STATISTICAL ANALYSIS PLAN

AR14.001

A RANDOMIZED, DOUBLE-BLIND, EFFICACY AND SAFETY STUDY OF AR 14 (AZILSARTAN MEDOXOMIL) TREATMENT AND WITHDRAWAL, FOLLOWED BY AN OPEN-LABEL EXTENSION, IN CHILDREN 6 TO LESS THAN 18 YEARS OF AGE WITH HYPERTENSION.

AUTHOR: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V7.0 (Dated 13Jan2020) for Protocol AR14.001.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	10Nov2017	[redacted]	Not Applicable – First Version.
2.0	16Jul2018	[redacted]	Added appropriate figures. Added statistical analysis details for baseline characteristics and subgroup analysis.
3.0	20Sep2018	[redacted]	Updated as per Client's comments.
4.0	04Dec2018	[redacted]	Updated PROC MI code in Appendix.
5.0	14Jan2019	[redacted]	Updated Appendix 3 with the derived Low and High Lab criteria to be used for the outputs. Updated Appendix 5 Proc MI code. Updated section 4.4 PK analysis. Updated Appendix 1 with treatment and procedure details for each phase. Added appropriate baseline seDBP, SESBP or MAP in section 15.4.3.2.
6.0	19Mar2019	[redacted]	Updated section 3.2 and 3.5.
7.0	13Jan2020	[redacted]	Updated layout of entire SAP. Changed company name to [redacted]. Included references throughout relating to the open-label phase.

LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ACS	abnormal, clinically significant
AE	adverse event
ANCOVA	analysis of covariance
ANCS	abnormal, not clinically significant
AZM	azilsartan medoxomil
AZM-H	high dose azilsartan medoxomil
AZM-L	low dose azilsartan medoxomil
AZM-M	intermediate dose azilsartan medoxomil
BMI	body mass index
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CSR	clinical study report
DB	double-blind
DBL	database lock
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FAS	full analysis set
IVRS	interactive voice response system
IWRS	interactive web response system
LOCF	last observation carried forward
LS	least-squares
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed models for repeated measures
OL	open-label
PPS	per-protocol set
PT	preferred term

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SBP	systolic blood pressure
seDBP	seated diastolic blood pressure
seSBP	seated systolic blood pressure
SOC	system organ class
TEAE	treatment- emergent adverse event
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol AR14.001. It describes the data to be summarized and analyzed and the procedures for creating the statistical outputs. It includes specifics of the statistical analyses to be performed and presented in the final clinical study report (CSR).

This statistical analysis plan (SAP) is based on Protocol version 1.0, dated 20 February 2014.

A separate data monitoring committee (DMC) document was prepared for the DMC specific analyses.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is

- To evaluate the antihypertensive effect of azilsartan medoxomil (AZM) compared with placebo after a randomized, double-blind, withdrawal (Withdrawal Phase).

2.2. SECONDARY OBJECTIVES

The secondary objectives are

- To evaluate the antihypertensive effect of AZM compared with losartan during double-blind treatment (Double-Blind Phase).
- To evaluate the safety and tolerability of AZM relative to placebo and losartan during double-blind treatment, and of AZM during a long-term, open-label extension (OL Phase).

2.3. ADDITIONAL OBJECTIVES

The additional objective is:

- To assess the population pharmacokinetics of azilsartan derived from AZM (To be covered by a separate analysis plan).

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

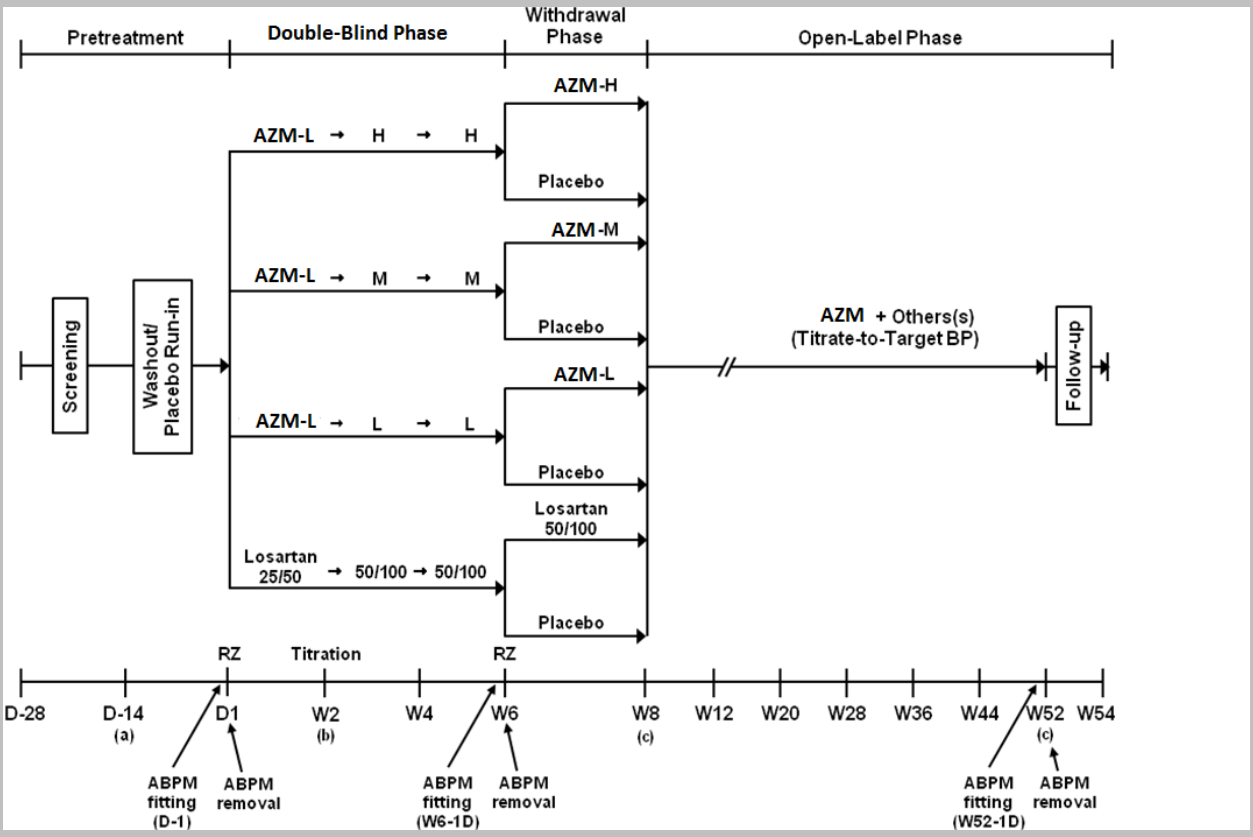
AR14.001 is a global phase 3, efficacy and safety study of AZM in children aged 6 to <18 years with primary or secondary hypertension. Approximately 260 subjects will participate in a 6- week, double-blind (DB), randomized, treatment phase (DB Phase), followed by a 2 week, double-blind, randomized placebo-controlled withdrawal (Withdrawal Phase). In the DB Phase, subjects will be randomized (1:1:1:1) to 1 of 4 treatment arms AZM (low [AZM-L], intermediate [AZM-M] or high [AZM-H]) using 4 doses (10, 20, 40, and 80 mg) or losartan. The dose of AZM or losartan used will be dependent on the subject's weight. In the Withdrawal Phase, subjects will be randomized (1:1) to continue taking their previously assigned active treatment or to be switched to placebo. In the Withdrawal Phase, subjects will be randomized (1:1) to continue taking their previously assigned active treatment or to be switched to placebo.

This study also includes a 44-week, Open-label extension (OL Phase) in which all subjects will receive AZM and other antihypertensive medications (if needed) according to a titrate-to-target blood pressure (BP) algorithm. The study will be conducted at approximately 120 sites. BP will be assessed in the clinic throughout the study, and subjects may also participate in a 24-hour ambulatory blood pressure monitoring (ABPM) procedure at Baseline, at the end the DB Phase and at the end of the OL Phase.

Due to lower than expected standard deviation, the sample size was reduced to approximately 213 by Protocol Amendment 01 (Section 13.3).

Refer to Table A: Schematic of Study Design for an overview of the study design.

Table A: **Schematic of Study Design**



AZM-L=low-dose AZM, AZM-M=intermediate-dose AZM, AZM-H=high-dose AZM, RZ=Randomization, D=Day, W=Week.

(a) β-blocker use should be tapered off gradually during the first week of the washout. If the seated diastolic blood pressure (seDBP) remains below inclusion criterion #4 (Section 7.1 of the Protocol) after the washout, it can be extended in 1-week increments up to 2 times, for a maximum washout of 4 weeks (for currently treated subjects only). Placebo should continue during the extension(s).

(b) All subjects randomized to AZM-M, AZM-H or losartan will be force-titrated at Week 2.

(c) If possible, the procedures planned for Week 8 or 52 should be completed at the time of discontinuation for subjects who prematurely withdraw from DB or OL treatment, respectively.

3.2. RANDOMIZATION

The investigator or investigator's designee will access the interactive (voice/web) response system (IVRS/IWRS) at Screening to obtain the subject's study number. The investigator or the investigator's designee will utilize the IVRS/IWRS to enter the subject into the Placebo Run-in Phase. The IVRS/IWRS will also be used to randomize the subject into the DB Phase and later the Withdrawal Phase. The DB Phase

randomization will be stratified by age (Tanner stage <3, ≥3), weight (≥25 to <50 kg, ≥50 kg), and race (non-Black, Black).

Enrolment caps will also be applied to randomization to ensure a percentage of subjects with secondary hypertension of approximately 40%-60% and to ensure that no more than ≈25% of subjects are post-renal transplant subjects and no more than ≈60% of subjects weigh greater than or equal to 50 kg at Baseline. Randomization for the Withdrawal Phase will be stratified by the treatment received in the DB Phase (i.e., AZM-L, AZM-M, or AZM-H or losartan).

Protocol Amendment 01, dated 12 Dec 2018, revised the number of secondary hypertensive subjects and < 50 kg subjects due to difficulty in recruiting these subpopulations. The expected number of secondary hypertensive subjects and subjects weighing less than 50 kg was not achieved. The revised expected percentage of subjects with secondary hypertension and subjects weighing less than 50 kg will be at least 20% of the total subject population.

3.3. TREATMENTS AND DOSING

Eligible subjects in the DB phase will be randomized into 1 of 4 DB treatment arms using an IVRS/IWRS. The 4 treatment groups include (1) AZM-L, (2) AZM-M, or (3) AZM-H or (4) losartan.

The dose (or tablet strengths) taken by each subject will be dependent on treatment assignment. All subjects randomized to AZM will initiate treatment at 10 mg. Subjects assigned to the AZM-M group will be force-titrated at Week 2 to the final randomized dose of 20 mg which will be maintained for the final 4 weeks of the DB Phase. Subjects assigned to the AZM-H group will be force-titrated at Week 2 to the final randomized dose of 40 mg or 80 mg, with the lower of the 2 possible doses being received by subjects who weigh <50 kg and the higher dose being received by subjects who are ≥50 kg. Similarly, subjects who are randomized to losartan will initiate treatment at a low dose (25/50 mg) and force titrated at Week 2 to the final losartan dose (50/100 mg).

Similarly, subjects who are randomized to losartan and weighing < 50 kg will initiate treatment at the 25 mg dose and force titrated at Week 2 to the 50 mg losartan dose. Subjects who weigh ≥ 50 kg will initiate treatment at 50 mg and forced titrated at Week 2 to the 100 mg losartan dose.

In the Withdrawal Phase, subjects will be re-randomized using IVRS/IWRS to continue receiving their previously assigned active treatment or placebo.

At the beginning of the OL Phase, all subjects will be dispensed AZM 10 mg, which can be titrated to higher dose(s) (up to 40 mg for subjects <50 kg or up to 80 mg for subjects ≥50 kg) and additional medication(s) may be added if needed to achieve BP targets during the OL extension. Because body weight is likely to change, dose adjustments may occur during the OL Phase if growth assessments (height and weight) made at Week 8/Visit 9 or at any visit scheduled during the extension necessitate a dose by weight adjustment. Refer to Table B: Treatment Arms for a summary of the 4 treatment arms.

Table B: **Treatment Arms**

Treatment	Body Weight (a)	Double-Blind, Phase		Withdrawal Phase
		Wks 0-2	Wks 2-6	Wks 6-8
AZM-L	≥25 to <50 kg	10 mg	10 mg	10 mg or placebo
	≥50 kg	10 mg	10 mg	10 mg or placebo
AZM-M	≥25 to <50 kg	10 mg	20 mg	20 mg or placebo
	≥50 kg	10 mg	20 mg	20 mg or placebo
AZM-H	≥25 to <50 kg	10 mg	40 mg	40 mg or placebo
	≥50 kg	10 mg	80 mg	80 mg or placebo
Losartan	≥25 to <50 kg	25 mg	50 mg	50 mg or placebo
	≥50 kg	50 mg	100 mg	100 mg or placebo

Body Weight (a)	Open-Label Phase	
	Wks 8-12	Wks 12-52
≥25 to <50 kg	AZM 10 mg	AZM 10, 20, or 40 mg (b)
≥50 kg	AZM 20 mg	AZM 20, 40, or 80 mg (b)

L=low, M=intermediate, H=high.

(a) The body weight category assigned at Baseline for each subject will remain unchanged throughout the DB Phase and Withdrawal Phase. During the OL Phase, weight category will be determined at each scheduled visit and the dose of medication should be adjusted accordingly.
(b) In the OL Phase, AZM can be titrated and/or other antihypertensive medications can be added to achieve and maintain target BP.

Subjects <50 kg will be required to swallow 2 tablets with a maximum diameter of 7.5 mm and thickness of 4.2 mm and 1 capsule with a maximum length of 15.64 mm and thickness of 7.42 mm as their daily dose. Subjects ≥50 kg will be required to swallow 2 tablets with a maximum diameter of 9.5 mm and thickness of 5.3 mm and 1 capsule with a maximum length of 16.19 mm and thickness of 8.30 mm as their daily dose.

3.4. SCHEDULE OF EVENTS

Schedule of events can be found in Section 9.3 of the Protocol.

3.5. SAMPLE SIZE

Original Protocol text:
Assuming a standard deviation (SD) of 10.5 mm Hg and an overall 10% dropout rate (i.e., the DB and Withdrawal Phases), 195 subjects randomized to AZM into the DB Phase (65/arm) will provide 80% power to detect a difference of 4.5 mmHg between AZM (pooled) and placebo by a 2-sample t-test of the mean seDBP change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase at the 0.05 significance level (2-sided).

Revised Sample Size Justification (From Protocol Amendment 01, dated 12 December 2018):
Upon review of pooled blinded data of the primary endpoint, the SD was 7.82 which was much less than what was previously specified. Taking into consideration variability in the SD, an SD estimate of 8.3 is used in the revised sample size (all other assumptions being the same) below. Assuming an SD of 8.3 mm Hg and an overall 10% dropout rate (i.e., the DB and Withdrawal Phases), approximately 208 subjects randomized to AZM or losartan during the DB Phase (52/arm) will provide >80% power to detect a difference of 4.5 mmHg between AZM (pooled) and placebo by a 2-sample t-test of the mean seDBP change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase at the 0.05 significance level (2-sided).

3.6. CHANGES TO ANALYSIS FROM PROTOCOL

Refer to Section 3.5.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses DMC meetings.
- Interim Analysis.
- Final Analysis.

4.1. DATA MONITORING COMMITTEE

A DMC Charter, describing the methodology and presentation of results and access to results will be provided by [redacted] as a separate document.

4.2. INTERIM ANALYSIS

A formal interim analysis will take place for this study after all subjects have completed the Withdrawal

Phase and after complete and final data (i.e., all relevant data issues have been resolved) for the Withdrawal and DB phases have been entered and locked into the clinical database. Subject treatment assignments will be unblinded for this interim analysis. The interim analysis will include the primary and secondary endpoints along with all additional efficacy and safety endpoints related to the DB and Withdrawal Phases. Since this interim analysis will be performed on final data for the Withdrawal and DB Phases, no alpha spending correction will be needed.

Derivations and definitions for the interim analysis will be based on those required for the final analysis contained in this analysis plan, unless deviations are stated within the text. Only safety and efficacy outputs for the DB and Withdrawal phase, will be provided for the interim analysis.

This formal interim planned analysis identified in this SAP will be performed by [redacted] Biostatistics following Sponsor Authorization of this SAP, Database Lock of DB and Withdrawal phases, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

4.3. FINAL ANALYSIS

The planned analyses for the open-label phase, identified in this SAP, will be performed by [redacted] following Sponsor Authorization of this Statistical Analysis Plan and Final Database Lock.

4.4. PHARMACOKINETIC ANALYSIS

No Pharmacokinetic (PK) Analysis will not be performed by [redacted]. A third party ([redacted]) will be responsible for the PK analysis.

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled (ENR) set will contain all subjects whose parent/legal guardian provide informed consent on behalf of their child for this study.

A subject will be programmatically included in the ENR analysis set if the participant has a date of informed consent in the database as recorded on the Demography (DEMOG) and Screen Failure Form (SFL_IVRS) electronic case report form (eCRF).

5.2. ALL SUBJECTS RANDOMIZED SET [RND]

The all subjects randomized (RND) set will contain all subjects in the ENR set who were randomized to study medication.

A participant will be programmatically included in the RND analysis set if the participant has a randomization number derived from an external randomization sheet, created by the IVRS/IWRS, and used in the randomization module of the eCRF. The randomization schedule will be sent to the [redacted] biostatistician as a password protected EXCEL sheet via email.

For analysis and presentations based on the RND analysis set, participants will be analyzed according to the assigned treatment, regardless of the treatment received.

5.3. FULL ANALYSIS SET [FAS]

The definition for FAS, as follows, will be applied independently for both the DB Phase and Withdrawal Phase of the study. The FAS will include all randomized subjects who receive at least 1 dose of the double-blind study medication for the respective study phase. Subjects will be analyzed according to the treatment group to which they are randomized.

5.4. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all subjects who receive at least one dose of study medication. Subjects will be analyzed according to the study medication they received for the study phase being summarized.

If there is any uncertainty concerning a subject's treatment status, then they will be assumed treated for the purposes of analysis.

5.5. PER PROTOCOL SET [PPS]

The per protocol analysis set (PPS) will contain all subjects in the FAS excluding those identified as major protocol violators. Major deviations from the protocol leading to exclusion from the PPS will be identified prior to database lock, but may likely include relevant entry criteria, receiving incorrect treatment assignment, taking prohibited medication, non-compliance to dosing schedule and deviation from study procedures. For the PPS major protocol violation, focus will be placed on violations that may confound the interpretation of the primary endpoint. Therefore, protocol deviations during the follow-up phase, for example, wouldn't be considered major violation for exclusion from the PPS.

Primary and Secondary efficacy analyses using the PPS will be performed.

5.6 PHARMACOKINETIC SET [PK]

The pharmacokinetic set analysis set (PK) will contain all subjects who receive at least one dose of study medication. A subject will be included in the analysis only when there is at least 1 measurable concentration of plasma. PK analysis will not be performed by [redacted]. A third party ([redacted]) will perform the PK analysis.

6. GENERAL CONSIDERATIONS

The FAS will be the primary data set used for efficacy analyses of the DB Phase and the Withdrawal Phase, unless otherwise specified. Efficacy analysis (FAS, PPS) will use planned treatment and Safety Analysis will use actual treatment. All routine safety analysis will be based on the SAF. All analysis of data (i.e., efficacy and safety) from the OL Phase will use the SAF and subjects will be summarized overall (i.e., all subjects together) and by status of additional antihypertensive use (i.e., AZM alone versus AZM plus additional antihypertensives).

6.1. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Study day will be calculated as follows:

- If the date of the event is on or after the reference date, then:
  - Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  - Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-treatment.

For subjects randomized but not treated, baseline is defined as the last non-missing measurement taken on or before randomization.

6.3. ENDPOINTS

The primary endpoint for this study is

- Change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in trough clinic seDBP between AZM and placebo.

Secondary endpoints for this study are:

- Change from Week 6/Final Visit of the DB Phase to Week 8/ Final Visit of the Withdrawal Phase in trough clinic seDBP and mean arterial pressure (MAP) between AZM and placebo.
- Change from baseline in trough clinic seDBP, seated systolic blood pressure (seSBP), and MAP to Week 6/Final Visit of the DB Phase for AZM and losartan.
- Percentage of subjects who achieve target BP (seDBP, seSBP, both) at Week 8/Final Visit of the Withdrawal Phase, with the target defined as <90th percentile for age, gender, and height.

Safety Endpoints for this study are:

- Adverse events (AEs).
- Physical examination.
- Laboratory tests.
- 12-lead electrocardiogram (ECG) finding.
- Vital signs.
- Anthropometric (height, weight, and body mass index z-scores) measurements.

Additional Endpoints for this study are:

- Change from baseline in trough clinic seDBP, seSBP and MAP at all visits of the DB Phase, excluding the Week 6/Final Visit for AZM and losartan.
- Change from baseline in trough clinic seDBP, seSBP and MAP at all visits of the OL Phase, including Week 52/Final Visit.
- Percentage of subjects who achieve the following additional BP targets (for seSBP, seDBP and both):
- All Subjects:
    - $<90^{th}$ percentile at Week 6/Final Visit of the DB Phase and Week 52/Final Visit of the OL Phase
    - in subjects with chronic kidney disease (CKD).
    - $<90^{th}$ percentile at Weeks 6, 8, and 52/Final Visits of the DB Phase, Withdrawal Phase, and OL Phase, respectively.
    - $<50^{th}$ percentile at Weeks 6, 8, and 52/Final Visits of the DB Phase, Withdrawal Phase, and OL Phase, respectively.
    - Estimation of the exposure using population pharmacokinetics of azilsartan.

Exploratory Endpoints are:

- Change from baseline to Week 6/Final Visit of the DB Phase and to Week 52/Final Visit of the OL Phase in 24-hour, 12-hour, daytime, night time, and trough DBP and SBP by ABPM.
- AZM dose response for change from baseline to Week 6/Final Visit of the DB Phase in clinic seDBP and seSBP.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Measurements from unscheduled visits will not be included in by-visit summaries but may contribute to the final visit or last observation carried forward (LOCF) value, or best/ worst case value where required.

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Data collected at early termination visits will be mapped to the next planned visit number for that subject. For by-visit summaries, only visits in which a measure was scheduled to be collected will be summarized. Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. SUMMARY STATISTICS

Unless otherwise specified for presentations:

- The default summary statistics for numeric variables are as follows:
  - Number of observations (n).
  - Arithmetic mean.
  - Standard deviation (SD).
  - Minimum (Min).
  - Median.
  - Maximum (Max).

- The default summary statistics for categorical variables are as follows:
  - Number of observations (n).
  - Percentage of subjects with non-missing data per category.

Percentages will be rounded to one decimal place. However, for counts frequencies that are greater than 0, if the calculated percent would round to 0%, then <0.1% will be displayed instead. Likewise, for counts frequencies that are less than the total possible, if the calculated percentage would round to 100%, then >99.9% will be displayed instead. The denominator for each percentage will be the total number of subjects with non-missing data in the treatment group and population (analysis population) being presented, unless otherwise specified.

6.7. STATISTICAL TESTS

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and/or 2-sided 95% confidence interval (CI).

6.8. PRECISION

All values will be rounded using the SAS® function ROUND, as the last step prior to presentation. All computed percentages (%) will be presented using one decimal place. Categories with a '0' count will not display the percentage (%) value. If the original data has N decimal places (as derived from the raw data), then the summary statistics for quantitative data will contain the following number of decimal places (to a maximum of 3 places):

- Minimum and maximum: N
- Mean and median: N + 1
- SD: N+ 2

P-values greater than or equal to 0.001 and less than or equal to 0.999 will be rounded to 3 significant digits and presented with three decimal places. Any p-value less than 0.001 will be presented as '<0.001', while p-values greater than 0.999 will be presented as '>0.999'. CIs will be presented to one more decimal place than the raw data.

6.9. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X (Post-baseline visit) – Baseline Value
    - If baseline is missing, change from baseline will be presented as missing in the listing. That is, no imputation for change from baseline will be performed.

Calculation of BP Percentile:
"The fourth report on diagnosis, evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf) will be used to calculate BP Percentile.

6.10. SOFTWARE VERSION

All analyses will be conducted using SAS® version 9.4, or higher, on the WINDOWS 32 bit operating system.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Week 6/Final Visit of the DB Phase seDBP.
- Baseline seDBP.
- Baseline seSBP.
- Baseline MAP.
- Treatment during DB Phase (AZM low, med, high dose and losartan).
- Treatment during Withdrawal Phase, (AZM low, med, high and placebo).
- Treatment for study drug (AZM low, med, high).
- Age (Tanner stage <3, ≥3).
- Weight (<50 kg, ≥50 kg).
- Race Group (Black or African American, Non- Black or African American).

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms is not stratified by country/ center.
Center pooling will not be carried out for use in analyses for this study.

7.3. MISSING DATA

Missing safety data (not considering dates) will not be imputed.
For efficacy data, two different methods will be used.

- Multiple Imputation: using the Markov Chain Monte Carlo method.
- Last-observation-carried-forward (LOCF): the last post baseline double-blind observed value will be carried forward where data are missing (e.g., the subject has missing data or has dropped out of the study).

Details for how to handle missing efficacy data are in section 15.1 - 15.2 of this analysis plan.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

To control for multiplicity of the type 1 error, the following sequential testing procedure will be employed in

the analysis of the primary endpoint using an analysis of covariance (ANCOVA) model and estimate statements: Step 1, the mean AZM effect versus placebo will be tested, if statistically significant then testing will continue to the next step; Step 2, AZM high dose effect versus placebo will be tested, if statistically significant then testing will continue to the next step; Step 3, AZM med dose effect versus placebo will be tested, if statistically significant then testing will continue to the next step; Step 4, AZM low dose effect versus placebo will be tested.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted on the primary endpoint and secondary endpoints. Statistical analysis will be conducted (comparing Pooled AZM vs Placebo) within each subgroup and the p-value will be reported.
The following subgroups will be assessed and described within the exploratory analysis sections:

- Gender:
  - Female
  - Male
- Age (Tanner stage):
  - Tanner stage <3
  - Tanner stage ≥3
- Race in 2 categories:
  - Black or African American.
  - Non- Black or African American (American Indian or Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, White).
- Weight Group:
  - <50 kg
  - ≥50 kg
- Chronic Kidney Disease
  - Yes
  - No
- Region:
  - US
  - Non-US
- Diagnosis:
  - Primary Hypertension
  - Secondary Hypertension
- Renal Transplant
  - Yes
  - No

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, listings, and figures (TLFs) to be provided by [redacted] Biostatistics.

Note that verbatim terms, specifications (for example the reason a specific assessment was not done) and all variables in the TLF shells that contain the suffix (eCRF) contain verbatim text that may include spelling mistakes. Verbatim text will be presented in the listings "as is" and no manual "hard-coding" corrections of such data will be made.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

The number and percentage of subjects in each disposition category will be presented; there will be no inferential analysis of subject disposition data.

Disposition of all enrolled but not randomized subjects will be tabulated according to screen failure/run-in failure, including primary reason for screen/run-in failure (pretreatment event, major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, did not meet entrance criteria, other) as entered on the electronic case report form (eCRF).

Disposition of all randomized subjects will be tabulated by study phase, treatment group, pooled AZM (for DB and Withdrawal phases only) and overall. Treatments for DB phase are Losartan, AZM low dose, AZM intermediate dose, AZM high dose. Treatments for Withdrawal phase are Placebo, Losartan, AZM low dose, AZM intermediate dose, AZM high dose. Treatments for OL phase are AZM alone, AZM plus additional antihypertensive.

Primary reasons for discontinuation of study drug/visits, as entered on the eCRF, will be tabulated by phase and treatment group; the reasons include adverse event, major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy, lack of efficacy, PI discretion and other.

Major protocol deviations will be summarized for RND by phase, treatment group, pooled AZM (for DB and Withdrawal phases only) and overall. Protocol deviations will be presented in a data listing. Also, violation of Inclusion/Exclusion criteria will be listed for RND.

The number of subjects included in each analysis population will be summarized by phase, treatment group, pooled AZM (for DB and Withdrawal phases only) and overall.
Subject disposition, study discontinuation and study visit dates and times will be listed based on RND.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented based on RND.

Statistical testing will be carried out and the p-value will be reported for demographic or other baseline characteristics. T-test will be done for continuous variables and Chi-square test will be done for categorical variables.

The following demographic and baseline characteristics will be summarized using descriptive statistics and p-value for each study phase (DB, Withdrawal, OL) by treatment group, pooled AZM (for DB and Withdrawal phases only) and overall:

- Age (years)
- Tanner Stage (<3, ≥3)
- Race
- Race Group (Black or African American, Non- Black or African American)
- Ethnicity
- Gender
- Height (cm)
- Weight (kg)
- Weight Group (<50 kg, ≥50 kg)
- Body Mass Index (BMI)
- Diagnosis of Chronic Kidney Disease
- Renal Transplant
- Hypertension Diagnosis (Primary or Secondary Hypertension)
- Baseline Sitting DBP
- Baseline Sitting SBP
- Baseline Standing DBP
- Baseline Standing SBP
- Baseline ABPM DBP
- Baseline ABPM SBP
- Female Reproductive Status
- Current Hypertensive Medication
- Glomerular Filtration Rate

All individual demographic and baseline characteristics will be listed by site and subject number.

11. MEDICAL HISTORY

Hypertension and other relevant Medical History information are collected on eCRF Medical History – Hypertension and Medical History pages and will be presented for the SAF.

- Other relevant Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or higher.
    - Medical History conditions are defined as those conditions which stop prior to or at Screening.
    - Other relevant Medical History will be presented by system organ class (SOC) and preferred term (PT).

Hypertension and other relevant medical history will be summarized for subjects in each study phase (DB, Withdrawal, OL) by treatment group, pooled AZM (for DB and Withdrawal phases only) and overall. A list of medical history per subject will be presented.

12. MEDICATIONS

Medication History includes medications that stopped at or within 30 days prior to signing of informed consent (Informed consent date > medication end date ≥ Informed consent date -30).

See Appendix 2 for handling of partial dates for medications.

- For Double Blind Phase:

Concomitant medications include medications started at or within 30 days prior to signing of informed consent through end of the double blind phase (informed consent date -30 ≤ medication start date ≤ end of double blind study date) or ended before the first dose of the study medication in the withdrawal phase as well as medications started before 30 days prior to signing of informed consent but stopped on at or after signing of informed consent (medication start date< informed consent date -30 and medication end date≥ informed consent date).

- For Withdrawal phase:

Concomitant medications include medications started prior to, on or after the first dose of study medication in the withdrawal phase and ended on or after the date of first dose of study medication in the withdrawal phase or were ongoing till the end of the withdrawal phase.

- For Open Label:

Concomitant medications include medications started prior to, on or after the first dose of study medication in the Open Label phase and ended on or after the date of first dose of study medication in the Open Label phase or were ongoing till the end of the Open Label phase.

Medication History and Concomitant Medication information for Single or Double-Blind phase are collected on the concomitant medication page in the eCRF and concomitant medication information for Open Label phase is collected on concomitant medication – open label page in the eCRF. They will be presented for the SAF and coded using World Health Organization Drug Dictionary (WHO-DD).

Medication History and Concomitant Medications will be presented by treatment group for different phases

based on Safety population. The summary of Medication History and Concomitant Medication will be provided by Therapeutic Classification (2nd level of ATC) and preferred medication name. Therapeutic Classification will be sorted alphabetically. Preferred Medication Names are sorted by decreasing total number of subjects. Preferred Medication Names are sorted by decreasing total number of subjects.

In the summaries, subjects experiencing more than one medication within the same therapeutic class and preferred name will be counted only once.

Concomitant medications will be listed for the RND.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented by phase based on SAF.

The date of first study medication administration during DB phase will be taken from the eCRF "In-clinic dosing" form at Day 1. The date of last study medication during DB phase will be taken from the eCRF "In-clinic dosing" form at Week 6 (if subject complete the DB phase) or "End of Study Drug" form. The date of first study medication during withdrawal phase will be taken from the eCRF "Prior dose" form at Week 6. The date of last study medication during Withdrawal phase will be taken from eCRF "In-clinic dosing" form at Week 8 (if subject complete the Withdrawal phase) or "End of Study Drug" form. The date of first study medication administration during OL phase will be taken from the eCRF "In-clinic dosing" form at Week 8. The date of last study medication during Open Label phase will be taken from the eCRF "Prior dose" form at Week 54 (if subject complete the Open Label phase) or "End of Study Drug" form.

13.1. DERIVATIONS

For each phase, the derivation of study medication exposure is calculated as following:

Duration of exposure (days) = date of last study medication administration in the phase – date of first study medication administration + 1.

14. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for the SAF.

14.1. DERIVATIONS

Compliance with study medication—based on the drug accountability data—will be calculated as the number of tablets taken (total dispensed – total returned) divided by the prescribed number of tablets

expressed as a percentage, see calculations below. For the OL extension phase of the study, dosing is 1 tablet orally per day for study drug AZM.

For the run-in, double-blind and withdrawal phases of the study, dosing is 2 tablets and 1 capsule orally per day for the study drug and it is assumed that the subject should take medication from the visit day at which their medication is initially dispensed to their last medication return date. For example, for double-blind phase, the initial dispense date is Day 1 and the last return date is Week 6, then the subject should have taken 2 tablets and 1 capsule on Days 1 to the day before Week 6. Assuming that the day before Week 6 for the subject is Day 42, the total number of prescribed tablets would be 42×3 = 126

Θ = Number of capsules required to be taken per day.

- "Per Visit" Compliance to study medication will be calculated as follows:

$$\frac{\{([\text{N of Capsules dispensed at Visit X(n}-1)] - [\text{N of Capsules returned at Visit X(n)}])\} \div \Theta}{[\text{Date of Visit Xn}] - [\text{Date of Dispensing at Visit Xn}-1]} \times 100$$

- Compliance to study medication per phase (Visit X(n) is the last visit in the phase) will be calculated as follows:

$$\frac{\begin{array}{c}\{([\text{N of Capsules dispensed at Visit 1}] - [\text{N of Capsules returned at Visit 2}]) \\ +\cdots+ \\ ([\text{N of Capsules dispensed at Visit X(n}-1)] - [\text{N of Capsules returned at Visit X(n)}])\} \div \Theta\end{array}}{[\text{Date of Visit X(n)}] - [\text{Date of Dispensing at Visit 1}]} \times 100$$

For subjects who permanently stop the study medication, the "Date of Visit X(n)" will be replaced by the date of study withdrawal.

15. EFFICACY OUTCOMES

At each visit, three serial sitting BP measurements will be obtained and the average (arithmetic mean) of the 3 serial measurements will be used for the efficacy analysis.

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

Change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in trough clinic seated diastolic blood pressure (seDBP) between AZM and placebo which is collected in the eCRF.

15.1.2. Missing Data Methods for Primary Efficacy Variable(s)

The primary analysis will use multiple imputations for missing data, supported by sensitivity analysis using observed data. Multiple imputation is a stochastic parameter estimation method for partially observed data. Missing data will be assumed to follow an arbitrary missing data pattern, and a multivariate response model will be fitted separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method. This method of imputation draws each missing value from its conditional distribution, given the observed data (baseline and post baseline values of the parameter) expected to be predictive of the missing pattern. Details on MCMC method is found in Appendix 5.

15.1.3. Primary Analysis of Primary Efficacy Variable(s)

The primary objective of this study is to evaluate the antihypertensive effect of AZM compared with placebo after a randomized, double-blind, withdrawal (Withdrawal Phase).

The primary efficacy analysis will be performed for the FAS. The primary analysis will exclude subjects that were treated with losartan during the DB Phase.

The primary efficacy variable analysis will be an ANCOVA model with treatment (AZM low, med, high and placebo), age (Tanner stage <3, ≥3), race (Black or African American, Non- Black or African American) and weight (<50 kg, ≥50 kg) as fixed effects, and Week 6/Final Visit of the DB Phase seDBP as a covariate. The primary comparison, mean (i.e. pooled) AZM effect versus placebo, will be made using an ANCOVA contrast statement. Comparisons between each AZM dose to placebo will also be done from the framework of the above ANCOVA using contrast statements.

To control for multiplicity of the type 1 error, the sequential testing procedure mentioned in Section 7.4 will be employed in the analysis of the primary endpoint.

Summary of observed seDBP at Week 6 and Week 8 will be presented. Change in seDBP from Week 6 to Week 8 and the results from the analysis (Least square (LS) means, Standard Error, LS Mean Difference (SE), P-value and 95% Confidence Interval for Difference in LS means) will also be presented.

Profile plots (line with symbol at each visit with +/- 1 SE error bars) will be displayed for observed seDBP and boxplot will be displayed for the change in seDBP from Week 6 to Week 8.

15.1.4. Sensitivity Analysis of Primary Efficacy Variable(s)

Sensitivity analysis of primary efficacy variable will be based on observed data and the analysis will be conducted by using the same ANCOVA model mentioned above with observed seDBP only.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the FAS.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1.

Change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in trough clinic seSBP and MAP between AZM and placebo.
Clinic seSBP and seDBP are collected from eCRF and MAP is calculated as following.

- $MAP = seSBP + \frac{2\,(seDBP)}{3}$

15.2.1.2.

Change from baseline in trough clinic seDBP, seSBP, and MAP at Week 6/Final Visit for AZM and losartan.
Clinic seDBP and seSBP are collected from eCRF and MAP is calculated using formula mentioned above.

15.2.1.3.

Percentage of subjects who achieve target BP (seDBP, seSBP, both) at Week 8/Final Visit of the Withdrawal Phase, with the target defined as <90th percentile for age, gender, and height.

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

15.2.2.1.

The same multiple imputations for missing data as primary endpoint (Section 15.1.2) will be used for Change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in trough clinic seSBP and MAP.

15.2.2.2.

For change from baseline in trough clinic seDBP, seSBP, and MAP to Week 6/Final Visit, last observation carried forward (LOCF) method for missing data will be used for the sensitivity analysis. In the LOCF analysis data set, the last post baseline double-blind observed value will be carried forward and used for all subsequent scheduled time points in the DB Phase where data are missing (e.g., the subject has missing data or has dropped out of the study).

15.2.2.3.

For analysis of percentage of subjects who achieve target BP at Week 8/Final Visit of the Withdrawal Phase will be based on LOCF. Sensitivity analysis will be done using multiple imputation

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

15.2.3.1.

Change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in trough clinic seSBP and MAP will be analyzed using an ANCOVA model with treatment (AZM low, med, high and placebo), age (Tanner stage <3, ≥3), race (Black or African American, Non- Black or African American) and weight (<50 kg, ≥50 kg) as fixed effects, and baseline value (seDBP or MAP) as a covariate. The comparison, mean (i.e., pooled) AZM effect versus placebo, will be made using an ANCOVA contrast statement. Comparisons between each AZM dose to placebo will also be done from the framework of the above ANCOVA using contrast statements.
This analysis will exclude subjects that were treated with losartan during the DB Phase. There will be no sequential testing procedure for this analysis.
Profile plots (line with symbol at each visit with +/- 1 SE error bars) will be displayed for observed seSBP and MAP and boxplot will be displayed for the change in seSBP and MAP from Week 6 to Week 8.

15.2.3.2.

Change from baseline in trough clinic seDBP, seSBP, and MAP at Week 6/Final Visit, will be analyzed with a mixed models for repeated measure (MMRM) with treatment (AZM low, med, high dose and losartan), time point (Week 2, Week 4, Week 6), treatment by time interaction, age (Tanner stage <3, ≥3), race (Black or African American, Non- Black or African American) and weight (<50 kg, ≥50 kg) as fixed effects, and corresponding baseline value (seDBP, seSBP, MAP) as a covariate. An unstructured covariance matrix will be used to model the within-subject variation-covariance errors. The comparison, mean (i.e., pooled) AZM effect versus losartan, will be made using contrast statement. Comparisons between each AZM dose to losartan will be done from the framework of the above MMRM. Observed data will be used to perform MMRM. Sensitivity analyses will be performed including ANCOVA at each time point using last observation carried forward (LOCF).
In case of non-convergence, the following tests in sequence will be used: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure.
Profile plots (line with symbol at each visit with +/- 1 SE error bars) will be displayed for the change in seDBP, seSBP and seMAP from baseline to Week 6.

15.2.3.3.

The analysis of subject who achieves target BP (seDBP, seSBP, both) at Week 8/Final Visit of the Withdrawal Phase, with the target defined as <90th percentile for age, gender, and height, will be conducted using logistic models with treatment (AZM low, med, high and placebo), age (Tanner stage <3, ≥3), race (Black or African American, Non- Black or African American)and weight (<50 kg, ≥50 kg) as fixed effects and baseline clinic seated BP as a covariate. The analysis will be based on LOCF data. Sensitivity analysis will be done using multiple imputation. The number and percentage of subjects who achieved target BP at Week 8/Final Visit of the Withdrawal Phase will be presented, along with the odds ratios and associated 95% CIs.
Percentage will be calculated as:
Number of subjects with target blood pressure / Number of subjects with BP at week 8Profile plots (line with

symbol at each visit with +/- 1 SE error bars) will be displayed for the change in seDBP, seSBP and seMAP from baseline to Week 8.

15.3. ADDITIONAL EFFICACY

15.3.1. ADDITIONAL EFFICACY VARIABLES & DERIVATIONS

15.3.1.1.

Change from baseline in trough clinic seDBP, seSBP, and MAP at all visits of the DB Phase, excluding the Week 6/Final Visit (Week 2 and Week 4) for AZM and losartan.

15.3.1.2.

Change from baseline in trough clinic seDBP, seSBP, and MAP at all visits of the OL Phase, including Week 52/Final Visit.

15.3.1.3.

Percentage of subjects who achieve the following additional BP targets (for seSBP, seDBP, both):

All Subjects:
- <90th percentile at Week 6 and Week 52/Final Visit of the DB Phase and OL Phase.

Subjects with chronic kidney disease (CKD):
- <90th percentile at Weeks 6, 8, and 52/Final Visits of the DB Phase, Withdrawal Phase, and OL Phase.
- <50th percentile at Weeks 6, 8, and 52/Final Visits of the DB Phase, Withdrawal Phase, and OL Phase.

15.3.1.4.

Estimation of the exposure using population pharmacokinetics of azilsartan. (This will not be covered by this SAP or performed by [redacted]. A third party (Takeda) will be responsible for the PK analysis).

15.3.2. MISSING DATA METHODS FOR ADDITIONAL EFFICACY VARIABLE(S)

15.3.2.1.

For Change from baseline in trough clinic seDBP, seSBP, and MAP at Week 2 and Week 4 of the DB Phase, last observation carried forward (LOCF) method for missing data will be used for the sensitivity analysis.

15.3.2.2.

Observed change from baseline in trough clinic seDBP, seSBP, and MAP at all visits of the OL Phase will be

used, including Week 52/Final Visit, no method will be used for missing data.

15.3.2.3.

For the analysis of subjects who achieve the BP targets at Week 6/Final Visit of DB phase and Week 8/Final Visit of Withdrawal phase (for seSBP, seDBP, both), LOCF will be used. Sensitivity analyses on trough seDBP, seSBP, and MAP will be performed on observed values and using multiple imputation for missing trough BP data. No missing data will be used for percentage of subjects who achieve the BP targets at Week 52.

15.3.3. Analysis of Additional Efficacy Variables

15.3.3.1.

Change from baseline in trough clinic seDBP, seSBP, and MAP at visits Week 2 and Week 4 of DB Phase will be will be analyzed using the same MMRM model that is described in section 15.2.3.2 and the result will come from the same model as well.

15.3.3.2.

No statistical model will be used for Change from Baseline in trough clinic seDBP, seSBP, and MAP at all visits of the OL Phase, including Week 52/Final Visit. Only descriptive statistics will be provided

15.3.3.3.

The analysis for whether a subject who achieves the BP targets at Week 6/Final Visit in the DB Phase (for seSBP, seDBP, both), will be logistic models on observed data with treatment (AZM low, med, high dose and losartan), age (Tanner stage <3, ≥3), race (Black or African American, Non- Black or African American) and weight (<50 kg, ≥50 kg) as fixed effects and baseline clinic seated BP as a covariate. The number and percentage of subjects who achieved target BP will be presented, along with the odds ratios and associated 95% CIs. Sensitivity analyses on trough seDBP, seSBP, and both will be performed for DB analysis on observed values and using multiple imputation for missing trough BP data to assess the impact of LOCF methodology and drop-outs. For Week 52/Final Visit of the OL Phase, the number and percentage of subjects who achieve the BP targets will be provided.

For subjects with CKD, the analysis for weather a subject who achieves the BP targets at week 6/Final Visit in the DB phase and week 8/Final visit in the WD phase (for seSBP, seDBP, both), will be logistic models on observed data with treatment (AZM low, med, high dose and losartan), age (Tanner stage <3, ≥3), race (Black or African American, Non- Black or African American) and weight (<50 kg, ≥50 kg) as fixed effects and baseline clinic seated BP as a covariate. The number and percentage of subjects who achieved target BP will be presented, along with the odds ratios and associated 95% CIs. . Sensitivity analyses on trough seDBP, seSBP, and both will be performed for DB analysis on observed values and using multiple imputation for missing trough BP data to assess the impact of LOCF methodology and drop-outs. For Week 52/Final Visit of the OL Phase, the number and percentage of subjects with CKD who achieve the BP targets will be provided.

15.4. EXPLORATORY EFFICACY

15.4.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

15.4.1.1.

Change from baseline to Week 6/Final Visit of the DB Phase and to Week 52/Final Visit of the OL Phase in 24-hour, 12-hour, daytime, night time, and trough DBP and SBP by ABPM.

15.4.1.2.

AZM dose response for change from Baseline to Week 6/Final Visit of the DB Phase, Week 2 and Week 4 of the DB Phase in clinic seDBP, seSBP and MAP.

15.4.1.3.

Primary endpoint and secondary endpoints for subgroup analysis.

15.4.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY VARIABLE(S)

15.4.2.1.

For ABPM results, no missing data method will be used.

15.4.2.2.

For analysis of AZM dose response of the DB phase, LOCF will be used for missing data.

15.4.2.3.

Same method for missing data will be used for subgroup analysis of primary and secondary endpoints as that in Section 15.1.2 and 15.2.2.

15.4.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

15.4.3.1.

For Change from Baseline to Week 6/Final Visit of the DB Phase in 24-hour, 12-hour, daytime, night time, and trough DBP and SBP by ABPM, descriptive statistics will be provided for the change from Baseline as well as the difference between each AZM treatment and losartan for 24-hour, 12-hour, daytime, night time, and trough ABPM SBP/DBP. For Change from Baseline to Week 52/Final Visit of the OL Phase in 24-hour, 12-hour, daytime, night time, and trough DBP and SBP by ABPM, descriptive statistics will be provided for the change from Baseline for 24-hour, 12-hour, daytime, night time, and trough ABPM SBP/DBP.

Daytime is defined as 6 am – 9:59 pm
Nighttime is defined as 10 pm - 5:59 am
Profile plots (line with symbol at each visit with +/- 1 SE error bars) will be displayed for the observed seDBP and seSBP and the change in seDBP and seSBP from baseline to Week 6 and to Week 52 in 24-hour, 12-hour, daytime, night time by ABPM.

15.4.3.2.

Exploratory dose response analysis using only AZM low, med and high dose groups, for change from Baseline to Week 6/ Final Visit, Week 2, Week 4 of the DB Phase in clinic seDBP, seSBP and MAP will be performed using linear regression model with weight adjusted dose (mg/kg) as the continuous covariate. LOCF will be used for missing data. The intercept with Standard Error and estimate of the coefficient with Standard Error will be displayed with the summaries. Additionally, an ANCOVA with treatment, age and weight as fixed effects, and baseline seDBP, seSBP or MAP as covariate will be performed to assess between-group comparisons.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

Safety analyses will be presented separately for the different study phases (i.e., DB, Withdrawal, and OL Phases). Summaries for the DB and Withdrawal Phases will be by Overall (i.e., all subjects), AZM treated subjects (pooled), and by the individual treatments; summaries for the OL Phase will by Overall and by status of additional antihypertensive use (i.e., AZM alone and AZM plus additional antihypertensive).

For safety analysis, baseline value for the DB Phase analyses will be the last available value prior to the first dose of DB Phase study drug. Baseline value for the Withdrawal Phase will be the last available value from the DB Phase. Baseline value for the OL Phase will be the last available value prior to the first dose of DB Phase study drug.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 20.0 or higher.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication and no more than 14 days (30 days for SAEs) after the last dose of study drug. TEAEs will be defined within each study phase.

For the DB Phase, TEAEs will include events whose date of onset occurred after the first dose of double-blind study drug and before the first dose of withdrawal study drug, or within 14 days (30 days for serious AEs) after the last dose of the double-blind study drug for subjects who did not enter the withdrawal study phase.

For the Withdrawal Phase, TEAEs will include events whose date of onset occurred after the first dose of withdrawal study drug and before the first dose of open-label study drug, or within 14 days (30 days for serious AEs) after the last dose of the withdrawal study drug for subjects who did not enter the open-label study phase. For those subjects who switched from AZM to Placebo in WD phase, all AEs occurred on the first 3 days of WD period will be attributed to AZM.

For the OL Phase, TEAEs, will include events whose date of onset occurred after the first dose of open-label study drug and within 14 days (30 days for serious AEs) after the last dose of the open-label study drug. See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include all AEs (TEAEs and Non-TEAEs).

16.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

16.1.1.1.Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

16.1.1.2.Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as ”Unrelated”, “Unlikely”, “Possibly”, “Probably” and “Definitely” (increasing severity of relationship). Missing relationship will be classified as related. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.
A list of TEAEs will be presented.

16.1.2. SERIOUS TREATMENT EMERGENT ADVERSE EVENTS

Serious Treatment Emergent Adverse Events (SAEs) are those events recorded as ”Serious” on the Adverse

Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared.
A list of Serious TEAEs will be presented.

16.1.3. TREATMENT EMERGENT ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared.
A list of TEAEs leading to death will be presented.

16.1.4. ALL ADVERSE EVENTS LEADING TO DEATH

AEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF. A summary of AEs leading to death and discontinuation by SOC and PT will be presented.
A list of All AEs leading to death will be presented.

16.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study by laboratory parameter. Presentations will use SI Units.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of markedly abnormal values according to central laboratory reference ranges
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)
- Listing of values meeting markedly abnormal criteria

Sample collection information will be listed. Lab results will be listed for Hematology, Chemistry and Urinalysis respectively. Lab results which are out of normal range, or meet the markedly abnormal, will also be listed respectively for Hematology, Chemistry and Urinalysis.

Number and percentage of subjects with elevated creatinine will be summarized by visit.

16.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative safety (and other) laboratory assessments will also be identified in accordance with the predefined markedly abnormal criteria as presented in provided in Appendix 3.

16.3. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

Corrected QT interval will be calculated by Arbor or designee and will not be recorded on the CRF.
High Low criteria in listing will be derived using table in Appendix 6.

A list of ECG evaluations will be provided as well.

16.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Sitting/Standing Systolic Blood Pressure (mmHg)
- Sitting/Standing Diastolic Blood Pressure (mmHg)
- Sitting/Standing Pulse Rate (bpm)

At each visit, three serial sitting BP measurements will be obtained and the average (arithmetic mean) of the 3 serial measurements will be used for the summary.

Descriptive summaries by visit and change from baseline will be provided for vital sign data.

16.5. PHYSICAL EXAMINATION

Physical examination data will be listed.

16.6. OTHER SAFETY ASSESSMENTS

The following summaries will be provided for anthropometric data:

- Height z-score
- Weight z-score
- BMI z-score

Height, weight and BMI are collected on the Weight and Height page of eCRF.

Z-score will be calculated using CDC growth charts. The detail is explained in Appendix 4.

Descriptive summaries by visit and change from baseline will be provided for anthropometric data.

17. REFERENCES

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

Outputs will be presented according to the following:

- Output File Naming Conventions:
  - File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.
  - As far as possible, output files should be in RTF format, although .DOC files are also permitted.
  - The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. T14_3_01_1.RTF).
- Paper Size, Orientation and Margins

	Landscape	Portrait
Paper Size	U.S. Letter (8.5 x 11 inch)	U.S. Letter (8.5 x 11 inch)
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® Specifications:		
PAGESIZE	46 (8-point size, Courier)	67 (8-point size, Courier)
	41 (9-point size, Courier)	60 (9-point size, Courier)
LINESIZE	134 (8-point size, Courier)	93 (8-point size, Courier)
	119 (9-point size, Courier)	82 (9-point size, Courier)

- Fonts

- The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. Single spacing should be used for all text.
- Figures should have a default font of "Courier New".
- This can be achieved by using the following options in SAS®:

- goptions
- gunit = pct
- cback = white
- colors = (black)
- hby = 2.4
- ftext = "TimesRoman"
- htext = 2.5
- device = cgmof97l
- gaccess = gsasfile;
- filename gsasfile "….cgm";
- Spacing:
  - There must be a minimum of 1 blank space between columns (preferably 2).
- Missing values:
  - A "0" should be used to indicate a zero frequency.
  - A blank will be used to indicate missing data in an end-of-text table or patient listing.
  - Figure output conventions:
  - Figures should be provided in RTF files using the SAS® Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS®.
  - The CGM file itself should contain the title or footer.
  - The image should be clear and of high quality when viewed in the Word document, and when printed.
  - In general, boxes around the figures should be used.

DATES & TIMES

Dates will be shown in ddmmmyyyy format, time of day in hh:mm format and datetime values as "ddmmmyyyy; hh:mm". In case of partial dates or time of day, missing information will be replaced by dashes.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Phase	Treatment Group	For Tables and Graphs
Double Blind Phase	Losartan	Losartan
	AZM low	AZM-L
	AZM Intermediate	AZM-M
	AZM High	AZM-H
Withdrawal Phase	Placebo	Placebo
	Losartan	Losartan
	AZM low	AZM-L
	AZM Intermediate	AZM-M
	AZM High	AZM-H
Open Label Phase	AZM Only	AZM Only
	AZM plus additional antihypertensives	AZM Plus

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening /Visit 1	Scr /V1
Washout/Placebo Run-In /Visit 2	PRI /V2
D-1/ Visit 3	D-1 /V3
D1/ Visit 4	D1 /V4
Week 2 / Visit 5	W2 / V5
Week 4 / Visit 6	W4 / V6
Week6 – 1D / Visit 7	W6-1D / V7
Week 6 / Visit 8	W6 / V8
Week 8 / Visit 9	W8 / V9
Week 12 / Visit 10	W12 / V10
Week 20 / Visit 11	W20 / V11
Week 28 / Visit 12	W28 / V12
Week 36 / Visit 13	W36 / V13
Week 44 / Visit 14	W44 / V14
Week 52 – 1D /Visit 15	W 52 –1D / V15
Week 52 /Visit 16	W52 / V16
Week 54 /Visit 17	W54 / V17

DEFINITION OF PHASES AND TREATMENT ASSIGNMENT:

Visit4/D1 - Visit 8/W6 = Double Blind Phase
Visit 8/W6 - Visit9/W8 = Withdrawal Phase

Visit9/W8 - Visit16/W52 = Open Label Phase

All the data collected for procedures (Con Meds, Vital Signs, AE assessments, Laboratory tests, Pregnancy tests) at Visit 8/ W6 will be used as visit 8/W6/last visit of DB phase in DB analysis and as WD phase baseline in WD phase analysis because all the measurements are taken before WD phase drug is given to the subjects at Visit 8/W6.

All the data collected for procedure (Con Meds, Vital Signs, Physical Examination, AE assessments, Laboratory tests, Pregnancy tests, ECG) at Visit9/ W8 will be used as visit 9/W8/last visit of WD Phase in WD phase analysis and OL baseline in OL analysis because all the measurements are taken before OL drug is given to the subjects at Visit 9/ W8.

Visit 4/Day 1 - First day of Double-Blind Dose
Visit 8/Week 6 - First day of Withdrawal Phase Dose
Visit 9/Week 8 – First day of Open Label Dose

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Site-subject ID,
- Randomized treatment group (or treatment received if it's a safety output), first by active dose [by ascending dose group] and then control/ placebo
- Phase
- Visit
- Date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

GENERAL DISPLAY

When a table/listing is split in multiple pages, the footnotes added to explain the table/listing should be displayed on each page of the table/listing and not only on the last one.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	If Informed consent year and AE start year is same and study med start year is later, impute start date to informed consent date. If study med start year and AE start year is same, impute start date to study med start date If study med start year is earlier then 2016, impute the start date to first day of the year Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR MEDICATION HISTORY / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If Informed consent date > medication end date ≥ Informed consent date -30, assign as Medication History If start date >= study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If Informed consent date > medication end date ≥ Informed consent date -30, assign as medication history If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If Informed consent date > medication end date ≥ Informed consent date -30, assign as medication history If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If Informed consent date > medication end date ≥ Informed consent date -30, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a medication history If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If Informed consent date > medication end date ≥ Informed consent date -30, assign as medication history If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If Informed consent date > medication end date ≥ Informed consent date -30, assign as medication history If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. **MARKEDLY ABNORMAL CRITERIA**

LAB CATEGORY	**LAB NAME**	**SEX**	**LOW CRITERIA**	**HIGH CRITERIA**	**DERIVED CRITERIA LOW** ***(USE FOR OUTPUTS)***	**DERIVED CRITERIA HIGH** ***(USE FOR OUTPUTS)***
Hematology	Hemoglobin	M/F	< Baseline – 3 g/dL	--	<Baseline - 30 g/L	
Hematology	Hematocrit	M/F	< 0.8 x Baseline	--	<0.8 x Baseline	
Hematology	RBC count	M/F	< 0.8 x Baseline	--	<0.8 x Baseline	

Hematology	WBC count	M/F	< 2 x 103/mm3	> 20 x 103/mm3	<2 x 10^9/L	>20 x 10^9/L
Hematology	Platelet count	M/F	< 50 x 103/mm3	> 700 x 103/mm3	<50 x 10^9/L	>700 x 10^9/L
Chemistry	ALT	M/F	--	>3x ULN		>3 x ULN
Chemistry	AST	M/F	--	>3x ULN		>3 x ULN
Chemistry	GGT	M/F	--	>3x ULN		>3 x ULN
Chemistry	Alkaline phosphatase	M/F	--	>3x ULN		>3 x ULN
Chemistry	Total bilirubin	M/F	--	>2.0x ULN		>2.0 x ULN
Chemistry	Albumin	M/F	<2.5 g/dL	--	<25 g/L	
Chemistry	Total protein	M/F	<0.8x LLN	>1.2x ULN	<0.8 x LLN	>1.2 x ULN
Chemistry	Creatinine	M/F	--	>1.5 x Baseline		>1.5 x Baseline
Chemistry	Sodium	M/F	<130 mEq/L	>150 mEq/L	<130 mmol/L	>150 mmol/L
Chemistry	Potassium	M/F	<3.0 mEq/L	>6.0 mEq/L	<3.0 mmol/L	>6.0 mmol/L
Chemistry	Blood Urea Nitrogen	M/F	--	>3x ULN		>3 x ULN
Chemistry	Calcium	M/F	<0.8x LLN	>1.2x ULN	<0.8 x LLN	>1.2 x ULN
Chemistry	Creatine kinase	M/F	--	>10x ULN		>10 x ULN
Chemistry	Uric Acid	M	--	>10.5 mg/dL		>625 umol/L
Chemistry	Uric Acid	F	--	>8.5 mg/dL		>506 umol/L
Urinalysis	Blood	M/F	--	≥1+		>=1+
Urinalysis	Glucose	M/F	--	≥1+		>=1+
Urinalysis	Ketones	M/F	--	≥2+		>=2+
Urinalysis	Casts	M/F	--	Any		Any
Urinalysis	Casts	M/F	--	Any		Any
Urinalysis	Microscopic RBCs*	M/F	--	≥5/hpf		>=5/hpf
Urinalysis	Microscopic RBCs*	M/F	--	≥5/hpf		>=5/hpf
Urinalysis	Microscopic WBC	M/F	--	≥20/hpf		>=20/hpf
Urinalysis	pH	M/F	<=4	>=8	<=4	>=8

Urinalysis	Protein	M/F	--	>=1+		>=1+
Urinalysis	Specific Gravity	M/F	<1.005	--	<1.005	

APPENDIX 4. Z-SCORE CALCULATION USING CDC GROWTH CURVE

- **Step 1**: Download the SAS program (cdc-source-code.sas[SAS -8KB]) and the reference data file (CDCref_d.sas7bdat). Do not alter these files, but move them to a folder (directory) that SAS can access.

- **Step 2**: Create a libname statement in your SAS program to point at the folder location of 'CDCref_d.sas7bdat'. An example would be:
libname refdir 'c:\sas\growth charts\cdc\data';

Note the SAS code expects this name to be ***refdir***; do not change this name.

- **Step 3: Set your existing dataset containing height, weight, sex, age and other variables into a temporary dataset, named *mydata*. Variables in your dataset should be renamed and coded as follows:**

Table 1

Variable	Description
agemos	Child's age in months; must be present. The program assumes you know the number of months to the nearest day based on the dates of birth and examination. For example, if a child was born on Oct 1, 2007 and was examined on Nov 15, 2011, the child's age would be 1506 days or 49.48 months. In everyday usage, this age would be stated as 4 years or as 49 months. However, if 49 months were used as the age of all children who were between 49.0 and <50 months in your data, the estimated z-scores would be slightly too high because, on average, these children would be taller, weigh more, and have a higher BMI than children who are exactly 49.0 months of age. This bias would be greater if only completed years of age were known, and the age of all children between 4 and <5 years was represented as 48 months. If age is known only as the completed number of months (as is data from NHANES 1988-1994 and 1999-2010), consider adding 0.5 so that the maximum error would be 15 days. If age is given as the completed number of years, multiply by 12 and consider adding 6.
sex	Coded as 1 for boys and 2 for girls.

height	Height in cm. This is either standing height (for children who are ≥ 24 months of age or recumbent length (for children < 24 months of age); both are input as height. If standing height was measured for some children less than 24 months of age, you should add 0.8 cm to these values (see page 8 of http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf[PDF-5.4MB]). If recumbent length was measured for some children who are ≥ 24 months of age, subtract 0.8 cm.
weight	Weight (kg)
bmi	BMI (Weight (kg) /Height (m)^2). If your data doesn't contain BMI, the program calculates it. If BMI is present in your data, the program will not overwrite it.
headcir	Head circumference (cm)

Z-scores and percentiles for variables that are not in ***mydata*** will be coded as missing (.) in the output dataset (named ***_cdcdata***). Sex (coded as 1 for boys and 2 for girls) and agemos must be in ***mydata***. It's unlikely that the SAS code will overwrite other variables in your dataset, but you should avoid having variable names that begin with an underscore, such as _bmi.

- **Step 4**: Copy and paste the following line into your SAS program after the line (or lines) in step #3**.** %include 'c:\sas\growth charts\cdc\data\CDC-source-code.sas'; run;

If necessary, change this statement to point at the folder containing the downloaded 'CDC-source-code.sas' file.

This tells your SAS program to run the statements in 'CDC-source-code.sas'.

- **Step 5**: Submit the %include statement. This will create a dataset, named ***_cdcdata***, which contains all of your original variables along with z-scores, percentiles, and flags for extreme values. The names and descriptions of these new variables in ***_cdcdata*** are in Table 2. Additional information on the extreme z-scores is given in a separate section that follows the "Example SAS Code".

Table 2: Z-Scores, percentiles, and extreme (biologically implausible, BIV) values in output dataset, ***_cdcdata***

Description	Variable	Cutoff for Extreme Z-Scores

	Percentile	Z-score	Modified Z-score to Identify Extreme Values	Flag for Extreme Values	Low z-score (Flag coded as -1)	High z-score (Flag coded as +1)
Weight-for-age for children between 0 and 239 (inclusive) months of age	wapct	waz	_Fwaz	_bivwt	< -5	> 8*
Height-for-age for children between 0 and 239 (inclusive) months of age.	hapct	haz	_Fhaz	_bivht	< -5	>4*
Weight-for-height for children with heights between 45 and 121 cm (this height range approximately covers ages 0 to 6 y)	whpct	whz	_Fwhz	_bivwh	< -4	>8*
BMI-for-age for children between 24 and 239 months of age	bmipct	bmiz	_Fbmiz	_bivbmi	< -4	>8*
Head circumference-for-age for children between 0 and 35 (inclusive) months of age	headcpct	headcz	_Fheadcz	_bivhc	< -5	>5

* Changed in 2016. Additional information is below

- **Step 6:** Examine the new dataset, ***_cdcdata***, with PROC MEANS or some other procedure to verify that the z-scores and other variables have been created. If a variable in Table 1 was not in your original dataset (e.g., head circumference), the output dataset will indicate that all values for the percentiles and z-scores of this variable are missing. If values for other variables are unexpectedly missing, make sure that you've renamed, and recoded variables as indicated in Table 1 and that your SAS dataset is named ***mydata***. The program should not modify your original data but will add new variables to your original dataset.

Example SAS code corresponding to steps 2 to 6. You can simply cut and paste these lines into a SAS program, but you'll need to change the libname and %include statements to point at the folders containing the downloaded files.

```
libname refdir 'c:\sas\growth charts\cdc\data';
data mydata; set whatever-your-original-dataset-is-named;
%include 'c:\sas\growth charts\cdc\data\CDC-source-code.sas';
proc means data=_cdcdata; run;
```

APPENDIX 5. MONTE CARLO MARKOV CHAIN (MCMC)

MONTE CARLO MARKOV CHAIN (MCMC)

- Step 1: PROC MI will be applied to create monotone data.

SUBJID – subject ID number
TRT – Treatment Arm – Placebo (TRT=4), AZM-L (TRT=1), AZM-M (TRT=2) and AZM-H (TRT=3))
TRT1 – AZM-L Arm
TRT2 – AZM-M Arm
TRT3 – AZM-H Arm
WGTGRP – Weight group (<50, >=50)
TANSGRP – Tanner Stage (< 3, >=3)
RACEGRP – Race Group (Black or African American, Non-Black or African American)
SCORE_0 - seDBP at time-point 0 (BASELINE, D1)
SCORE_1 - post-baseline visits 1(W2)
SCORE_2 - visit 2 (W4)
SCORE_3 – visit 3 (W6/final visit of DB phase)
SCORE_5 - visit 5 (w8/final visit of WD phase)

```
proc mi data=datain out=datain_mono nimpute=100 seed=123;
     var trt1 trt2 trt3 wgtgrp tansgrp racegrp score_0 score_1 score_2 score_3 score_5;
mcmc chain=multiple impute=monotone;
run;

proc sort data=datain_mono;
 by _Imputation_ trt;
run;
```

- Step 2: PROC MI will be applied to the monotone data to complete the imputation.

```
proc mi data=datain_mono out=datain_reg seed=465 nimpute=1;
 by _imputation_ trt;
 var trt wgtgrp tansgrp racegrp score_0 score_1 score_2 score_3 score_5;
 class trt wgtgrp tansgrp racegrp;
 monotone regression;
run;
```

- Step 3: Transform the imputed dataset so that for each subject, we will compute a change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of Withdrawal Phase in the trough seated diastolic blood pressure (seDBP)

```
data datain_reg1;
```

```
 set datain_reg;
 score_c=score_5 - score_3;
run;
```

- Step 4: PROC MIXED

```
proc mixed data=datain_reg1;
 by _imputation_;
 class trt;
 model score_c= trt wgtgrp tansgrp racegrp score_3/solution covb;
 ods output lsmestimates=est_mi;
 lsmeans trt/diff=control('4') cl;
 lsmestimate trt 'Pooled AZM vs Placebo' 1 1 1 -3/divisor=3 cl;
 lsmestimate trt 'AZM-L vs Placebo' 1 0 0 -1;
 lsmestimate trt 'AZM-M vs Placebo' 0 1 0 -1;
 lsmestimate trt 'AZM-H vs Placebo' 0 0 1 -1;
 lsmestimate trt 'AZM-L' 1 0 0 0;
 lsmestimate trt 'AZM-M' 0 1 0 0;
 lsmestimate trt 'AZM-H' 0 0 1 0;
 lsmestimate trt 'Placebo' 0 0 0 1;
 lsmestimate trt 'AZM-Pooled' 1 1 1 0/divisor=3 cl;
run;
```

- Step 5: Results from all ANCOVA analysis are then combined together for overall inference using PROC MIANALYZE

```
proc sort data=est_mi;
 by label;
run;

proc mianalyze data=est_mi;
  ods output ParameterEstimates=parms;
  modeleffects estimate;
  stderr;
  by label;
run;
```

APPENDIX 6. ECG HIGH LOW CRITERIA

New normal limits for the pediatric electrocardiogram

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Table 2 Lead-independent ECG measurements for boys (upper row) and girls (lower row): median (2nd percentile, 98th percentile)

Lead	0–1 months	1–3 months	3–6 months	6–12 months	1–3 years	3–5 years	5–8 years	8–12 years	12–16 years
Heart rate (beats . min $^{-1}$)	160 (129, 192)	152 (126, 187)	134 (**112**, **165**)	128 (106, 194)	**119** (97, **155**)	98 (73, 123)	88 (62, 113)	78 (55, **101**)	73 (**48**, **99**)
	155 (136, 216)	154 (126, 200)	139 (**122**, **191**)	134 (106, 187)	**128** (95, **178**)	101 (78, 124)	89 (68, 115)	80 (58, **110**)	76 (**54**, **107**)
P axis (°)	56 (13, 99)	52 (10, 73)	49 (− 5, 70)	49 (9, 87)	48 (− 12, 78)	43 (− 13, 69)	41 (− 54, 72)	39 (− 17, 76)	40 (− 24, 76)
	52 (24, 80)	48 (20, 77)	51 (16, 80)	50 (14, 69)	47 (1, 90)	44 (− 6, 90)	42 (− 13, 77)	42 (− 15, 82)	45 (− 18, 77)
P duration (ms)	78 (64, 85)	79 (65, 98)	81 (64, 103)	80 (66, 96)	80 (63, 113)	87 (67, 102)	92 (73, 108)	98 (78, 117)	100 (82, 118)
	79 (69, 106)	78 (62, 105)	78 (63, 106)	80 (64, 07)	83 (62, 104)	84 (66, 101)	89 (71, 107)	94 (75, 114)	98 (78, 122)
PR interval (ms)	99 (77, 120)	98 (85, 120)	106 (87, 134)	114 (82, 141)	118 (86, 151)	121 (98, 152)	129 (99, 160)	134 (105, 174)	139 (107, 178)
	101 (91, 121)	99 (78, 133)	106 (84, 127)	109 (88, 133)	113 (78, 147)	123 (99, 153)	124 (92, 156)	129 (103, 163)	135 (106, 176)
QRS axis (°)	97 (75, 140)	87 (37, 138)	66 (− 6, 107)	68 (14, 122)	64 (− 4, 118)	70 (7, 112)	70 (− 10, 112)	70 (− 21, 114)	65 (− 9, 112)
	110 (63, 155)	80 (39, 121)	70 (17, 108)	67 (1, 102)	69 (2, 121)	69 (3, 106)	74 (27, 117)	66 (5, 117)	66 (5, 101)
QRS duration (ms)	67 (50, 85)	64 (52, 77)	66 (54, **85**)	**69** (52, **86**)	**71** (54, 88)	**75** (58, 92)	**80** (63, 98)	**85** (67, 103)	**91** (**78**, 111)
	67 (54, 79)	63 (48, 77)	64 (50, **78**)	**64** (52, **80**)	**68** (54, 85)	**71** (58, 88)	**77** (59, 95)	**82** (66, 99)	**87** (**72**, 106)
QTc interval (ms)*	413 (378, 448)	419 (**396**, 458)	422 (391, 453)	411 (379, 449)	412 (383, 455)	412 (377, 448)	411 (371, 443)	411 (373, 440)	407 (362, 449)
	420 (379, 462)	424 (**381**, 454)	418 (386, 448)	414 (381, 446)	417 (381, 447)	415 (388, 442)	409 (375, 449)	410 (365, 447)	414 (370, 457)

Bold values indicate that the 95% confidence intervals of the percentile estimates for boys and girls do not overlap.

*Corrected QT interval, according to Bazett's formula: $QTc = QT \cdot \sqrt{\frac{\text{heart rate}}{60}}$.