2
RR_DBP_LOGREG	T	Logistic regression for response rates at Week 8 for sitting diastolic blood pressure (SiDBP) as measured by OBPM	PPS		LAYLOGR
CRR_SBP	T	Control and response rates at Week 8 for sitting systolic blood pressure (SiSBP) as measured by OBPM	PPS		LAYCAT002
CR_SBP_LOGREG1	T	Logistic regression for control rates at Week 8 for sitting systolic blood pressure (SiSBP) as measured by OBPM < 140 mmHg	PPS		LAYLOGR

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
CR_SBP_LOGREG2	T	Logistic regression for control rates at Week 8 for sitting systolic blood pressure (SiSBP) as measured by OBPM < 135 mmHg	PPS		LAYLOGR
CR_SBP_LOGREG_MCP1	T	Logistic regression for control rates at Week 8 for sitting systolic blood pressure (SiSBP) as measured by OBPM < 140 mmHg - MCP-Mod test for dose-response	PPS		LAYMCP1
CR_SBP_LOGREG_MCP2	T	Logistic regression for control rates at Week 8 for sitting systolic blood pressure (SiSBP) as measured by OBPM < 140 mmHg - MCP-Mod estimation of dose-response	PPS		LAYMCP2
RR_SBP_LOGREG	T	Logistic regression for response rates at Week 8 for sitting systolic blood pressure (SiSBP) as measured by OBPM	PPS		LAYLOGR
24H_DBP_CHG	T	Change from baseline to Week 8 in 24-hour mean diastolic blood pressure (DBP) as measured by ABPM by treatment group	PPS		LAYBASE001
24H_DBP_ANCOVA	T	ANCOVA for change from baseline to Week 8 in 24-hour mean diastolic blood pressure (DBP) as measured by ABPM - ACT-132577 vs Placebo	PPS	Yes	LAYBETW001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
24H_DBP_ANCOVA_L	T	ANCOVA for change from baseline to Week 8 in 24-hour mean diastolic blood pressure (DBP) as measured by ABPM - Lisinopril vs Placebo	PPS	Yes	LAYBETW001
24H_SBP_CHG	T	Change from baseline to Week 8 in 24-hour mean systolic blood pressure (SBP) as measured by ABPM by treatment group	PPS		LAYBASE001
24H_SBP_ANCOVA_L	T	ANCOVA for change from baseline to Week 8 in 24-hour mean systolic blood pressure (SBP) as measured by ABPM - Lisinopril vs Placebo	PPS	Yes	LAYBETW001
OBPM	L	Listing of mean trough sitting diastolic (SiDBP), mean trough sitting systolic blood pressure (SiSBP) and pulse rate measured by OBPM with control and response rates	FAS		L_OBPM
ABPM24_DBP_BAS	F	Mean diastolic blood pressure (DBP) per hour as measured by ABPM at baseline	PPS		LAY_ABPM
ABPM24_DBP_WK8	F	Mean diastolic blood pressure (DBP) per hour as measured by ABPM at Week 8	PPS		LAY_ABPM

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
ABPM24_DBP_WK8_DIF	F	Difference in mean diastolic blood pressure (DBP) per hour as measured by ABPM	PPS		LAY_ABPM
ABPM24_DBP_TTPR	T	Trough to peak ratio for diastolic blood pressure (DBP) measured by ABPM	PPS		LAY_TTPR
ABPM24_SBP_BAS	F	Mean systolic blood pressure (SBP) per hour as measured by ABPM at baseline	PPS		LAY_ABPM
ABPM24_SBP_WK8	F	Mean systolic blood pressure (SBP) per hour as measured by ABPM at Week 8	PPS		LAY_ABPM
ABPM24_SBP_WK8_DIF	F	Difference in mean systolic blood pressure (SBP) per hour as measured by ABPM	PPS		LAY_ABPM
ABPM24_SBP_TTPR	T	Trough to peak ratio for systolic blood pressure (SBP) measured by ABPM	PPS		LAY_TTPR

* T = Summary Table; F = Figure.
ABPM = ambulatory blood pressure monitoring; ANCOVA = analysis of covariance; DBP = diastolic blood pressure; FAS = Full Analysis Set; MCP-Mod = Multiple Comparison Procedure – Modeling; OBPM = automated office blood pressure measurement; PPS = Per-Protocol Set; SBP = systolic blood pressure; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
ABPM analyses are based on the subset of the PPS described in Section 5.5.
Age category: < 65 vs ≥ 65 years.

13.8 Other efficacy analyses

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DAY_DBP_CHG	T	Change from baseline to Week 8 in 24-hour mean daytime diastolic blood pressure (DBP) as measured by ABPM by treatment group	PPS		LAYBASE001

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DAY_DBP_ ANCOVA	T	ANCOVA for change from baseline to Week 8 in mean daytime diastolic blood pressure (DBP) as measured by ABPM	PPS		LAYBETW0 01
NIGHT_DBP _CHG	T	Change from baseline to Week 8 in 24-hour mean night time diastolic blood pressure (DBP) as measured by ABPM by treatment group	PPS		LAYBASE0 01
NIGHT_DBP _ANCOVA	T	ANCOVA for change from baseline to Week 8 in mean night time diastolic blood pressure (DBP) as measured by ABPM	PPS		LAYBETW0 01
DAY_SBP_ CHG	T	Change from baseline to Week 8 in 24-hour mean daytime systolic blood pressure (DBP) as measured by ABPM by treatment group	PPS		LAYBASE0 01
DAY_SBP_ ANCOVA	T	ANCOVA for change from baseline to Week 8 in mean daytime systolic blood pressure (SBP) as measured by ABPM	PPS		LAYBETW0 01
NIGHT_SBP _CHG	T	Change from baseline to Week 8 in 24-hour mean night time systolic blood pressure (SBP) as measured by ABPM by treatment group	PPS		LAYBASE0 01

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
NIGHT_SBP_ANCOVA	T	ANCOVA for change from baseline to Week 8 in mean night time systolic blood pressure (SBP) as measured by ABPM	PPS		LAYBETW001
MIXED_DBP_W2_W4_W8_W10	T	Mixed model for changes from baseline to Weeks 2, 4, 8 and 10 in mean trough sitting diastolic blood pressure (SiDBP, OC) as measured by OBPM	PPS		LAYBETW001
MIXED_SBP_W2_W4_W8_W10	T	Mixed model for changes from baseline to Weeks 2, 4, 8 and 10 in mean trough sitting systolic blood pressure (SiSBP, OC) as measured by OBPM	PPS		LAYBETW001
ABPM	L	Listing of individual diastolic and systolic blood pressure measured by ABPM	FAS		LSTCSR0932
DN_ABPM	L	Listing of 24-hour mean, daytime mean and night time mean diastolic and systolic blood pressure measured by ABPM	FAS		LSTCSR0932

* T = Summary Table; L = Listing.
ABPM = ambulatory blood pressure monitoring; ANCOVA = analysis of covariance; DBP = diastolic blood pressure; FAS = Full Analysis Set; MCP-Mod = Multiple Comparison Procedure – Modeling; OBPM = automated office blood pressure measurement; PPS = Per-Protocol Set; SBP = systolic blood pressure; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.
ABPM analyses are based on the subset of PPS subjects describe d in Section 5.5.

13.9 Safety analyses

13.9.1 Adverse events

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
AEOV	T	Overview of double-blind treatment-emergent adverse events (AEs)	SAF	Yes	LAYAE004
TEAESCPR	T	Double-blind treatment-emergent adverse events (AEs) by primary system organ class (SOC) and preferred term	SAF		LAYAE001
TEAEPR	T	Double-blind treatment-emergent adverse events (AEs) by preferred term	SAF		LAYAE002
TEAERESCPR	T	Double-blind treatment-emergent adverse events (AEs) *related to study treatment* by primary system organ class (SOC) and preferred term	SAF		LAYAE001
TEAEREPR	T	Double-blind treatment-emergent adverse events (AEs) *related to study treatment* by preferred term	SAF		LAYAE002
TEAEPRIN	T	Double-blind treatment-emergent adverse events (AEs) by maximum intensity	SAF		LAYAE003
AEOV	T	Overview of run-in treatment-emergent adverse events (AEs)	RIS		LAYAE004
TEAEPR	T	Run-in treatment-emergent adverse events (AEs) by preferred term	RIS		LAYAE002

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
AE	L	Listing of adverse events (AEs)	RIS		LSTCSR071

* T = Summary Table; L = Listing.
AE = adverse event; RIS = Run-in Set; SAF = Safety Set.

13.9.2 Deaths

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
DEATH	L	Listing of deaths	SAF		LSTCSR072

* L= Listing,
SAF=Safety set.

13.9.3 Serious adverse events

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
TESAESCPR	T	Double-blind treatment-emergent serious adverse events (SAEs) by primary system organ class (SOC) and preferred term	SAF	Yes	LAYAE001
TESAEPR	T	Double-blind treatment-emergent serious adverse events (SAEs) by preferred term	SAF		LAYAE002
TESAERESCPR	T	Double-blind treatment-emergent serious adverse events (SAEs) *related to study treatment* by preferred term	SAF		LAYAE002

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
TESAEPR	T	Run-in treatment-emergent serious adverse events (SAEs) by preferred term	RIS		LAYAE002
SAE	L	Listing of serious adverse events (SAEs)	RIS		LSTCSR071

* T = Summary Table; L = Listing.
RIS = Run-in Set; SAE = serious adverse event; SAF = Safety Set; SOC = system organ class.

13.9.4 Adverse events leading to treatment discontinuation

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout(AEs)
TEAEPDSCPR	T	Double-blind treatment-emergent adverse events (AEs) leading to premature discontinuation of study treatment by primary system organ class (SOC) and preferred term	SAF	Yes	LAYAE001
TEAEPDPR	T	Double-blind treatment-emergent adverse events (AEs) leading to premature discontinuation of study treatment by preferred term	SAF		LAYAE002
TEAEPDPR	T	Run-in treatment-emergent adverse events (AEs) leading to premature discontinuation of study treatment by preferred term	RIS		LAYAE002
AEPD	L	Listing of adverse events (AEs) leading to premature discontinuation of study treatment	SCR		LSTCSR071

* T = Summary Table; L = Listing.
AE = adverse event; RIS = Run-in Set; SAF = Safety Set; SOC = system organ class.

13.10 Electrocardiogram (ECG)

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
ECG_CHG	T	ECG parameters: changes from baseline to end of double-blind treatment	SAF		LAYBASE001
ECGQTCPT	T	Number of subjects with double-blind treatment-emergent ECG abnormalities (based on Fridericia's formula)	SAF		LAYECG001
ECGMA	L	Listing of 12-lead ECG variables in subjects with at least one double-blind treatment-emergent ECG abnormalities	SAF		LSTCSR0931
ECG	L	Listing of 12-lead ECG variables and abnormalities	SCR		LSTCSR093

* T = Summary Table; L = Listing.
ECG = electrocardiogram; SAF = Safety Set; SCR = Screened Set.

13.11 Laboratory tests

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
HEMAV_VIS	T	Hematology parameters: absolute values by visit	SAF		LAYLAB003a
HEM_CHG	T	Hematology parameters: changes from baseline to post-baseline visits	SAF	Yes	LAYLAB002a

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
HEM_CHG	F	Mean change from baseline to post-baseline visits in hemoglobin by treatment group	SAF		LAYTIME
CHEAV_VIS	T	Chemistry parameters: absolute values by visit	SAF		LAYLAB003a
CHE_CHG	T	Chemistry parameters: changes from baseline to post-baseline visits	SAF		LAYLAB002a
UACRAV_VIS	T	Urine parameter: UACR absolute values by visit	SAF		LAYLAB003a
UACR_CHG	T	Urine parameter: UACR changes from baseline to post-baseline visits	SAF	Yes	LAYLAB002a
	T	Definition of abnormal laboratory values	NA		
HEM_TEMA	T	Hematology parameters: treatment-emergent marked abnormalities	SAF		LAYLAB001
CHE_TEMA	T	Chemistry parameters: treatment-emergent marked abnormalities	SAF		LAYLAB001
CHE_ALT_BIL	T	Number of subjects with ALT > 3 × ULN and bilirubin > 2 × ULN	SAF		LAYCAT002

Output name	Display*	Title (Description)	Analysis set(s)	Key	Mock layout
LABMLA	L	Listing of definitions of marked laboratory abnormality	-		L_LABMLA
LAB	L	Listing of individual laboratory measurements (SI units)	SCR		LSTCSR081
HEM_CHG	F	Density of change from baseline to post-baseline visits in hemoglobin by treatment group	SAF		LAYDENS
HEM_MCPMOD1	T	MCP-Mod test for dose-response in change from baseline to Week 8 in hemoglobin	SAF		LAYMCP1
HEM_MCPMOD2	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in hemoglobin	SAF		LAYMCP2
HEM_MCPMOD	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in hemoglobin	SAF		LAYMCP3

* T = Summary Table; L = Listing; F = Figure.
ALT = alanine aminotransferase; MCP-Mod = Multiple Comparison Procedure – Modeling; SAF = Safety Set; SCR = Screened Set; SI = Standard International; UACR = urine albumin-to-creatinine ratio; ULN =upper limit of normal; NA = not applicable.

13.12 Physical examination, vital signs and body weight

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
VSW_VIS	T	Pulse rate and body weight: values by visit	SAF		LAYBASE001
VSW_CHG	T	Pulse rate and body weight: changes from baseline to post-baseline visit	SAF	Yes	LAYBASE001
VSW_CHG	F	Mean change from baseline to post-baseline visits in body weight by treatment group	SAF		LAYTIME
VSW_CHG	F	Density of change from baseline to post-baseline visits in body weight by treatment group	SAF		LAYDENS
VSW	L	Listing of pulse rate and body weight	SCR		LSTCSR091
PHYSF	L	Listing of physical findings	SCR		LSTCSR094
WGT_MCPMOD1	T	MCP-Mod test for dose-response in change from baseline to Week 8 in body weight	SAF		LAYMCP1
WGT_MCPMOD2	T	MCP-Mod estimation of dose-response in change from baseline to Week 8 in body weight	SAF		LAYMCP2
WGT_MCPMOD	F	MCP-Mod estimation of dose-response in change from baseline to Week 8 in body weight	SAF		LAYMCP3

* T = Summary Table; L = Listing; F = Figure.
MCP-Mod = Multiple Comparison Procedure – Modeling; SAF = Safety Set; SCR = Screened Set.

13.13 Other safety variables

Not applicable.

13.14 Other evaluations

13.14.1 PK

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
PRDEVPK	T	Protocol deviations leading to exclusion from PK set	FAS		LAYPD002
PK1	T	Summary of [redacted] ACT 132577 plasma concentrations in the double-blind treatment period	PK		LAYPKPD
PKAGE	T	Summary of [redacted] ACT 132577 plasma concentrations in the double-blind treatment period - by age category	PK		LAYPKSUB
PKGEN	T	Summary of [redacted] ACT 132577 plasma concentrations in the double-blind treatment period - by gender	PK		LAYPKSUB
PKRACE	T	Summary of [redacted] ACT 132577 plasma concentrations in the double-blind treatment period - by race	PK		LAYPKSUB
PKTROUGH	L	Listing of individual [redacted] ACT-132577 plasma concentrations in the double-blind treatment period	PK		LSTCSR051b

* T = Summary Table, L = Listing.
PK = pharmacokinetic.

13.14.2 PD

Output name	Display *	Title (Description)	Analysis set(s)	Key	Mock layout
PD1	T	Summary of trough ET-1 plasma concentrations in the double-blind treatment period	PK		LAYPKPD
PDTROUGH	L	Listing of individual trough ET-1 plasma concentrations in the double-blind treatment period	PK		LSTCSR051b

* T = Summary Table, L = Listing.
ET = endothelin; PK = pharmacokinetic.

14 REFERENCES

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15 APPENDICES

A. Protocol synopsis

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 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 confirmation of hypertension are offered the possibility of having their BP measured (at trough if subjects are on antihypertensive 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 between 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] 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 once a day (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 (ERAs) and PDE5 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.

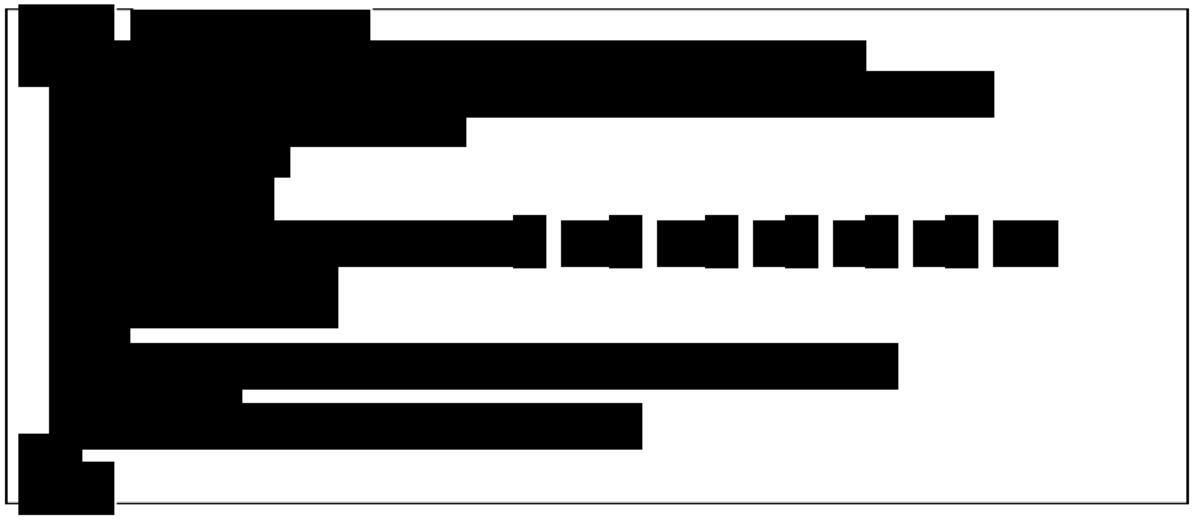
B. Calculation of mean blood pressure measurements based on ABPM

Example code. The SAS code to implement the trapezoidal rule

$$\int_a^b f(x)\,dx \approx \frac{1}{2}\sum_{k=1}^{N}(x_{k+1}-x_k)\,(f(x_{k+1})+f(x_k))\,.$$

is given below. Here it is assumed that the input data set (&dset) contains variables *subjid, visitcd, abgrpid* (to separate ABPMs of the same subject at the same visit, in the unlikely event that two ABPMs were taken).

Variable *ABBPTM* contains the 48-hour clock time of the measurement. **For measurements taken on the second day 24 hours will be added to the 24-hour clock time.** Variables ABDIA and ABSYS contain the DBP and SBP (mmHg), respectively.



Example data. The data plotted in Figure 1 are:

ABPM date blood pressure reading	ABPM time of blood pressure reading	ABPM diastolic blood pressure (mmHg)	ABPM systolic blood pressure (mmHg)
18MAY2016	10:29	107	146
18MAY2016	10:31	100	150
18MAY2016	10:33	103	154
18MAY2016	10:35	101	157
18MAY2016	10:40	100	144
18MAY2016	11:00	107	146

ABPM date blood pressure reading	ABPM time of blood pressure reading	ABPM diastolic blood pressure (mmHg)	ABPM systolic blood pressure (mmHg)
18MAY2016	11:20	100	146
18MAY2016	11:40	114	150
18MAY2016	12:00	109	140
18MAY2016	12:23	122	167
18MAY2016	12:43	73	91
18MAY2016	13:00	109	148
18MAY2016	13:20	95	147
18MAY2016	13:40	94	141
18MAY2016	14:00	95	126
18MAY2016	14:20	89	120
18MAY2016	14:40	84	135
18MAY2016	15:00	96	140
18MAY2016	15:20	95	139
18MAY2016	15:40	82	138
18MAY2016	16:03	100	135
18MAY2016	16:23	103	144
18MAY2016	16:40	98	137
18MAY2016	17:20	102	147
18MAY2016	17:43	93	145
18MAY2016	18:00	93	159
18MAY2016	18:20	107	151
18MAY2016	18:40	95	135
18MAY2016	19:00	100	129
18MAY2016	19:20	99	130
18MAY2016	19:40	96	129
18MAY2016	20:00	101	129
18MAY2016	20:20	94	126
18MAY2016	20:40	91	124
18MAY2016	21:00	86	118
18MAY2016	21:23	83	116
18MAY2016	21:40	90	123
18MAY2016	22:00	86	121

ABPM date blood pressure reading	ABPM time of blood pressure reading	ABPM diastolic blood pressure (mmHg)	ABPM systolic blood pressure (mmHg)
18MAY2016	22:40	94	169
18MAY2016	23:00	95	150
18MAY2016	23:30	97	135
19MAY2016	00:03	144	180
19MAY2016	01:00	83	117
19MAY2016	01:30	74	129
19MAY2016	02:00	70	127
19MAY2016	02:30	62	124
19MAY2016	03:00	60	121
19MAY2016	03:30	66	127
19MAY2016	04:00	71	137
19MAY2016	04:30	95	140
19MAY2016	05:00	97	140
19MAY2016	05:30	92	161
19MAY2016	06:00	111	180
19MAY2016	06:20	115	178
19MAY2016	06:40	121	177
19MAY2016	07:00	117	173
19MAY2016	07:20	120	177
19MAY2016	07:40	112	173
19MAY2016	08:00	113	161
19MAY2016	08:20	130	221
19MAY2016	09:00	121	167
19MAY2016	09:20	100	177
19MAY2016	09:40	117	174
19MAY2016	10:20	117	179
19MAY2016	10:43	89	161
19MAY2016	11:00	92	190
19MAY2016	11:04	104	158

ABPM = ambulatory blood pressure monitoring.

Example calculations. The total duration of the ABPM (24h 35 mins) was shorter than 25 hours, so all measurements were included in the calculation of the 24-hour mean DBP and SBP for this subject at this visit. The calculations based on these data are:

- The areas under the DBP and SBP curves are 8,640,870 and 12,956,970 mmHg sec, respectively. Dividing both areas by the time span of 88,500 seconds gives a 24-hour means of 97.6 and 146.4 mmHg, respectively.
- The mean daytime DBP = (3,705,300 + 801,570) / (37,860 + 7440) = 99.5 mHg.
- The mean daytime SBP = (5,224,530 + 1,295,970) / (37,860 + 7440) = 143.9 mmHg.
- The mean night time DBP = 1,411,200 / 18,000 = 78.4 mmHg.
- The mean night time SBP = 2,438,100 / 18,000 = 135.5 mmHg.

Note that measurements between 21:00 on the first day and 01:00 on the second day (limits excluded) and between 06:00 and 09:00 on the second day (limits excluded) are included in the calculation of the 24-hour means, but not in the calculation of the daytime or night time means.

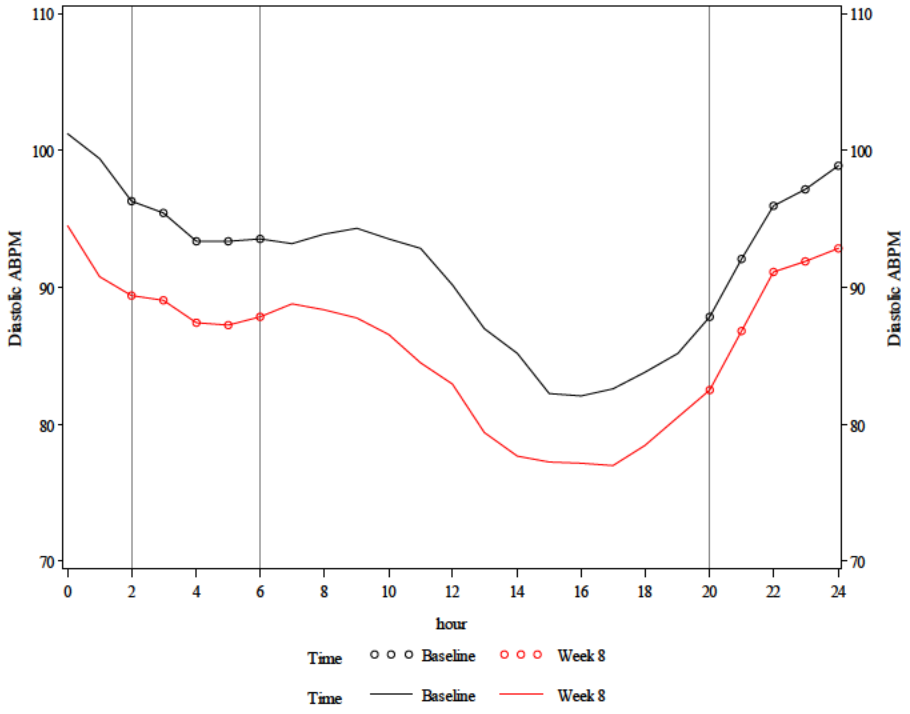
C. Calculation of trough-peak ratios based on ABPM

The figure below shows the mean diastolic ABPM by hour for a single treatment group at baseline (black) and Week 8 (red).

- The mean diastolic ABPM at trough is the average difference between the curves between 20 and 24 hours (circles)
- The mean diastolic ABPM at peak is the average difference between the curves between 2 and 6 hours (circles)

The trough to peak ratio for DBP based on ABPM is the ratio of the two.

The trough to peak ratio for SBP based on ABPM is calculated similarly.



D. Document history

Version	Effective Date	Reason
1.0	8 May 2017	New
2.0	15 May 2017	Update pre-unblinding

STATISTICAL ANALYSIS PLAN

FOR SAMPLE SIZE RE-ESTIMATION

STUDY AC-080A201

Purpose of Analysis	Blinded Sample Size Re-estimation
Investigational Drug	ACT-132577
Protocol Number	AC-080A201
Idorsia Document Number	D-17.086
Document Status/Version Number	Final Version 2
Date	3 November 2017

Author	[redacted], Expert Statistician
Reviewers	[redacted] Senior Expert Statistician
	[redacted], VP Science Medical Expert

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

BP	Blood pressure
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
MCP-Mod	Multiple Comparison Procedure - Modeling
OBPM	(Automated) office blood pressure measurement
PD	Protocol deviation
PPS	Per-Protocol Set
RND	All Randomized Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SiDBP	Sitting diastolic blood pressure
SiSBP	Sitting systolic blood pressure
SSR	Sample size re-estimation

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes statistical analyses required for the blinded sample size re-estimation (SSR) of Study AC-080A201, the Phase 2 dose-finding trial of the ACT-132577 project.

The objective is to provide the sizes of the Per-Protocol Set (PPS) and Full Analysis Set (FAS) which, given the observed variability at this point in time, will guarantee approximately 90% power to detect a dose response relationship and provide sufficient precision in the estimation of the dose response curve and of doses that will be selected for the Phase 3 program of ACT-132577.

The blinded SSR will be performed by the sponsor after 100 subjects have been randomized and their Week 8 blood pressure (BP) data are available for analysis. The sample size will be recalculated considering the overall standard deviation (SD) of the primary endpoint (change from baseline to Week 8 in mean trough sitting diastolic blood pressure [SiDBP], measured by automated office blood pressure measurement [OBPM]) in the Per-Protocol Set.

The re-calculated 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. It is anticipated that the size of the PPS will be at least 80% of the size of the FAS.

This SAP is based on Version 3 of the Protocol dated 30 May 2016 [D-16.063].

Version 2 of this SAP was generated in order to make editorial corrections—no changes were made to analyses or statistical content—and to reflect the transfer of ownership of ACT-132577. ACT-132577 was previously developed by Actelion Pharmaceuticals Ltd. Actelion was recently acquired by Johnson & Johnson. As part of this transaction, Actelion spun off its drug discovery operations and early stage clinical development assets into an independent biopharmaceutical company, Idorsia Pharmaceuticals Ltd (Idorsia). ACT-132577 is now owned by Idorsia.

2 STUDY DESIGN AND FLOW

2.1 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 1000 subjects are expected to be enrolled into the study (i.e., entered the run-in phase), 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.

2.2 Study visit and assessment schedule

Table 1 shows the study visit and assessments schedule.

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 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.

3 OBJECTIVES

The objective of this Sample Size Re-estimation is to provide the sizes of the PPS and FAS which, given the observed variability at this point in time, will guarantee approximately 90% power to detect a dose response relationship and provide sufficient precision in the estimation of the dose response curve and of doses that will be selected for the Phase 3 program of ACT-132577.

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

Not applicable.

5 DEFINITIONS OF VARIABLES

Baseline refers to the last non-missing value before double-blind treatment start date.

5.1 Screening failures

Not applicable.

5.2 Subject characteristics

Not applicable.

5.3 Study treatment exposure and compliance

Not applicable.

5.4 Study discontinuation

Not applicable.

5.5 Efficacy variables

5.5.1 Primary efficacy endpoint(s)

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

Here, baseline is defined as in Section 5 and Week 8 is the time window of Visit 7 [Section 11.1]. OBPM SiDBP is measured by BpTRU® (automated; average over five measurements) and is collected via electronic data transfer from an external [redacted]. It will not be (re-)calculated by the sponsor.

All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the time windows described in Section 11.1.

5.5.2 Secondary efficacy endpoint

Of the secondary efficacy endpoints defined in the protocol, the following is considered as supportive for the sample size re-estimation:

- Change from baseline to Week 8 of double-blind treatment period (Period II) in mean trough SiSBP, measured by OBPM.

Here, baseline is defined as in Section 5 and Week 8 is the time window of Visit 7 [Section 11.1]. OBPM SiSBP is collected via electronic data transfer and will not be (re-)calculated by the sponsor.

All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the time windows described in Section 11.1.

5.6 Safety variables

Not applicable.

6 DEFINITION OF PROTOCOL DEVIATIONS

For the purpose of this SSR only two major protocol deviations (PDs) will be considered in the definition of the PPS [see Section 7.1.3].

- Not completing the double-blind treatment period: no Week 8 (i.e., time window Visit 7) efficacy data available.
- Use of forbidden medication, indicated as protocol deviation (PD code list version 2, PV_MM.503).

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 All Randomized Set

The All Randomized Set (RND) includes all subjects with answer 'YES' to the question 'Was the subject randomized?' in the **Randomization** eCRF.

7.1.2 Full Analysis Set

The FAS includes all subjects in the RND Set, who have a baseline mean trough SiDBP.

7.1.3 Per-Protocol Set

The PPS includes all subjects from the FAS who have a mean trough SiDBP at Week 8 (i.e., time window Visit 7) and did not use forbidden medication deviation as defined in Section 6.

8 DEFINITION OF SUBGROUPS

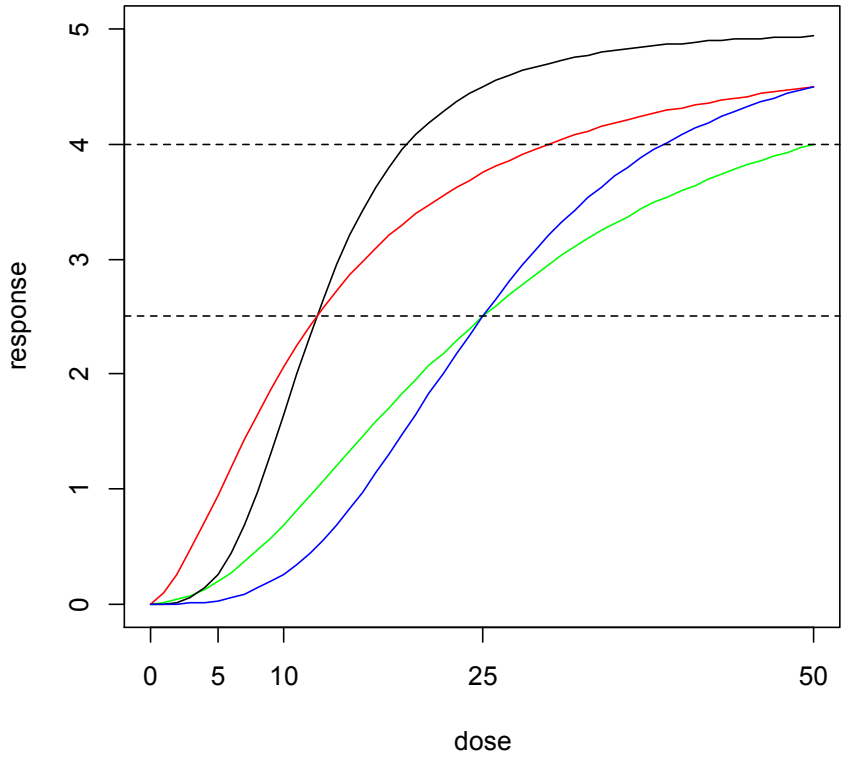
Not applicable.

9 GENERAL STATISTICAL METHODOLOGY

A blinded SSR will be performed by the sponsor after 100 subjects have been randomized and their Week 8 (time window Visit 7) OBPM data are available for analysis. The SSR will consider the overall standard deviation (i.e., based on pooled treatment groups as the SSR is blinded) of the primary endpoint (change from baseline to Week 8 [time window Visit 7] in mean trough SiDBP, measured by OBPM) in the PPS.

The primary endpoint (change from baseline to Week 8 [time window Visit 7] of double-blind treatment period in mean trough SiDBP) will be analyzed using the MCP-Mod approach [Bretz 2005, Pinheiro 2006, EMA 2013]. The blinded SSR will be based on the average power achieved in the MCP-Mod approach, to detect a dose response when the 'true' dose-response curve is among the four curves displayed in Figure 1 (copied from protocol figure 2). All four assume 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 1 Dose response relationships used in power calculations

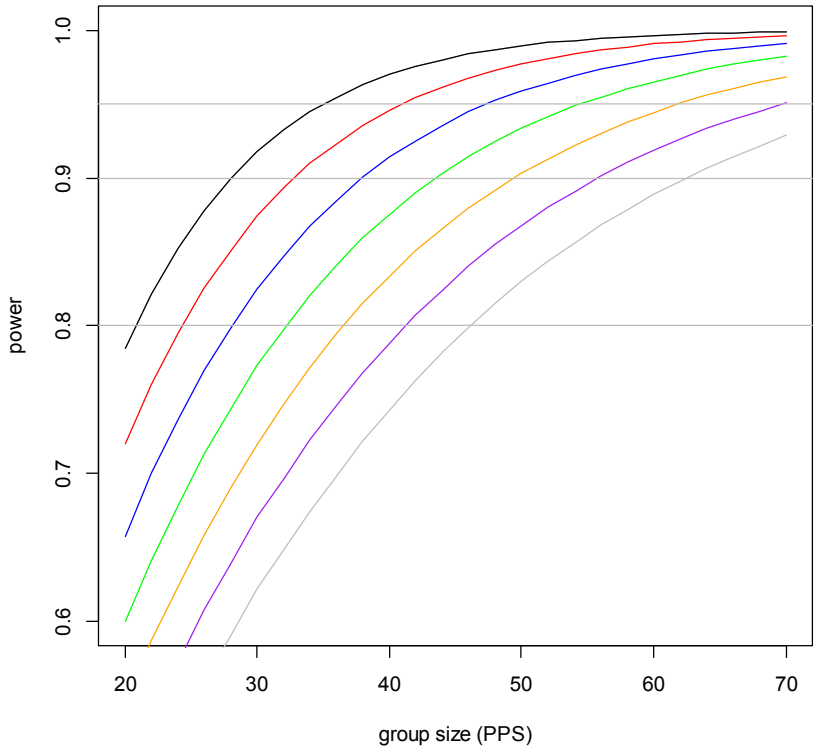


For each of the four dose-response curves the power will be calculated using the powMCT function in the R-package DoseFinding [Bornkamp 2016]. R-code is included in Appendix 15.1.

The calculation requires an estimate of the standard deviation of the primary endpoint [see Section 10.6] in the PPS. The *average* power is displayed in Figure 2 for primary endpoint SDs ranging from 6–9 mmHg. (For the original sample size calculation 9 mmHg was assumed and > 95% power was required for each of the four scenarios separately.)

Figure 2 Average power to detect dose response

Black SD = 6.0; Red SD = 6.5; Blue SD = 7.0; Green SD = 7.5; Orange SD = 8.0; Purple SD = 8.5; Grey SD = 9.0.



The associated sample sizes (PPS) for 80–95% average power are given in Table 2.

Table 2 Sample size (PPS) needed for 80–95% power to detect a dose-response across 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
85% power							
- PPS size	144	168	198	222	258	288	318
- per group*	24	28	33	37	43	48	53
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 of this protocol.
MCP-Mod = Multiple Comparison Procedure - Modeling; MCT = Multiple Contrast Test; PPS = Per-Protocol Set; SD = standard deviation.

Here, SD is the standard deviation of the primary endpoint (independent of treatment assignment, as this is blinded). 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%; simulation program in Appendix 15.2). The re-calculated 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 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 blinded 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 3.

Table 3 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]
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.
CI = confidence interval; PPS = Per-Protocol Set.

The re-calculated number of subjects randomized is expected to be between 300 subjects and the originally foreseen 540 subjects.

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

The SSR will be based on blinded data. No statistical testing will be performed.

10.2 General rules for data presentations

Output titles should include the name of the analysis set used for the analysis, and if specific period used, also the time period.

Table column headers should provide the number of subjects of the used analysis set.

The footer should provide the following information:

- the date and time of the data extraction from the database and the cut-off date,
- the date and time of the output generation,
- the SAS program that produces the output and the author,

No acronym/abbreviation should be used unless documented in the footer.

For categorical parameters, frequencies/numbers and percentages should be used. Percentages should be presented with one decimal place (e.g., 18.2%).

Descriptive statistics for continuous variables are given in Table 4.

Table 4 Descriptive statistics for continuous variables

Statistics	Display	Number of decimals	Example
N	N	None	99
Mean	Mean	Original digit + 1	45.2
Standard Deviation	Standard Deviation	Original digit + 1	38.5
Median	Median	Original digit + 1	45.3
Minimum–Maximum	Min–Max	Original digit	125–250
1st quartile (25%) – 3rd quartile (75%)	Q1–Q3	Original digit + 1	35.2–58.5

10.3 Display of patient disposition and analysis sets

The number of patients in the FAS and PPS will be tabulated on pooled treatment groups.

10.4 Analyses of subject characteristics

Not applicable.

10.5 Analysis of study treatment exposure and compliance

Not applicable.

10.6 Analysis of the primary efficacy variable(s)

The primary efficacy variable will be analyzed in the PPS and FAS, based on pooled treatment groups.

10.6.1 Hypothesis and statistical model

Not applicable.

10.6.2 Handling of missing data

The PPS analysis will be based on observed data.

In the FAS, last post-baseline measurement will be carried forward.

10.6.3 Main analysis

The changes from baseline to Weeks 2, 4 and 8 of double-blind treatment period (time window Visits 5, 6 and 7 respectively) in mean trough SiDBP (measured by OBPM) will be summarized using descriptive statistics.

The distribution of the changes from baseline in SiDBP will be displayed in a density plot.

10.7 Analysis of the secondary efficacy variables

Secondary efficacy endpoints will be analyzed in the PPS.

The changes from baseline to Weeks 2, 4 and 8 of double-blind treatment period (time window Visits 5, 6 and 7, respectively) in mean trough SiSBP (measured by OBPM) will be summarized using descriptive statistics.

The distribution of the changes from baseline in SiSBP will be displayed in a density plot.

10.8 Analysis of other efficacy variables

Not applicable.

10.9 Analysis of safety variables

Not applicable.

10.10 Analysis of quality of life variables

Not applicable.

10.11 Analysis of pharmacoeconomic variables

Not applicable.

10.12 Analysis of epidemiological measures and risk-benefit evaluations

Not applicable.

10.13 Analysis of pharmacodynamic variables

Not applicable.

10.14 Analysis of pharmacokinetic variables

Not applicable.

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Time windows

To allow analysis of data at the relevant planned (scheduled) visits, all recorded assessments, including unscheduled ones, are re-assigned to the most appropriate visit according to the best fitting time-window for that visit [see Table 5].

Table 5 Visit time windows

Visit	Period	Target day	Min day	Max day
1	I: Run-in	–42	–	–35
2		–28	–34	–18
3		–7	–17	–4
4[a]		–1	–3	–1
5[b]	II: Double-blind	14	1	21
6[b]		28	22	42
7[b]		55	43	EOT
8[c]	III: Follow-up	70	EOT	No limit

[a]Measurements mapped to Visit 4 must be before randomization; otherwise map to Visit 3
[b]Measurements mapped to Visit 5, 6 or 7 must be before the patient's EOT; otherwise map to Visit 8
[c]Measurements taken on Visit 8 must be after the patient's EOT; otherwise map to Visit 7
EOT = End-of-Treatment.

If more than one assessment falls within the same time window, the closest value to the planned time point will be assigned to the re-mapped visit. In the event of equidistant values from the planned time point, the last assessment will be considered for the analyses.

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

Not applicable.

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

All outputs will be generated based on blinded data.

The TLF naming conventions consider three components: ***Type*** (T, L, F), ***Name*** (free text, in general not more than eight characters, but if required to maintain uniqueness, up to a maximum of ten characters), ***Suffix*** (for example, for analysis sets, or subgroups, not longer than four characters) – multiple suffixes can be added. Components/suffixes are separated by '_'. Example: T_TEAE_RND, summary table (T) of treatment-emergent adverse events (TEAE) on all randomized analysis set (RND).

13.1 Subject disposition

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
ANSETOV	T	Composition of FAS and PPS	RND	T1

*T = Summary table, L = Listing, F = Figure, **RND = All Randomized Set, FAS = Full Analysis Set, PPS = Per-Protocol Set

13.2 Subject characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
DEM	T	Demographic Characteristics	R	T2

* T = Summary table, L = Listing, F = Figure, **SC = Screened Analysis Set, R =All Randomized Set

13.3 Primary efficacy variable

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
DIA_OBPM_CHG	T	Change from baseline in Sitting Diastolic Blood Pressure as Measured by OBPM by Visit	FAS, PPS	T3
DIA_OBPM_CHG	F	Distribution of Change from baseline in Sitting Diastolic Blood Pressure as Measured by OBPM by Visit	PPS	F1

*T = Summary table, L = Listing, F = Figure, **RND = All Randomized Set, FAS = Full Analysis Set, PPS = Per-Protocol Set

13.4 Secondary efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
SYS_OBPM_CHG	T	Change from baseline in Sitting Systolic Blood Pressure as Measured by OBPM by Visit	PPS	T3
SYS_OBPM_CHG	F	Distribution of Change from baseline in Sitting Systolic Blood Pressure as Measured by OBPM by Visit	PPS	F1
COR_OBPM_CHG	F	Correlation between change from baseline in Diastolic and Systolic Blood Pressure by Visit	PPS	F2

*T = Summary table, L = Listing, F = Figure, **RND = All Randomized Set, FAS = Full Analysis Set, PPS = Per-Protocol Set

14 REFERENCES

[Bornkamp 2016] Bornkamp B, Pinheiro J, Bretz F. Planning and Analyzing Dose Finding experiments. Retrieved from: cran.r-project.org/web/packages/DoseFinding

[Bretz 2005] Bretz F, Pinheiro, JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies Biometrics. 2005;61:738–48.

[Clopper 1934] Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

[Pinheiro 2006] Pinheiro JC, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures, J Biopharm Stat. 2006;16:639–56.

[EMA 2013] EMA/CHMP/SAWP/757052/2013. Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty.

15 APPENDICES

15.1 Layouts

15.1.1 Layout T1

ACT-132577
Protocol: AC-080A201/Essential Hypertension
<Title>
Analysis set: <analysis set>

<overall, site x>

	Blinded Treatment N = XX n (%)
Subjects Randomized	xx (yy.y)
Subjects Included in FAS	xx (yy.y)
Subjects Included in PPS	xx (yy.y)

Output: XXXX, Produced by xxxxxxxx on ddmmmyyyy hh:mm (CET), Data Extraction Date: ddmmmyyyy, Cut-Off Date: ddmmmyyyy
Program: prod_ccm/program_output/program_name.sas
Page x of x

15.1.2 Layout T2

ACT-132577
Protocol: AC-080A201/Essential Hypertension
<Title>
Analysis set: <analysis set>

	Blinded Treatment N = XX
Age (years)	
n	xx
Mean	xx.xx
Standard Deviation	xx.xx
Median	xx.x
Q1, Q3	xx.x, xx.x
Min, Max	xx.x, xx.x
Sex [n (%)]	
Females	xx (xx.x)
Males	xx (xx.x)
Missing	xx (xx.x)
Race [n (%)]	
Black or African American	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)
Asian	xx (xx.x)
White	xx (xx.x)
Other	xx (xx.x)
Missing	xx (xx.x)
Ethnicity [n (%)]	
Hispanic or Latino	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)
Missing	xx (xx.x)

Output: XXXX, Produced by xxxxxxxx on ddmmmyyyy hh:mm (CET), Data Extraction Date: ddmmmyyyy, Cut-Off Date: ddmmmyyyy
Program: prod_ccm/program_output/program_name.sas
Page x of x

15.1.3 Layout T3

ACT-132577
Protocol: AC-080A201/Essential Hypertension
<Title>
Analysis set: <analysis set>

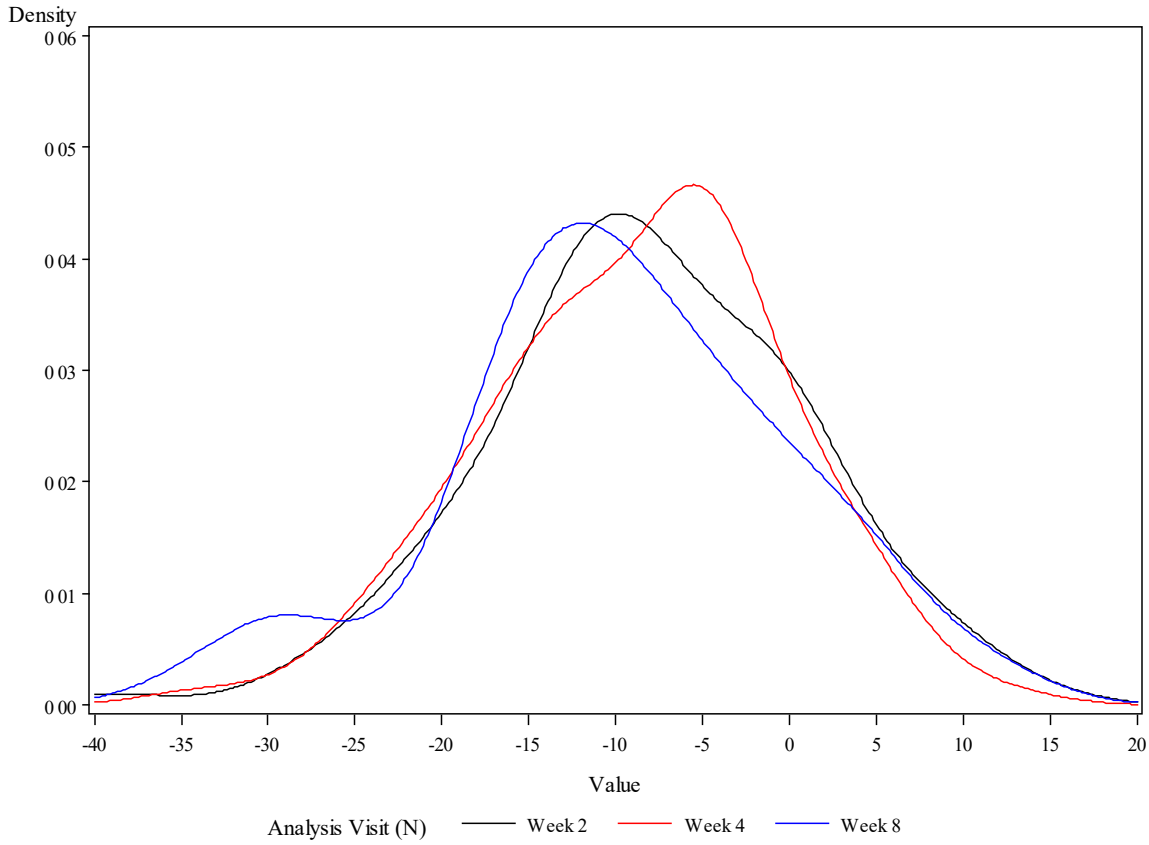
<Parameter (unit)>, Time point x>

	Blinded Treatment N = XX
Observed Values At Baseline	
n	xx
Mean	xx.xx
Standard Deviation	xx.xx
Median	xx.x
Q1, Q3	xxx.x, xxx.x
Min, Max	xx.x, xx.x
Observed Values At <Time point x>	
n	xx
Mean	xx.xx
Standard Deviation	xx.xx
Median	xx.x
Q1, Q3	xxx.x, xxx.x
Min, Max	xx.x, xx.x
Absolute Change from Baseline to <Time point x>	
n	xx
Mean	xx.xx
Standard Deviation	xx.xx
Median	xx.x
Q1, Q3	xxx.x, xxx.x
Min, Max	xx.x, xx.x

Output: XXXX, Produced by xxxxxxxx on ddmmmyyyy hh:mm (CET), Data Extraction Date: ddmmmyyyy, Cut-Off Date: ddmmmyyyy
Program: prod_ccm/program_output/program_name.sas
Page x of x

15.1.4 Layout F1

```
ACT-132577
Protocol: AC-080A201/Essential Hypertension
<Title>
Analysis set: <analysis set>
<Parameter (unit)>
```



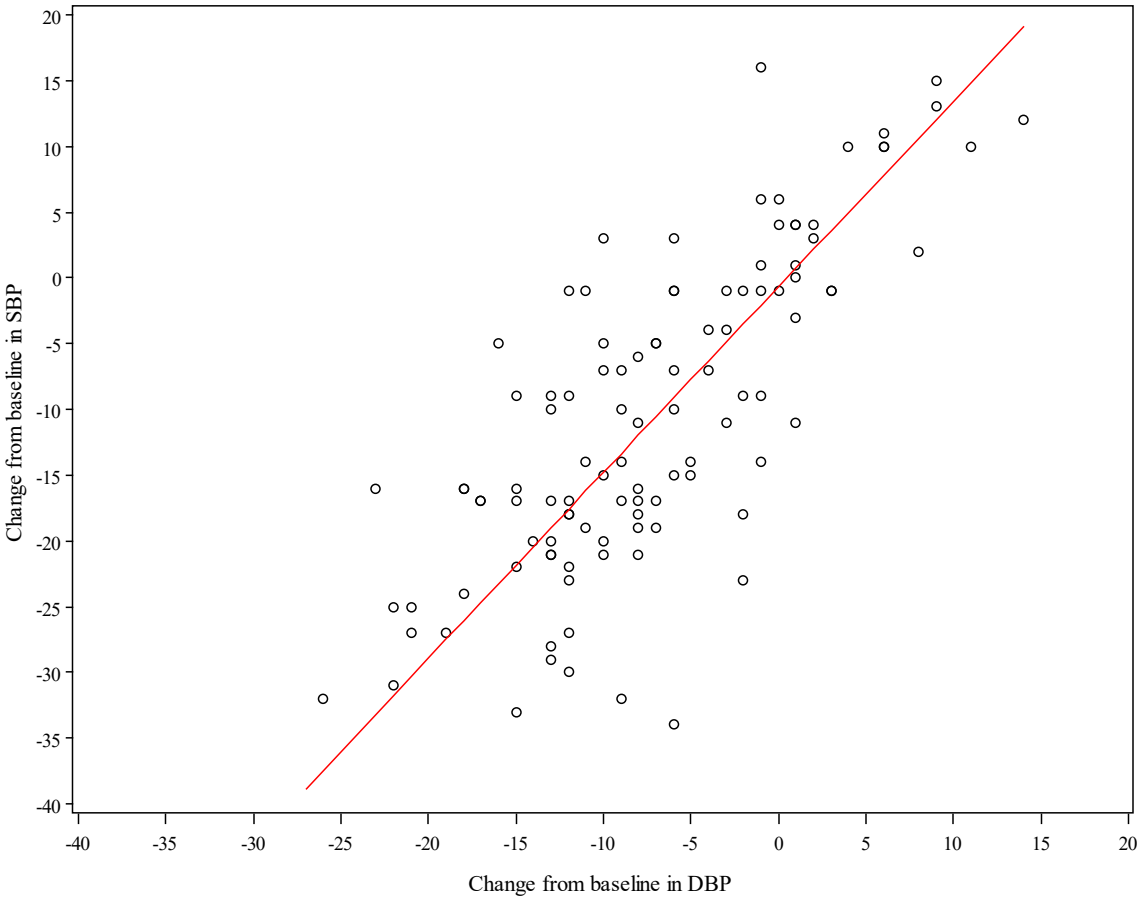
Some possible SAS statements

```
proc kde data=<dset>;
  by avisitn;
  univar chg (bwm=1)/ out=dens gridl=-40 gridu=20;
run;

proc gplot data=dens;
  plot density*value=avisitn/ haxis=axis1 vaxis=axis2;
  symbol1 c=black i=j l=1;
  symbol2 c=red i=j l=1;
  symbol3 c=blue i=j l=1;
  axis1 order=(-40 to 20 by 5) minor=none;
  axis2 order=(0 to 0.06 by 0.01) minor=none;
run;
```

15.1.5 Layout F2

ACT-132577
Protocol: AC-080A201/Essential Hypertension
<Title>
Analysis set: <analysis set>



Some possible SAS statements
* <dset> has change from baseline in DBP (cdbp) and in SBP (csbp)in separate columns;

```
proc corr data=<dset>;
  by avisitn;
  var csbp cdbp;
run;

proc glm data=botht noprint;
  by avisitn;
  model csbp=cdbp;
  output out=glmout predicted=pred;
run;

proc sort;
  by avisitn cdbp;
run;

proc gplot;
  by avisitn;
  plot (csbp pred)*cdbp/ overlay;
 run;
```

15.2 R Program for power MCP-Mod approach

```
# powerDRssr.R JUN 2016

#setwd("<To be completed>")


## PRELIMINARIES

sigEmax <- function (ed50, ed90)
{
e0 <- 0
emax <- 1
hill <- log(9)/(log(ed90)-log(ed50))
c(ed50, round(hill,2))
} # Emax

# get ed50 and hill
# based on ed50 and ed90
black <- sigEmax (ed50=0.125, ed90=0.25)
red <- sigEmax (ed50=0.125, ed90=0.50)
blue <- sigEmax (ed50=0.25,  ed90=0.50)
green <- sigEmax (ed50=0.25,  ed90=0.75)


## FUNCTIONS

powerMCT <-function (doses, sigma, n, true){

candMod <- Mods(linear = NULL, linlog = NULL, quadratic = -0.5, emax = 0.5,
                sigEmax = c(0.5, 0.5), logistic = c(0.5, 0.5), doses = doses)
contMat <- optContr(candMod, w = rep(n,length(doses)))
trueMod <- Mods(sigEmax = true, doses = doses)

power <- powMCT(contMat = contMat, altModels = trueMod, alpha = 0.05, alternative = "two.sided", n = n, sigma = sigma,
                placAdj = FALSE, df = NA, critV = TRUE, control = mvtnorm.control())
power
}


## MAIN
```

```
# load DoseFinding package
library(DoseFinding)

# doses in the study
d4 <- c(0, 0.05, 0.10, 0.25, 0.5)

# power
sigs <- seq (6,9,0.5)
nn <- seq (20,70,1)

pow<-matrix(NA,length(sigs)*length(nn),6)
k <- 1
for (i in 1:length(sigs)){
  for (j in 1:length(nn)){
    pow[k,1] <- sigs[i]
    pow[k,2] <- nn[j]
    pow[k,3] <- round(powerMCT (d4, sigs[i]/5,   nn[j], black), 3)
    pow[k,4] <- round(powerMCT (d4, sigs[i]/4.5, nn[j], red),   3)
    pow[k,5] <- round(powerMCT (d4, sigs[i]/4.5, nn[j], blue),  3)
    pow[k,6] <- round(powerMCT (d4, sigs[i]/4,   nn[j], green), 3)
    k <- k+1
  } # j
} # i

plot(pow[pow[,1]==6,2], rowMeans(pow[pow[,1]==6,3:6]), type="l", col="grey",
     xlab="group size (PPS)", ylab="power", xlim=c(20,70), ylim=c(0.6,1))
cols <- c("black","red","blue","green","orange","purple","grey")

for (i in 1:7){
sel <- pow[pow[,1]==sigs[i],]
lines(sel[,2], rowMeans(sel[,3:6]), col=cols[i])
}
abline (h=c(0.8, 0.9, 0.95), col="grey")
```

15.3 R Program to compare group standard deviations

```
# simSD.R JUL 2016

# FUNCTIONS

sim <- function (n,means,sd,seed){
  set.seed(seed)
  print(means)
  k <- length (means)
  var <- matrix(NA,nrep,2)
  for (i in 1:nrep){
    y <- rep(means, each=n) + rnorm(n*k, 0, sd)
    var[i,1] <- var(y) # overall variance
    x <- rep (1:k, each=n)
    A<-aov(y~as.factor(x))
    var[i,2] <- sum(A$residuals^2)/A$df.residual # within group variance
  }
var <- colMeans(var)
print (round(c(var,var[1]/var[2]),2))
sd <- sqrt(var)
round(c(sd,sd[1]/sd[2]),2)
}


# MAIN

nrep <- 1000

m <- seq(0,5,length.out=6)
sim(n=90, means=m, sd=8, seed=1331)

m <- seq(0,6,length.out=6)
sim(n=90, means=m, sd=8, seed=1332)

m <- seq(0,8,length.out=6)
sim(n=90, means=m, sd=8, seed=1333)
```