PROTOCOL

A Randomized, Double-Blind, Efficacy and Safety Study of AR14 (AZILSARTAN MEDOXOMIL) Treatment and Withdrawal, Followed by an Open-Label Extension, in Children 6 to Less Than 18 Years of Age With Hypertension.

Evaluation of AR14 (AZILSARTAN MEDOXOMIL) in Pediatric Hypertension (Children 6 to <18 Years)

Sponsor:	**Arbor Pharmaceuticals, LLC.**		
Study Number:	AR14.001		
IND Number:	71,867	**EudraCT Number:**	2014-000674-18
Compound:	AZILSARTAN MEDOXOMIL		
Date:	12 December 2018	**Amendment Number:**	01

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Arbor sponsored European investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers and relevant guidelines will be provided to the site.

Issue	United States Contact	Latin America Contact	Europe and South Africa Contact
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted]	[redacted]	[redacted]

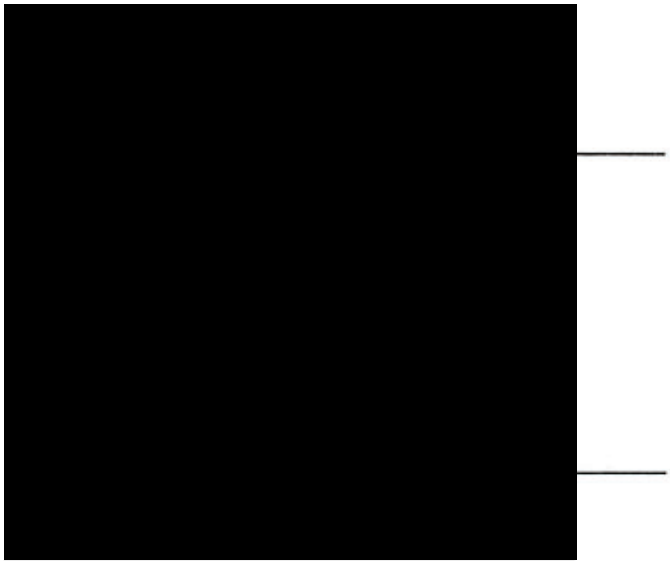
1.2 Approval

REPRESENTATIVES OF ARBOR

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURE



INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Terms outlined in FDA Form 1572

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in the study reference manual.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

2.0 STUDY SUMMARY

Name of Sponsor(s): Arbor Pharmaceuticals	**Compound:** azilsartan medoxomil	
Title of Protocol: A Randomized, Double-Blind, Efficacy and Safety Study of AZILSARTAN MEDOXOMIL Treatment and Withdrawal, Followed by an Open-Label Extension, in Children 6 to Less Than 18 Years of Age With Hypertension	**IND No.:** 71,867	**EudraCT No.:** 2014-000674-18
Study Number: AR14.001	**Phase:** 3	

Study Design:

This is a global phase 3 efficacy and safety study of AZILSARTAN MEDOXOMIL (AZM) in children aged 6 to <18 years with primary or secondary hypertension. At least 213 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 phase (Withdrawal Phase). In the DB Phase, subjects will be randomized (1:1:1:1) to 1 of 4 treatment arms low, intermediate or high dose AZM 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. This study also includes a 44-week, open-label (OL) 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.

Blood pressure 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 of the DB Phase and at the end of the OL Phase.

The duration of Screening can be a maximum of 2 weeks. After clinical laboratory tests results are available and eligibility criteria have been verified, qualified subjects will enter a 2-week single-blind placebo run-in period. For currently treated subjects, the placebo run-in will also serve as a washout period, and antihypertensive medications will be discontinued at Visit 2; however, β-blockers should be tapered off gradually during the first week of the washout. Therefore, all currently treated subjects will have a minimum of 7 drug-free days prior to their qualifying clinic seDBP assessment and subsequent randomization.

Qualified **currently treated subjects** will be eligible for randomization after the Washout/Placebo Run-in if their seDBP is ≥95th percentile for age, gender, and height or ≥90th percentile for age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present. If a subject's seDBP remains <95th percentile for age, gender, and height or <90th percentile if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present after the Washout/Placebo Run-in, the washout may be extended in 1 week increments up to 2 times, for a maximum possible washout of 4 weeks, as long as seated systolic blood pressure (seSBP) also remains below this threshold. Placebo should be continued during the extension(s). Subjects whose seDBP remains below the entry criteria after the extensions will not be eligible for randomization to the double-blind treatment phase and shall be discontinued from the study and referred back to their treating physicians to resume appropriate antihypertensive treatment.

Qualified **currently untreated subjects** will have their BP assessed on 3 occasions prior to randomization including Day -1 (or Day 1 for subjects not participating in ABPM). (The initial 2 assessments may occur at Visit 1/Day -28 and Visit 2/Day -14 or as determined by the investigator). The average seDBP at each of these 3 visits must be ≥95th percentile for age, gender, and height or ≥90th percentile for age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present to be eligible for randomization.

Eligible subjects will be randomized into 1 of 4 double-blind treatment arms using an interactive (voice/web) response system (IVRS/IWRS). The 4 treatment groups include (1) low-dose AZM (AZM-L), (2) intermediate-dose AZM (AZM-M) or (3) high-dose AZM (AZM-H) or (4) losartan.

The dose taken by each subject will be dependent on treatment assignment. Subjects assigned to AZM-M, AZM-H or

losartan will initiate treatment at a low dose that will be force-titrated at Week 2 to the final randomized dose, which will be maintained for the final 4 weeks of the DB Phase. In the Withdrawal Phase, subjects will be re-randomized using IVRS/IWRS to continue receiving their previously assigned active treatment or placebo.

Additional clinic visits will be scheduled at Weeks 2, 4, and 6 of the DB Phase. During the DB Phase blood sampling will be performed for population pharmacokinetics.

The first dose of study drug of the Withdrawal Phase will be administered at Week 6/Visit 8 after removal of the ABPM device (if applicable) and the final trough vital sign measures of the DB Phase are recorded. Study drug will also be dispensed at Week 6. Subjects will return to the clinic at Week 8/Visit 9 to begin the OL Phase. The first dose of study drug of the OL Phase will be administered at Week 8/Visit 9 after the final trough vital sign measures of the Withdrawal Phase are recorded.

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 antihypertensive medication may be added if needed to achieve and maintain a target BP of <90th percentile for age, gender, and height. For subjects with chronic kidney disease, a lower BP target may be utilized at the investigator's discretion. If add-on therapy is needed, the type of medication (eg a calcium channel blocker, such as amlodipine, a diuretic, such as hydrochlorothiazide, or a beta-blocker such as metoprolol) added will be determined per the investigator's clinical judgment. 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.

In the event that down-titration or temporary or permanent discontinuation of antihypertensive medication is indicated, dose reduction or discontinuation should begin preferably with the additional antihypertensive drug(s) first, before the dose of AZM is reduced or discontinued. During the OL Phase subjects may continue participation in the study if AZM is temporarily discontinued for less than 2 weeks. Treatment with a dose of AZM that is above the highest dose allowed for the body weight category (ie, 80 mg in a subject <50 kg) is not allowed.

The first scheduled titration visit of the OL Phase is at Week 12/Visit 10, which is 4 weeks after the initiation of OL treatment; however, an additional unscheduled visit may be requested earlier at the investigator's discretion to titrate subjects not controlled on the initial AZM 10 mg dose. After Week 12, for subjects whose BP is controlled and medications remain unchanged, visits will be scheduled at 8-week intervals (ie, Weeks 20, 28, 36, 44, and 52). However, if further medication adjustment is needed, the subject will be required to return to the site for a vital sign evaluation at an unscheduled visit within 2 to 4 weeks after each change until medications are stable. Investigators may request laboratory tests (including the renal safety laboratory subpanel: sodium, potassium, chloride, blood urea nitrogen, creatinine, cystatin C, estimated glomerular filtration rate [eGFR]) if deemed clinically necessary during unscheduled visits.

While adjustments to antihypertensive medications can occur at scheduled and unscheduled visits, it is recommended that subjects are treated for approximately 4 weeks at the same dose level before any dose change and/or additional medication is introduced unless there are reasonable medical and/or safety concerns. Investigators will be required to discuss such cases with the medical monitor and provide the rationale for changes outside of the algorithm provided.

Each subject will also be provided with a home BP monitoring device and a BP diary at Week 8/Visit 9 so that daily BP measures can be recorded and reviewed by the investigator during the OL Phase.

Each subject will be followed at a clinic visit approximately 2 weeks after study completion (ie Week 54/Visit 17) or discontinuation for a health status update and adverse event (AE) assessment.

Primary Objectives:

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

Secondary Objectives:

To evaluate the antihypertensive effect of AZM compared with losartan during randomized, 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, OL extension (OL Phase).	
Subject Population: Children aged 6 to <18 years with primary or secondary hypertension.	
Number of Subjects: Per treatment group: approximately 53 Estimated total: at least 213	**Number of Sites:** Approximately 120 sites
Dose Levels: Placebo AZM 10 mg AZM 20 mg AZM 40 mg AZM 80 mg Losartan 25 mg Losartan 50 mg Losartan 100 mg All treatments will be given once daily	**Route of Administration:** Oral
Duration of Treatment: 52 weeks	**Period of Evaluation:** Approximately 58 weeks

Main Criteria for Inclusion:

- The subject has hypertension (primary or secondary) defined as clinic seDBP ≥95th percentile (by age, gender, and height) or ≥90th percentile (by age, gender, height) if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present.
  a) If currently treated: The subject has a documented historical diagnosis of hypertension AND a post-washout clinic seDBP meeting the above criteria on Day -1 (or Day 1 for subjects not participating in ABPM).
  b) If currently untreated: The subject has elevated seDBP meeting the above criteria on 3 separate occasions before Randomization, including on Day -1 (or Day 1 for subjects not participating in ABPM).
- The subject is male or female and aged 6 to <18 years at Baseline and weighs at least 25 kg.
- The subject agrees to continue their previously implemented nonpharmacological life style modifications if begun prior to Screening. Note: For subjects participating in a weight loss program, the weight maintenance phase must have begun at least 30 days prior to Screening/Visit 1.
- Subjects may be renal transplant patients if time post-transplant has been greater than 6 months prior to Screening, with stable graft function (and eGFR ≥30 mL/min/1.73 m^2) for at least 6 months, stable use of immunosuppressive therapy for at least 30 days prior to Screening, and documented evidence that there is no transplant renal artery stenosis.
- The subject is untreated, or willing, and in the opinion of their treating physician, can safely be withdrawn from previous antihypertensive medications for a maximum of 4 weeks (if a washout extension is required) prior to randomization.

Main Criteria for Exclusion:

- The subject has a clinic seSBP greater than 15 mm Hg and/or seDBP greater than 10 mm Hg above the 99th percentile for age, gender, and height as confirmed by the average (arithmetic mean) of 3 serial clinic seated BP measurements at Screening/Visit 1.
- The subject has a diagnosis of malignant or accelerated hypertension.

- The subject is currently treated with more than 2 antihypertensive agents.
- The subject or parent/legal guardian is not willing for the subject's previous antihypertensive medications to be stopped.
- The subject has participated in the intensive, active weight-loss phase of a weight-loss program within 30 days prior to Screening/Visit 1.
- The subject has any of the following: severe renal impairment (eGFR <30 mL/min/1.73 m^2 by the Schwartz formula); is currently undergoing dialysis treatment; renovascular disease affecting both kidneys or a solitary kidney; severe nephrotic syndrome not in remission; or serum albumin <2.5 g/dL.
- The subject has a history or clinical manifestations of severe cardiovascular, hepato-biliary, gastrointestinal, endocrine-metabolic (eg, hyperthyroidism, Cushing's syndrome), hematologic, immunologic, genito-urinary, or psychiatric disease, cancer, and/or any conditions that would interfere with the health status of the subject through study participation, or would jeopardize study integrity in the opinion of the investigator.
- The subject is suffering from uncorrected coarctation of the aorta, or hemodynamically significant left ventricular outflow tract obstruction due to eg, aortic valvular disease, or is likely to undergo a procedure known to affect blood pressure (eg, repair of arterial anomalies) during the course of the study.
- The subject is poorly controlled diabetic defined as having a glycosylated hemoglobin value >8.5% at Screening/Visit 1.
- The subject has hyperkalemia as defined by the central laboratory's normal reference range or any pertinent electrolyte disorders at Screening/Visit 1.

Main Criteria for Evaluation and Analyses:

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 seSBP and mean arterial pressure (MAP).
- Change from Baseline in trough clinic seDBP, seSBP, and MAP Week 6/Final Visit 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:

AEs, physical examination, laboratory tests, 12-lead ECG findings, vital signs, and anthropometric (height, weight, and body mass index z-scores) measurements.

Statistical Considerations:

Unless otherwise specified all statistical tests will be 2-sided, and p-values will be rounded to 3 significant digits prior to accessing for statistical significance at the 0.05 level

The primary analysis for the primary endpoint, change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in clinic seDBP, will be an analysis of covariance (ANCOVA) model with treatment (AZM low, med, high and placebo), age (Tanner stage <3, ≥3) and weight (<50 kg, ≥50 kg) as fixed effects, and Week 6/Final Visit of the DB Phase seDBP as covariate. For the primary analysis the placebo group will exclude subjects that were treated with losartan during the DB Phase. The primary comparison, mean (ie, pooled) AZM effect versus placebo, will be made using 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 following sequential testing procedure will be employed in the analysis of the primary endpoint using the above described ANCOVA model and contrast 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 .

The primary analysis will use multiple imputations for missing data, supported by sensitivity analysis using observed data. Multiple imputations 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 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.

Secondary endpoints, change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase for clinic seSBP and MAP, will be analyzed using an ANCOVA model and contrast statements similar to what was used for the primary endpoint analysis, except the relevant baseline covariate term will be used in the analysis. These analyses will be performed without using the sequential testing procedure.

The analysis for the secondary endpoint, change from baseline to Week 6/Final Visit of the DB Phase, will be mixed models for repeated measure (MMRM) with treatment (AZM low, med, high dose and losartan), age (Tanner stage <3, ≥3) and weight (<50 kg, ≥50 kg) as fixed effects, and baseline seDBP as covariate. An unstructured covariance matrix will be used to model the within-subject variation-covariance errors. The primary comparison, mean (ie, 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. Additional sensitivity analyses will be performed including ANCOVA using observed case data and last observation carried forward (LOCF). Similar analyses will be performed for the secondary endpoints change from baseline in seSBP and MAP at Week 6/Final Visit of the DB Phase and each other visit of the DB Phase. Additional analyses, e.g, similar MMRM models with different factors, for the above endpoints may be performed where appropriate.

A logistic model with treatment, age and weight as fixed effects and baseline clinic BP as covariate will be used to analyze the percent of subjects achieving target BP at Week 8/Final Visit of the Withdrawal Phase. The odds ratio and associated 95% confidence interval (CI) will be estimated. Similar logistic regression may be performed on percent of subjects achieving target BP at Week 6/Final Visit of the DB Phase. The target blood pressures (percentiles by age, gender and height) evaluated as secondary or additional endpoints include the following (at Week 6/Final Visit of the DB Phase and at Week 8/Final Visit of the Withdrawal Phase):

- seDBP <90th percentile.
- seSBP <90th percentile.
- Both seDBP<90th percentile and seSBP< 90th percentile.

Safety variables will be summarized, using tabulations (counts and percentages) and descriptive statistics, separately for each study phase (ie, DB, Withdrawal, and OL Phases).

Sample Size Justification:

Prior to study start:

Assuming an SD of 10.5 mm Hg and an overall 10% dropout rate (ie, 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:

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 (ie, 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).

3.0 STUDY REFERENCE INFORMATION

3.1 Coordinating Investigator

Arbor will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area, and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.2 List of Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
AE	adverse event
AI	angiotensin I
AII	angiotensin II
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AT1	angiotensin II type 1 receptor
AUC	area under the plasma concentration-time curve
AZM	azilsartan medoxomil
AZM-H	high dose azilsartan medoxomil
AZM-L	low dose azilsartan medoxomil
AZM-M	intermediate dose azilsartan medoxomil
BB	beta blocker
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CCB	calcium channel blocker
CI	confidence interval
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CNS	central nervous system
DB	double-blind
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESCAPE	Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients
ESH	European Society of Hypertension
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
FAS	full analysis set

GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin
HBPM	home blood pressure monitoring
hCG	human chorionic gonadotropin
HCTZ	hydrochlorothiazide
HDPE	high-density polyethylene
IB	Investigator's Brochure
IC50	50% inhibitory concentration
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	Liver Function Test
LOCF	last observation carried forward
MAP	mean arterial pressure
MED ID	medication identification
MMRM	mixed models for repeated measures
NHLBI	National Heart, Lung, and Blood Institute
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
O/E	overencapsulated
OL	open-label
PPS	per-protocol set
PREA	Pediatric Research Equity Act
PTE	pretreatment event
RAAS	renin-angiotensin-aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
seDBP	seated diastolic blood pressure
seSBP	seated systolic blood pressure
TAK-491	azilsartan medoxomil
T1/2	terminal elimination half- life
TEAE	treatment- emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States

4.0 INTRODUCTION

4.1 Background

Arbor Pharmaceuticals, LLC. is developing the angiotensin II receptor blocker (ARB) azilsartan medoxomil (AZM, TAK-491, AR14) for the treatment of hypertension in pediatric patients. AZM has been evaluated in adult patients with primary (essential) hypertension by Takeda Pharmaceutical Company. AZM is approved for treatment of hypertensive adults in Europe, the United States (US), and other countries, including Mexico and Canada [1-4]. In the US, the overall prevalence of childhood hypertension is 2% to 5%, making it one of the most common chronic diseases of childhood [5]. Similarly, the overall prevalence of pediatric hypertension in European countries generally ranges between 2% to 4% [6-9]. The causes of pediatric hypertension are diverse and age dependent: in infants and children, hypertension is usually secondary to an underlying disorder, most commonly renal parenchymal or renovascular disease [10-13]. In older children and adolescents, primary hypertension is more prevalent and often associated with overweight or obesity [14-17]. The present study is being conducted to better understand the safety and efficacy of AZM as a treatment option for children and adolescents who are 6 to <18 years of age with primary or secondary hypertension.

4.1.1 Nonclinical

Azilsartan medoxomil is a prodrug of the active moiety, azilsartan (TAK-536). As a prodrug, azilsartan medoxomil is essentially devoid of pharmacological activity; therefore, azilsartan typically was used to conduct in vitro studies, and azilsartan medoxomil typically was used in the in vivo studies. In vitro, azilsartan demonstrated potent and selective affinity for angiotensin II type 1 (AT1) receptors, with a 50% inhibitory concentration (IC50) value of 0.62 nmol/L against [^{125}I]-Sar1-I1e8-AII binding to human AT1 receptors. Two major metabolites of azilsartan, M-I and M-II, were virtually inactive, with IC50 values of 2300 and 1100 nmol/L, respectively. The toxicity observed after administration of azilsartan and azilsartan medoxomil was similar to that reported for other AT1 receptor blockers; the majority of changes were attributed to the exaggerated pharmacologic activity of the compounds. Nonclinical toxicity studies with azilsartan medoxomil were performed using young adult animals (approximately 6 weeks old in rat studies and approximately 9 months old in dog studies). The kidneys in these animals were considered to be matured. In humans, the kidneys were considered to be matured at 2 years of age. Therefore, the safety of azilsartan medoxomil in the patient population in this study (6 to <18 years of ages) is considered to be adequately characterized by nonclinical toxicity studies using young adult animals. Further descriptions of the nonclinical findings are provided in Section 4.0 of the Investigator's Brochure (IB) [18].

4.1.2 Pharmacokinetics

Azilsartan medoxomil is rapidly and completely hydrolyzed to azilsartan in healthy subjects before reaching the systemic circulation, with no detectable salt free AZM in the plasma (Section

5.1.2 of the IB) [18]. Azilsartan undergoes metabolism to M-I and azilsartan M-II, with the most extensive metabolism to M-II via CYP2C9.

In adult studies, the pharmacokinetics of azilsartan (derived from AZM) did not differ by age (elderly vs younger adults), gender, or race; the effect of food on the pharmacokinetic profile was negligible, and there were no clinically meaningful drug-drug interactions associated with AZM. Multiple dose administration of AZM in subjects with mild and moderate hepatic impairment resulted in small (28%) and moderate (64%) increases of azilsartan total exposure (area under the plasma concentration-time curve [AUC]), respectively, but was well tolerated. Total exposure (AUC) to azilsartan, after a single dose of AZM, tended to be higher in subjects with renal impairment compared with healthy subjects, with increases of 30%, 25%, 95%, and 4% in subjects with mild, moderate, and severe renal impairment, and end-stage renal disease (ESRD), respectively [19]. These exposures remained 2-5-fold lower than what had been observed to be well tolerated in a separate high-dose (160 to 320 mg) pharmacokinetic study in healthy subjects [20]. In addition, the mean terminal-elimination half-life (T1/2) of azilsartan was not substantially different in subjects with renal impairment than in healthy subjects; therefore, daily dosing of AZM is not expected to result in accumulation of azilsartan. Exposure to and T1/2 for the metabolite M-II were both increased in patients with renal impairment compared with healthy subjects; however, as described in Section 5.1.3.3 of the IB, M-II is essentially inactive with an affinity for AT1 receptors that is 850-fold less than azilsartan and this metabolite was not associated with any significant findings in extensive toxicological evaluations [20].

Pharmacokinetic modeling and simulation of data from study TAK-491_109 [21] in pediatric subjects (6 to <17 years) indicate that the 20, 40, and 80 mg doses of AZM, each of which was demonstrated to be safe and effective in phase 3 trials of hypertensive adult patients, provide similar levels of exposure in children who weighed 50 to 100 kg as has been observed in adults. The 20 mg and 80 mg doses as well as a 10 mg dose will be evaluated in the higher weight group of this study (ie, ≥50 kg). A dose range that includes the 10, 20, and 40 mg strengths of AZM will be administered to lower weight subjects (ie, 25 to <50 kg) to maintain similar exposures in these children as was observed at the 20 to 80 mg doses in adults.

Further descriptions of the pharmacokinetic data are provided in Section 5.1 of the IB [18].

4.1.3 Pharmacodynamics

Administration of single and multiple doses of AZM or azilsartan increased plasma renin activity and angiotensin I (AI) and angiotensin II (AII) concentrations, and reduced plasma aldosterone concentrations. A cumulative effect was noted with multiple dosing of AZM; plasma renin activity and AI concentrations were at higher values. These findings are consistent with the mechanism of action of AZM (ie, AT1 receptor antagonism).

4.1.4 Efficacy

A comprehensive, phase 3, clinical development program for AZM has been conducted in which adult subjects with essential hypertension received AZM 20, 40, or 80 mg administered once daily.

The phase 3 program included 9 studies: 5 randomized, controlled, monotherapy studies of 6 weeks or 6 months duration; 2 additional randomized, controlled, 6-week studies in which AZM was coadministered with the thiazide-like diuretic chlorthalidone or the calcium channel blocker (CCB) amlodipine; and 2 open-label (OL) studies (01-06-TL-491-016 and 01-05-TL-491-006) of up to 32 and 56 weeks' duration, respectively.

The primary objectives of the AZM program were to compare the efficacy, safety, and tolerability of AZM monotherapy with placebo and also with 2 widely used and effective ARBs, olmesartan medoxomil and valsartan; a study comparing AZM with the angiotensin-converting enzyme (ACE) inhibitor ramipril was also conducted. Ambulatory blood pressure monitoring (ABPM) was performed in each of the randomized, controlled studies, and 24-hour mean systolic blood pressure (SBP) was the primary endpoint in all but 1 study.

4.1.4.1 Short-Term Placebo and/or Active-Controlled Monotherapy Studies

Statistically significant reductions in SBP and diastolic blood pressure (DBP) were observed with AZM compared with placebo and comparators (olmesartan medoxomil 40 mg and valsartan 320 mg). During treatment with AZM, most of the blood pressure (BP) reduction was observed at Week 2 and reached plateau by Week 4. Changes in clinic and ambulatory BP were consistent. There was a clinically meaningful yet diminished treatment response in Black subjects relative to White subjects or subjects of other race.

4.1.4.2 Long-Term Active-Controlled Studies

In two 24-week, controlled studies, AZM led to statistically significantly greater reductions in clinic and ambulatory BP relative to active comparators (valsartan 320 mg and ramipril 10 mg). During treatment with AZM, most of the BP reduction was observed at Week 2 and reached plateau by Week 4; a similar magnitude of BP reduction was maintained throughout the 24-week treatment period.

4.1.4.3 Efficacy During Coadministration

In controlled studies, coadministration of AZM 40 and 80 mg with chlorthalidone 25 mg or amlodipine 5 mg resulted in statistically significantly greater BP reductions compared with chlorthalidone or amlodipine monotherapy. In OL studies, additional BP reductions were observed when chlorthalidone or hydrochlorothiazide (HCTZ) was given as add-on therapy to subjects receiving AZM, but who needed additional BP reduction to reach their target.

4.1.5 Safety

In phase 3 studies, 4814 unique adult subjects aged 18 or older with essential hypertension received AZM 20, 40, or 80 mg administered once daily. The most frequently occurring treatment-emergent adverse events (TEAEs) observed with AZM were headache, dizziness, nasopharyngitis, urinary tract infection, dyslipidemia, fatigue, blood creatine kinase increased, edema peripheral, back pain, and diarrhea. The overall rates of permanent discontinuation were generally low and similar between AZM total and placebo (9.4% and 9.0%, respectively) in the

placebo-controlled monotherapy studies and between AZM total and active comparator (17.4% and 19.4%, respectively) in the long-term, active-controlled studies. No imbalances were observed between AZM and placebo or active comparator groups with respect to serious adverse events (SAEs).

With regard to clinical laboratory evaluations, increases in serum creatinine were observed with AZM treatment; the profile was consistent with the pharmacodynamic effect of AII blockade. These creatinine increases were observed in subjects with greater reductions in BP, and were generally transient or nonprogressive during treatment and reversed following study drug discontinuation. Most subjects with serum creatinine elevations were receiving coadministration with diuretics (chlorthalidone and to a lesser extent HCTZ).

AZM had no clinically meaningful effects on hematology, urinalysis, or chemistry parameters. A single dose of AZM 320 mg did not prolong QTc intervals and was well tolerated in healthy subjects.

Additional summaries of the efficacy and safety profile of AZM are provided in Sections 5.2 and 5.3 of the IB [18].

4.2 Rationale for the Proposed Study

To better understand the safety and efficacy of AZM as a treatment option for pediatric patients with primary or secondary hypertension, and in accordance with legislative and regulatory requirements both in the US and European Union (EU), Arbor has designed a pediatric development program for AZM. The main elements of the pediatric program include: (1) a pharmacokinetic study in children and adolescents and gender-matched healthy adults, (2) a phase 3 efficacy and safety study in children and adolescents (6 to <18 years), and (3) a phase 3 efficacy and safety study in young children (≥12 months and <25 kg). The scope and objectives of these studies have been presented to the Food and Drug Administration (FDA) as part of the Pediatric Research Equity Act (PREA) commitments and the Best Pharmaceuticals for Children Act (BPCA), in addition to the European Medicines Agency (EMA) as part of the Pediatric Investigation Plan (PIP) commitments.

The pharmacokinetic study, TAK-491_109 [21], was the first of the 3 pediatric studies to be initiated and results are available for the cohorts of subjects 6 to <17 years of age; as described in Section 6.2, data from these subjects provide support to proceed with the present efficacy and safety study (AR14.0001) in the 6 to 17 year age group. The present study is designed to evaluate 4 doses of AZM in the low, intermediate, and high dose treatment arms during 6 weeks of double-blind, randomized treatment (Double-Blind [DB] Phase), and to compare AZM to placebo and an active comparator (losartan) after a 2-week, double-blind, randomized withdrawal (Withdrawal Phase); the long-term safety and efficacy of AZM will also be evaluated during a 44-week, OL extension (OL Phase).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Secondary Objectives

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, OL extension (OL Phase).

5.1.3 Additional Objectives

To assess the population pharmacokinetics of azilsartan derived from AZM.

5.2 Endpoints

5.2.1 Primary Endpoint

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.

5.2.2 Secondary Endpoints

- Change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in trough clinic seated systolic blood pressure (seSBP) and mean arterial pressure (MAP) between AZM and placebo.
- Change from Baseline in trough clinic seDBP, seSBP, and MAP at Week 6/Final Visit 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.

5.2.3 Safety Endpoints

- Adverse events (AEs), physical examination, laboratory tests, 12-lead electrocardiogram (ECG) findings, vital signs, and anthropometric (height, weight, and body mass index [BMI] z-scores) measurements.

5.2.4 Additional Endpoints

- 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, 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.
- Estimation of the exposure using population pharmacokinetics of azilsartan.

5.2.5 Exploratory Endpoints

- 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.

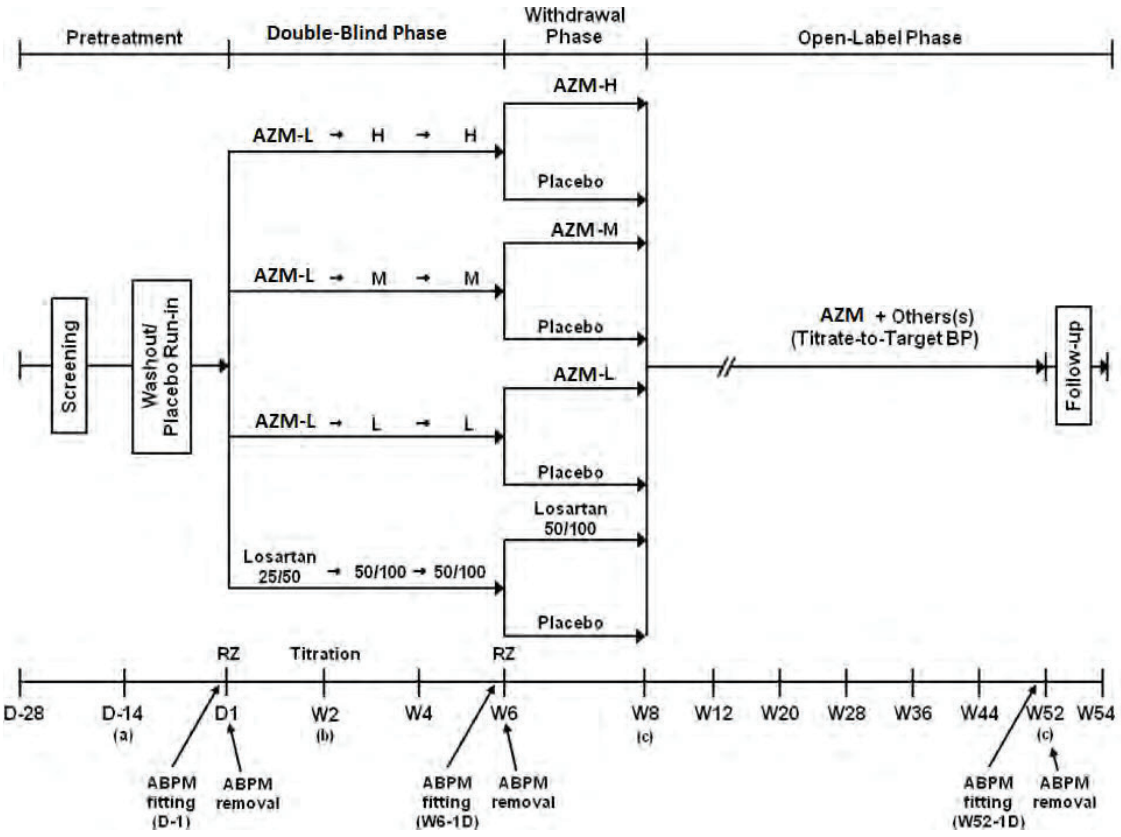
6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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. At least 213 subjects will participate in a 6-week, double-blind, 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) with AZM (high, intermediate, or low) using 4 doses (10, 20, 40, and 80 mg) or losartan. 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, OL extension (OL Phase) in which all subjects will receive AZM and other antihypertensive medications (if needed) according to a titrate-to-target 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 ABPM procedure at Baseline, at the end the DB Phase and at the end of the OL Phase.

A schematic of the study design is included as Figure 6.a. A schedule of study procedures is listed in Section 9.b.

Figure 6.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 seDBP remains below inclusion criterion #4 (Section 7.1) 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 double-blind or OL treatment, respectively.

6.1.1 Subjects

Children, both male and female, between 6 to <18 years of age at baseline with a historical or new diagnosis of primary or secondary hypertension who are a minimum weight of 25 kg will be evaluated for eligibility during Screening/Visit 1. Hypertension is defined as clinic seDBP ≥95th percentile for age, gender, and height or ≥90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present according to percentiles published in the US National Heart Lung and Blood Institute (NHLBI) Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents

[5]. As described in Section 9.1.5, BP will be measured 3 times at each visit, and the average of these serial measurements will serve as the BP value of the actual visit and be used for determination of subject eligibility.

Subjects can either be untreated or currently receiving no more than 2 antihypertensive drugs, are willing to discontinue their current therapy, and in the opinion of their treating physician, could safely discontinue current therapy. Prior to this amendment, the approximate expected percentage of subjects with secondary hypertension is between 40%-60% and no more than ≈25% of subjects will be post-renal transplant patients and no more than ≈60% of subjects will weigh greater than or equal to 50 kg at Baseline. Due to recruitment difficulties, 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.

6.1.2 Screening and Washout/Placebo Run-in Phase

The duration of Screening can be a maximum of 2 weeks. After clinical laboratory tests results are available and eligibility criteria have been verified (except inclusion criterion #4 and exclusion criterion #6 [Section 7.0]) qualified subjects will enter a 2-week, single-blind, placebo run-in period, with the first dose to be dispensed in the clinic. For currently treated subjects, the placebo run-in will also serve as a washout period, and antihypertensive medications will be discontinued at Visit 2; however, β-blockers (BBs) should be tapered off gradually during the first week of the washout. Therefore, all currently treated subjects will have a minimum of 7 drug-free days prior to their qualifying clinic seDBP assessment and subsequent randomization.

Qualified **currently treated subjects** will be eligible for randomization after the Washout/Placebo Run-in if their seDBP is ≥95th percentile for age, gender, and height or ≥90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present (ie, inclusion criterion #4 is satisfied) according to percentiles published in the US NHLBI Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [5]. If a subject's seDBP remains <95th percentile for age, gender, and height or <90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present after the Washout/Placebo Run-in (ie, does not satisfy inclusion criterion #4), the washout may be extended in 1 week increments up to 2 times, for a maximum possible washout of 4 weeks, as long as seSBP also remains below this threshold. Placebo should be continued during the extension(s). Subjects whose seDBP remains below the entry criteria after the extensions will not be eligible for randomization to the double-blind treatment phase and shall be discontinued from the study as a run-in failure and referred back to their treating physicians to resume appropriate antihypertensive treatment.

Qualified **currently untreated subjects** will have their BP assessed on 3 occasions prior to randomization including Day -1 (or Day 1 for subjects not participating in ABPM). (The initial 2 assessments may occur at Visit 1/Day -28 and Visit 2/Day -14 or as determined by the

investigator). The average seDBP at each of these 3 visits must be ≥95th percentile for age, gender, and height or ≥90th percentile for age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present according to percentiles published in the US NHLBI Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [5] to be eligible for randomization.

Treatment compliance will be evaluated and poorly compliant subjects (ie, >130% or <70% per exclusion criterion #6) will also be excluded before randomization.

6.1.3 Treatments and Dosing

Eligible subjects in the DB phase will be randomized into 1 of 4 double-blind treatment arms using an interactive (voice/web) response system (IVRS/IWRS). The 4 treatment groups include (1) high-dose AZM (AZM-H), (2) intermediate-dose AZM (AZM-M), or (3) low-dose AZM (AZM-L) or (4) losartan.

The dose taken by each subject will be dependent on treatment assignment. All subjects randomized to AZM will initiate treatment at 10 mg. Subjects assigned to AZM-M 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). The low dose and final dose of losartan given is based on the subject's weight strata (25 to < 50 kg; ≥ 50 kg). Please see Section 8.1.3 for more information on study medication.

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.

6.1.4 Double-Blind, Randomized Treatment Phases

6.1.4.1 Double-Blind Phase

Qualified subjects who meet the BP entry requirements (ie, seDBP ≥95th percentile for age, gender, and height or ≥90th percentile for age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present), including at Day -1/Visit 3 (or Day 1 for subjects not participating in ABPM) will be eligible for randomization. Currently treated subjects who have washed out of their antihypertensive medications but have a BP that remains

below the entry criteria at Day -1 (or Day 1 for subjects not participating in ABPM) may extend the Washout/Run-in Period as described in Section 6.1.2 as long as SBP also remains below the same threshold.

After a qualifying clinic seDBP has been confirmed and anthropomorphic measurements have been recorded, subjects who agree to participate in the ABPM procedure will be fitted with an ABPM device that will be worn for at least 24 hours. After the ABPM device is removed on Day 1/Visit 4, pretreatment vital signs and a full panel of clinical laboratory tests will be completed. Subjects who do not participate in the ABPM procedure will not visit the clinic on Day -1; for these subjects, the qualifying seDBP will be confirmed on Day 1 before randomization.

After the baseline procedures are conducted on Day1/Visit 4, all qualifying subjects will receive their first dose of randomized, double-blind study medication at the investigative site, and study medication will be dispensed. Study medication will be administered orally with water, at an agreed upon (by the site and subject) consistent time of day, with or without food, and will be administered in the clinic on days when a visit is scheduled.

Additional clinic visits will be scheduled at Weeks 2, 4, and 6 of the DB Phase. A renal subpanel (sodium, potassium, chloride, blood urea nitrogen [BUN], creatinine, cystatin C, estimated glomerular filtration rate [eGFR]) will be collected at Week 4/Visit 6, which corresponds to 2 weeks after study drug is force-titrated. The renal subpanel may be completed at an earlier unscheduled visit (ie, 5 to 7 days after Week 2/Visit 5) at the investigator's discretion.

An ABPM fitting visit will be scheduled the day before Week 6 (ie, Week 6 -1 Day) for subjects who have a baseline ABPM that meets quality criteria at Day1/Visit 4. Each subject will have the ABPM device removed the following day at Week 6/Visit 8, at least 24 hours after the fitting. During the DB Phase, blood sampling will be performed for population pharmacokinetics. Please see Table 9.b for a full list of the procedures to be completed during the DB Phase.

6.1.4.2 Withdrawal Phase

The first dose of study drug of the Withdrawal Phase will be administered at Week 6/Visit 8 after removal of the ABPM device (if applicable) and the final trough vital sign measures of the DB Phase are recorded. Study drug will also be dispensed at Week 6. Subjects will return to the clinic at Week 8/Visit 9 for a vital sign assessment, a full panel of clinical laboratory tests, a physical examination, ECG, and to begin the OL Phase.

Please see Table 9.b for a full list of the procedures to be completed during the Withdrawal Phase.

6.1.5 Open-Label Phase

Subjects will receive their first dose of OL AZM in the clinic and study drug will be dispensed at Week 8/Visit 9 after the final trough vital sign measures of the Withdrawal Phase are recorded. Each subject will also be provided with a home blood pressure monitoring (HBPM) device and a BP diary so that daily BP measures can be recorded and reviewed by the investigator during the OL Phase (see Section 9.1.16).

Instructions for drug administration during the OL Phase will be the same as during the double-blind (DB) phases; ie, study medication will be administered orally with water, at an agreed upon (by the site and subject) consistent time of day, with or without food, and will be administered in the clinic on days when a visit is scheduled.

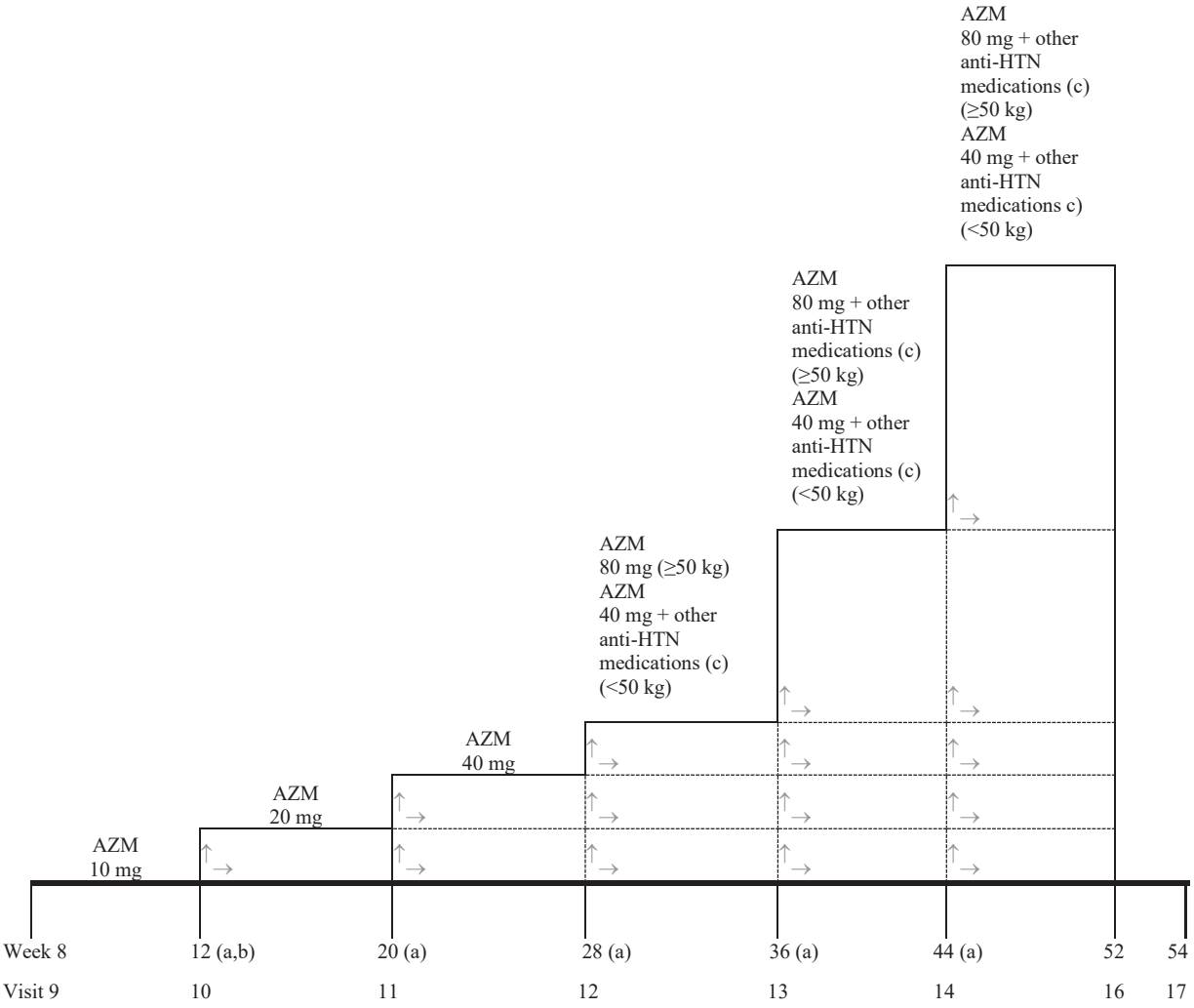
Throughout the OL Phase, subjects will be treated to achieve and maintain a target BP of <90th percentile for age, gender, and height. For subjects with CKD, a lower BP target may be utilized at the investigator's discretion. Evidence suggesting lower BP targets are appropriate and improve renal outcomes in this patient population is summarized in Section 6.2.6.

All subjects will start the OL Phase receiving 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 antihypertensive medications can be added if needed to achieve target BP. If add-on therapy is needed, the type of medication added (eg a calcium channel blocker, such as amlodipine, a diuretic, such as hydrochlorothiazide, or a beta-blocker such as metoprolol) will be determined per the investigator's clinical judgment. The recommended treatment algorithm for the OL Phase is provided in Figure 6.b.

In the event that down-titration or temporary or permanent discontinuation of antihypertensive medication is indicated, dose reduction or discontinuation should begin with the additional antihypertensive drug(s) first, before the dose of AZM is reduced or discontinued. During the OL Phase subjects may continue participation in the study if AZM is temporarily discontinued for less than 2 weeks. Treatment with a dose of AZM that is above the highest dose allowed for the body weight category (ie, to 80 mg in a subject <50 kg) is not allowed.

Because body weight is likely to change during the study, dose adjustments may occur in 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.

Figure 6.b Titration Algorithm for the Open-Label Extension Phase



anti-HTN=antihypertensive
Note: Maximum dose of AZM is dependent upon weight. Subjects ≥25 to <50 kg can be titrated to 20 or 40 mg. Subjects ≥50 kg can be titrated to 20, 40 or 80 mg.
(a) Adjustments to medications can occur at unscheduled visits as well as at the scheduled visits shown. However, it is recommended that subjects are treated for approximately 4 weeks at the same dose level before any dose change and/or additional medication is introduced unless there are reasonable medical and/or safety concerns. Investigators will be required to discuss such cases with the medical monitor and provide the rationale for changes outside of the algorithm.
(b) For subjects whose BP is controlled and medications remain unchanged, subsequent visits will be scheduled at 8-week intervals. If further medication adjustment is needed, the subject will be required to return to the clinic within 2 to 4 weeks after each change until medications are stable.
(c) The type of antihypertensive medication (eg a calcium channel blocker, such as amlodipine, a diuretic, such as hydrochlorothiazide, or a beta-blocker such as metoprolol) added will be determined per the investigator's clinical judgment.

The first scheduled titration visit of the OL Phase is at Week 12/Visit 10, which is 4 weeks after initiation of OL treatment; however, an additional unscheduled visit may be requested earlier at the investigator's discretion to titrate subjects not controlled on the initial AZM 10 mg dose. After

Week 12, for subjects whose BP is controlled and medications remain unchanged, visits will be scheduled at 8-week intervals (ie, Weeks 20, 28, 36, 44, and 52). However, if further medication adjustment is needed, the subject will be required to return to the site for a vital sign evaluation at an unscheduled visit within 2 to 4 weeks after each change until medications are stable. Investigators may request laboratory tests (including the renal safety laboratory subpanel: sodium, potassium, chloride, BUN, creatinine, cystatin C, eGFR) if deemed clinically necessary during unscheduled visits. While adjustments to antihypertensive medications can occur at scheduled and unscheduled visits, it is recommended that subjects are treated for approximately 4 weeks at the same dose level before any dose change and/or additional medication is introduced unless there are reasonable medical and/or safety concerns. Investigators will be required to discuss such cases with the medical monitor and provide the rationale for changes outside of the algorithm provided in Figure 6.b.

An optional third ABPM may be completed at the day before Week 52/Visit 16 (ie, Week 52 -1 Day) for subjects that had a baseline ABPM that met quality criteria, and subjects who participate in this procedure will return to the clinic at Week 52/Visit 17 approximately 24 hours after it is fitted for removal of the device and visit procedures.

Upon initiation of the OL Phase (Week 8/Visit 9), subjects and their parents/legal guardians, will be provided with an automated HBPM device and instructed to measure the subject's BP at home at least once daily for the remainder of the study, preferably immediately before dosing. A BP diary will be provided so that the daily measurements can be recorded and reviewed by the investigator. At each visit, the investigator will provide the subject (and parent/legal guardian) with a BP threshold and instructions to contact the investigative site if BP is at or above this threshold. The recommended threshold that would prompt contact with the site is an SBP and/or DBP by HBPM that is 15 or 10 mm Hg, respectively, above the 99th percentile for age, gender, and height [5]. See Section 7.5 for a description of criteria for withdrawal due to elevated blood pressure.

Each subject will be followed at a clinic visit approximately 2 weeks after study completion (ie, Week 54/Visit 17) or discontinuation for a health status update and AE assessment.

Please see Section 9.3 for a complete list of the procedures to be completed during the OL Phase.

6.1.6 Randomization Procedures

The investigator or investigator's designee will access the 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). Enrollment caps will also be applied to randomization to ensure a percentage of subjects with secondary hypertension of approximately 20% and to ensure that no more than ≈25% of subjects are post-renal transplant patients and no more than ≈80% 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 (ie, AZM-L, AZM-M, or AZM-H or losartan).

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Patient Selection

In the US, the overall prevalence of childhood hypertension is 2% to 5%, making it one of the most common chronic diseases of childhood [5]. Similarly, the overall prevalence of pediatric hypertension in European countries generally ranges between 2% to 4% [6-9]. The causes of pediatric hypertension are diverse and age dependent: in infants and children, hypertension is usually secondary to an underlying disorder, most commonly renal parenchymal or renovascular disease [10-13]. In older children and adolescents, primary hypertension is more prevalent and often associated with overweight or obesity [14-17].

The targeted percentage of subjects with secondary hypertension randomized in this study will be at least 20%. Accordingly, many subjects are anticipated to have hypertension associated with underlying CKD. However, subjects with severe renal impairment (eGFR <30 mL/min/ 1.73 m^2) or renal artery stenosis (unilateral or bilateral) will be excluded, as maintenance of adequate eGFR in patients with this condition is highly dependent on AII activity; subjects with hypertension secondary to uncorrected coarctation of the aorta will also be excluded. Subjects who are renal transplant patients will be allowed to enroll as long as renal graft function and immunosuppressive therapy (which alter BP) are stable. To maintain generalizability of the study results, the percentage of renal transplant patients will be monitored via IVRS/IWRS and a cap will be applied to maintain enrollment below ≈25%.

6.2.2 Dose Selection for AZM

Pharmacokinetic modeling and simulation of data from study TAK-491_109 [21] in pediatric subjects (6 to <17 years) indicate that the 20, 40, and 80 mg doses of AZM, each of which was demonstrated to be safe and effective in phase 3 trials of hypertensive adult patients, provide similar levels of exposure in children who weighed 50 to 100 kg as has been observed in adults. The 20 mg and 80 mg doses as well as a 10 mg dose will be evaluated in the higher weight group of this study (ie, ≥50 kg). A dose range that includes the 10, 20, and 40 mg strengths of AZM will be administered to lower weight subjects (ie, 25 to <50 kg) to maintain similar exposures in these children as was observed at the 20 to 80 mg doses in adults.

In order to ensure that a sufficient number of subjects in both weight categories are enrolled, the proportion of subjects ≥50 kg will be monitored via IVRS/IWRS and a cap will be applied to maintain enrollment of these subjects to below ≈80%.

6.2.3 Use of Placebo

Exposure to placebo will be restricted to the Washout/Placebo Run-in and the Withdrawal Phase. The standard duration of the Washout/Placebo Run-in is 2 weeks, although subjects whose BP remains controlled (ie, seDBP and seSBP <95th percentile or <90th percentile if chronic renal

disease, diabetes, heart failure or hypertensive target organ damage is present) after the washout and therefore do not qualify for randomization, may have the washout extended in 1-week increments for up to 2 additional weeks. The purpose of the Washout/Placebo Run-in is to establish a treatment-free baseline BP, as well as to reduce the influence of the placebo effect, prior to initiation of double-blind treatment. In addition, the run-in allows the opportunity to assess subject compliance with study medication (ie, placebo), and subjects who are not sufficiently compliant with single-blind placebo (ie, >130% or <70%) will not qualify for randomization.

In the Withdrawal Phase, half of the subjects will be randomized to receive 2 weeks of placebo treatment, while the other half will continue their current active treatment. The purpose of the randomized, placebo-controlled withdrawal is to allow for direct comparison between AZM and placebo, thereby facilitating estimation of a placebo-adjusted treatment effect for AZM.

Together, the maximum cumulative duration in which an uncontrolled subject may be untreated is 4 weeks, which will be divided into 2 non-consecutive phases. This maximum duration of exposure to placebo is regarded as safe based on meta-analysis of AE and SAE data from 10 pediatric hypertension trials that incorporated a 2 to 4 week, placebo treatment period [22]. Similarly, meta-analysis of safety data from adult hypertension trials indicated that short-term exposure to placebo (usually 4 to 8 weeks) did not increase risk of cardiovascular events relative to active therapy [23]. At any point of the study, a subject whose BP becomes elevated to greater than 15/10 mm Hg above the 99th percentile and is confirmed on repeat test will be discontinued.

6.2.4 Selection of Active Comparator

This study will evaluate the efficacy and safety of AZM relative to the active comparator losartan, which belongs to the ARB class and is approved for use in the pediatric population aged 6 years and older. The losartan tablets administered in the present study (ie, 25 to 50 mg in subjects <50 kg and 50 to 100 mg in patients ≥50 kg) are established as safe and effective in children ≥6 years of age [24,25].

6.2.5 Endpoint Selection

In a large meta-analysis of observational studies (61 studies, >1 million subjects) by Lewington et al, a continuous relationship between BP and cardiovascular risk was observed in adults throughout the normal range of usual BP to at least 115/75 mm Hg [26], such that each 10 mm Hg rise in SBP or 5 mm Hg rise in DBP was associated with a 40% increased risk of death by stroke and a 30% increased risk of death from ischemic heart disease. Moreover, interventional outcomes studies completed in adults have shown consistently that lowering BP in patients with hypertension reduces risk of cardiovascular events. Risk reduction is observed during treatment with various agents from multiple drug classes with disparate mechanisms of action, suggesting that benefit is derived largely from the decrease in BP rather than any particular property of a given drug.

While large interventional outcomes studies are lacking in the pediatric population, evidence to support an association between BP and cardiovascular risk is available from pathology and

biomarker studies. BP assessments completed in children and young adults either directly [27] or by estimation [28] correlated with atherosclerotic burden in the coronary arteries, and childhood hypertension has been shown to predict increased carotid intima media thickness in adulthood [29]. Similarly, the prevalence of left ventricular hypertrophy was shown to increase in adolescents as hypertension severity increases [30,31]. In addition to these relationships, a diagnosis of hypertension in childhood was shown to be associated with a significantly increased risk of premature death from endogenous causes [32].

The primary efficacy variable of the study is the change in trough clinic seDBP. The underlying pathophysiology associated with elevated BP in children is often different than in adults (ie, increased vascular resistance versus reduced arterial compliance); therefore, elevated DBP (or both elevated DBP and SBP) is more common in the pediatric hypertensive population, especially when compared with elderly adults who often present with isolated systolic hypertension due to age-related atherosclerotic stiffening of the arteries [33]. DBP is also associated with less physiological variability in children than SBP and this attribute may improve the ability to detect meaningful differences between doses and treatments [34]. The pathophysiology of pediatric hypertension, as well as the smaller intra-individual variability of DBP, justify selection of DBP as the primary endpoint; however, change in seSBP will also be evaluated thoroughly.

As described in Section 13.3, the sample size of this study (N=52/arm) provides >80% power (at the 0.05 significance level) to detect a treatment difference between AZM and placebo of 4.5 mm Hg in DBP. A treatment effect of this magnitude is considered clinically meaningful based on evidence from adult and pediatric studies summarized above, and as reflected in published treatment guidelines. According to European Society of Hypertension (ESH) and NHLBI guidelines for treatment of pediatric hypertension, a reduction in DBP of 4 to 5 mm Hg in the age range of subjects being recruited in this study corresponds to a shift from the 95th percentile (ie, the threshold for a hypertension diagnosis) to the 90th percentile (ie, conventional BP target) depending on age, gender, and height.

Throughout the study, clinic BP will be assessed with a sponsor-provided automated (oscillometric) device that has been validated for use in pediatric patients. Use of an automated device provides the additional advantage of reducing the impact of observer bias, which is inherently associated with manual measurements.

Changes in various parameters of DBP and SBP by ABPM will be evaluated as exploratory endpoints in this study. The utility of ABPM in adult hypertension is well established as both a diagnostic and prognostic tool [34-38]. In addition, ABPM is gaining acceptance in clinical practice as a useful diagnostic tool in children and adolescents [39,40]. For example, ambulatory BP readings may be useful in evaluating or confirming that BP control is maintained throughout the day in children with target organ damage, or to differentiate between primary and secondary forms of hypertension, which may exhibit different diurnal profiles [40,41]. Advantages of ABPM in the clinical trial setting include the ability to evaluate BP changes throughout the dosing interval and a reduced susceptibility to observer bias and placebo effect.

6.2.6 BP Targets in the Open-Label Phase

During the OL Phase, subjects will have their medication adjusted to maintain a BP target <90th percentile for age, gender, and height, which is consistent with ESH 2009 guidelines for management of hypertension in pediatric patients [39].

For subjects with CKD (eGFR <60 mL/min/1.73 m^2), antihypertensive therapy may be managed at the investigator's discretion to achieve greater BP reduction. While the US NHLBI guidelines for pediatric hypertension do not recommend a target lower than the 90th percentile for subjects with CKD [5], the ESH guidelines suggest children with CKD be treated to a BP target <75th percentile in the absence of proteinuria and to <50th percentile in the presence of proteinuria. This recommendation is based on evidence from the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial [41], which was a prospective, randomized comparison of intensive versus conventional BP control in 385 pediatric subjects with CKD. In ESCAPE, randomization to the intensive BP target (ie, 24-hour MAP <50th percentile for age) was associated with a 35% relative risk reduction in progression to ESRD compared with a conventional target (ie, 24-hour MAP between the 50th and 90th percentiles).

6.2.7 Population Pharmacokinetics

Pharmacokinetic blood samples will be collected at 3 study visits, and collection of these samples will be limited to days when blood draws are already scheduled for other purposes (ie, clinical safety laboratory tests). The data collected during this trial will be used to explore the relationship between pharmacokinetic parameters and covariates, such as body weight, age, and other factors as appropriate. Because pharmacodynamic endpoints are also being measured during the study, concentration-response relationships may also be investigated.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- The Data Monitoring Committee recommends that the study should be suspended or terminated.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an IRB/IEC or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization. If necessary, any diagnostic testing needed to confirm hypertension classification (ie, secondary or primary) must be completed before the Wash-out/Placebo Run-in.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject or parent/legal guardian is capable of understanding and complying with the protocol requirements.
2. The subject is capable of understanding (as far as their cognitive ability allows and as judged by the investigator and parent/legal guardian) an informed assent form or consent form (if of an appropriate age) and verbal explanations by the investigator. The subject is willing to give their written assent (if required by IRB/IEC) or consent (if of an appropriate age) to participate.
3. The subject's parent/legal guardian, if signing consent on behalf of their child, must (1) have understood the information contained in the informed consent document and had an opportunity to ask questions of the investigator and understands the answers, and (2) sign and date a written informed consent form on behalf of their child prior to the initiation of any study procedures.
4. The subject has hypertension (primary or secondary) defined as clinic seDBP ≥95th percentile (by age, gender, and height) or ≥90th percentile (by age, gender, height) if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present.
    a) If currently treated: The subject has a documented historical diagnosis of hypertension AND a post-washout clinic seDBP meeting the above criteria on Day -1 (or Day 1 for subjects not participating in ABPM).
    b) If currently untreated: The subject has elevated seDBP meeting the above criteria on 3 separate occasions before Randomization, including on Day -1 (or Day 1 for subjects not participating in ABPM).
5. The subject is male or female and aged 6 to <18 years at Baseline and weighs at least 25 kg.
6. Subjects <50 kg must have the ability to swallow a capsule or tablet with a maximum size of 15.64 mm in length and 7.42 mm in thickness, while subjects ≥50 kg must have the ability to swallow a tablet or capsule with a maximum size of 16.19 mm in length and 8.30 mm in thickness.
7. The subject agrees to continue their previously implemented nonpharmacological life style modifications if begun prior to Screening. Note: For subjects participating in a weight loss program, the weight maintenance phase must have begun at least 30 days prior to Screening/Visit 1.

8. Subjects may be renal transplant patients if time post-transplant has been greater than 6 months prior to Screening, with stable graft function (and eGFR ≥30 mL/min/1.73 m^2) for at least 6 months, stable use of immunosuppressive therapy for at least 30 days prior to Screening, and documented evidence that there is no transplant renal artery stenosis.
9. All female subjects who are of child bearing potential* (defined as females aged ≥12 years old and younger females who, at the discretion of the investigator, are deemed to be of reproductive potential) who are sexually active agree to routinely use adequate contraception* from Screening until the last dose of study medication. All female subjects aged ≥12 years old and younger females who, at the discretion of the investigator, are deemed to be of reproductive potential must provide a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1.

   *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

10. The subject is untreated, or willing, and in the opinion of their treating physician, can safely be withdrawn from previous antihypertensive medications for a maximum of 4 weeks (if a washout extension is required) prior to randomization.
11. The subject has clinical laboratory results (including clinical chemistry, hematology, and complete urinalysis) within the reference range for the testing central laboratory unless the results are deemed by the investigator to be stable and related to the subject's medical history and/or not clinically significant, with the exception of hyperkalemia or pertinent electrolyte disorders (exclusion criterion 16). Subjects with LFTs under the values specified by exclusion criterion 15 may be included provided the subject does meet the other criteria stated in that exclusion (i.e. active liver disease, jaundice and severe hepatic impairment),

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has a clinic seated SBP greater than 15 mm Hg and/or DBP greater than 10 mm Hg above the 99th percentile for age, gender, and height as confirmed by the average (arithmetic mean) of 3 serial clinic seated blood pressure measurements at Screening/Visit 1.
2. The subject has a diagnosis of malignant or accelerated hypertension.
3. The subject is currently treated with more than 2 antihypertensive agents.
4. The subject or parent/legal guardian is not willing for the subject's previous antihypertensive medications to be stopped.
5. The subject has participated in the intensive, active weight-loss phase of a weight-loss program within 30 days prior to Screening/Visit 1.

6. The subject was noncompliant (<70% or >130%) with single-blind study medication during the Placebo Run-in.
7. The subject is currently participating in another interventional study or has taken an investigational drug within 30 days prior to Screening/Visit 1.

   NOTE: This criterion does not apply to subjects who participated in a single-dose AZM study, nor does it apply to subjects who participated in observational studies that lacked an intervention or invasive procedure.
8. The subject or parent/legal guardian is an immediate family member, study site employee, or is in a dependent relationship (eg, spouse, parent, child, sibling) with a study site employee who is involved in the conduct of this study.
9. If female, the subject is pregnant or lactating or intending to become pregnant before or during participation in this study.
10. The subject has any of the following: severe renal impairment (eGFR <30 mL/min/1.73 m^2 by the Schwartz formula [42]); is currently undergoing dialysis treatment; renovascular disease affecting both kidneys or a solitary kidney; severe nephrotic syndrome not in remission; or serum albumin <2.5 g/dL.
11. The subject has a history or clinical manifestations of severe cardiovascular, hepato-biliary, gastrointestinal, endocrine-metabolic (eg, hyperthyroidism, Cushing's syndrome), hematologic, immunologic, genito-urinary, or psychiatric disease, cancer, and/or any conditions that would interfere with the health status of the subject through study participation, or would jeopardize study integrity in the opinion of the investigator.
12. The subject is suffering from uncorrected coarctation of the aorta, or hemodynamically significant left ventricular outflow tract obstruction due to eg, aortic valvular disease, or is likely to undergo a procedure known to affect blood pressure (eg, repair of arterial anomalies) during the course of the study.
13. The subject has a history and/or presence of a clinically significant abnormal 12-lead ECG that is not related to medical history and/or concomitant diseases and is indicative of an unstable condition as determined by the investigator or sponsor/designee.
14. The subject is poorly controlled diabetic defined as having a glycosylated hemoglobin (HbA1c) value >8.5% at Screening/Visit 1.
15. The subject has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the upper limit of normal, or total bilirubin ≥1.5 times the upper limit of normal, severe hepatic impairment, active liver disease of any etiology, or jaundice at Screening/Visit 1 (exception may be made for subjects with Gilbert's disease, as long as subjects do not have active symptoms, such as indicated above).
16. The subject has hyperkalemia as defined by the central laboratory's normal reference range or any pertinent electrolyte disorders at Screening/Visit 1.

17. The subject has a known history of hepatitis B, hepatitis C or human immunodeficiency virus infection at Screening.
18. The subject has a known hypersensitivity or allergy to any angiotensin type II receptor blockers or to any of the excipients in AZM or losartan formulations to be taken
19. The subject has a history of drug or alcohol abuse within 1 year prior to Screening/Visit 1 or positive urine drug/alcohol screen test result at Screening/Visit 1. Subjects ≥12 years of age or younger children if deemed necessary by the investigator and their parents/legal guardians are required to give consent to urine alcohol/drug screen testing to be considered for eligibility. Subjects who have a positive drug screen for known physician prescribed medications (e.g. amphetamines for ADHD), are not abusing the medication in the investigator's judgment and are not an excluded medication are eligible for the study.
20. The subject has taken or requires the use of any medications or supplements within the stated time periods that are excluded, unable to washout excluded medications or not on a stable dose as described in the Excluded Medications or Concomitant Medications sections of this protocol.

7.3 Excluded Medications and Treatments

Subjects or parents/legal guardians will be instructed not to change a dose of current medication or begin taking any new medications, including over-the-counter products, without first consulting the investigator. Results of the urine alcohol and drug screen performed at Visit 9 must be negative for the subject to continue in the study.

7.3.1 Washout/Placebo Run-in, Double-Blind and Withdrawal Phases: Excluded Medications

The following medications will be prohibited during the Washout/Run-in, DB and Withdrawal Phases. When appropriate, medications may be tapered-off gradually before double-blind treatment is initiated, but a minimum drug-free period of at least 7 days is required before randomization.

- All classes of antihypertensive drugs, including drugs that have an effect on BP but are prescribed for another indication, with the exception of concomitant medications listed in Section 7.3.2.
- Lithium.
- Monoamine oxidase inhibitors.
- Tricyclic antidepressants.
- Amphetamines or their derivatives (see Section 7.3.2 for exceptions).
- Dopamine agonists.

- Atypical antipsychotic agents.
- Anticonvulsants.
- Trazodone.
- Nitrates.

7.3.2 Washout/Placebo Run-in, Double-Blind and Withdrawal Phases: Concomitant Medications Allowed Conditionally

Conditional use of the following medications will be allowed in the Washout/Run-in, DB and Withdrawal Phases. These medications must be at a stable dose through the Week 8 visit (end of withdrawal phase) without changes unless absolutely medically necessary. Routine weaning and/or dose adjustments can be made during the open-label phase of the study:

- Diuretics, including loop-diuretics (eg, furosemide): Stable dose allowed if indicated for the treatment of oedema/CKD.
- Steroids: Systemic use is allowed at stable low/maintenance dose up to hydrocortisone 12 mg/m2/day (or the appropriate dose equivalent if other steroid is administered) for replacement therapy in subjects with adrenal insufficiency or other medical conditions. Immunosuppressive treatment in post renal transplant subjects or in subjects with glomerular disease with prednisolone is allowed at a maximum dose of 15 mg/m2 (0.5 mg/kg) (or the appropriate dose equivalent if other steroid is administered). Doses need to be stable at least 30 days prior to Screening as mandated by inclusion criterion #8Topical and inhaled corticosteroids (eg, for treatment of asthma) are also allowed at stable maintenance doses.
- Central nervous system (CNS) stimulants: Stable dose allowed if indicated for treatment of attention deficit hyperactivity disorder.
- Nonsteroidal anti-inflammatory drugs (NSAIDs): Use of NSAIDS is allowed if not used chronically (ie, more than 3 times per week). Maximum allowed daily dose of ibuprofen is 30 mg/kg/day in 3 to 4 divided doses (total daily maximum of 2.4 g). Acetaminophen (or paracetamol) is not excluded.

For diuretics, steroids, and CNS stimulants, a stable dose is defined as no dosage change in the preceding 30 days before Screening/Visit 1.

7.3.3 Open-Label Phase: Excluded Medications

The following medications are excluded during the OL Phase of the study.

- ARBs other than AZM.
- ACE inhibitors.
- Aliskiren.
- Chronic use of NSAIDs (ie, more than 3 times per week).

- Lithium.
- Monoamine oxidase inhibitors.
- Nitrates.

Results of the urine alcohol and drug screen performed at Visit 9 must be negative for the subject to continue in the study.

7.4 Diet, Fluid, Activity Control

Subjects will be encouraged to follow a healthy diet and maintain a constant food intake (including for optimal weight maintenance but not active weight loss) during the blinded phases of the study. Throughout the study, subjects should be advised to avoid foods high in sodium and to maintain good hydration. Subjects will also be instructed to maintain usual sleep habits, activity, and caffeine intake throughout the study, although excessively vigorous physical activities or contact sports should be avoided on ABPM days.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.13.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE. See Section 9.1.8.1 for instructions regarding withdrawal and follow-up of patients with acute decreases in renal function.
2. Major protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.

   Note: If the subject's clinic seSBP and/or seDBP is greater than 15/10 mm Hg above the 99th percentile at the site during any phase of the study, the subject should return within 48 hours for a repeat BP measurement. If BP remains elevated above this threshold at the repeat visit while the subject is receiving single-blind or double-blind treatment, the subject should be withdrawn and resume appropriate antihypertensive medication. Subjects who are receiving open-label treatment but whose blood pressure is confirmed to be elevated to greater than 15/10 mm Hg above the 99th percentile despite dose-titration and addition of other antihypertensive agents should also be withdrawn.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

- AZM 10 mg, 20 mg, 40 mg, 80 mg, or placebo orally administered tablets.
- Overencapsulated (O/E) losartan 25 mg, 50 mg, 100 mg, or placebo orally administered capsules.

8.1.1.1 AZM Investigational Drug

AZM 10 mg, 20 mg, 40 mg, 80 mg (azilsartan medoxomil) and matching placebo investigational drug is manufactured by Takeda Pharmaceutical Company, Osaka, Japan and will be supplied as plain white round tablets (product of Japan).

The AZM 10 mg and 20 mg doses are indistinguishable to each other with respect to size. The 10/20 mg, 40 mg, and 80 mg are all different sized tablets and each have a matching sized placebo tablet. The placebo for AZM 20 mg is being used to blind both the AZM 10 mg and AZM 20 mg doses as they are the same shape and size.

For the run-in, double-blind and withdrawal phases of the study, the tablets will be foil/foil blistered and packaged into 2-week child-resistant blister cards. Each tablet is connected to a white, round desiccant through a linked channel. Each blister card allows for 14 days of dosing with 6 additional spare daily doses. One blister card will be provided at each dispensing visit.

Each blister card of investigational study medication will be labeled with a single or multi-lingual label containing pertinent study information and country-specific regulatory caution statement.

Each blister card will consist of 40 tablets of either AZM 10 mg, 20 mg, 40 mg, 80 mg or placebo and 40 desiccants. Dosing is 2 tablets orally per day.

For the OL extension phase of the study, the tablets will be foil/foil blistered and packaged into a 4-week child-resistant blister card. Each tablet is connected to a white, round desiccant through a linked channel. Each blister card allows for 28 days of dosing with 12 additional spare daily doses. Each blister card will consist of 40 tablets of either AZM 10 mg, 20 mg, 40 mg or 80 mg and 40 desiccants. One blister card will be provided at each 4-week dispensing visit and 2 blister cards will be provided for each 8-week dispensing visit. Dosing is 1 tablet orally per day.

Each blister card of investigational study medication will be labeled with a single or multi-lingual label containing pertinent study information and country-specific regulatory caution statement.

An IVRS/IWRS program will be used to manage inventory, assist the site in dispensing the proper investigational drug to the subjects, record accountability and support the return to Arbor or designee of these investigational drugs after study completion.

8.1.1.2 Losartan Investigational Drug

Losartan Potassium (Cozaar) 25 mg, 50 mg and 100 mg tablets are manufactured for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ (made in France); or manufactured for Merck Sharp & Dohme Limited, Cramlington, Northumberland, United Kingdom (UK) (made in France, formulated in UK). Cozaar is a registered trademark of EI du Pont de Nemours and Company, Wilmington, Delaware, USA.

≥25 kg to <50 kg

Losartan 25 mg and 50 mg tablets will be O/E in Swedish orange opaque, size C- DB capsules. Matching placebo capsules will be manufactured. The capsules will be packaged in 75 cc wide-mouth, pharmaceutical-grade, round, white, high-density polyethylene (HDPE) bottles with a 38 mm child-resistant cap with 75M induction seal.

Each bottle for the Run-in segment will contain 20 placebo capsules. Each bottle for the Double-Blind and Withdrawal segments will contain 20 O/E losartan 25 mg, 50 mg, or matching placebo capsules. One bottle will be provided at each dispensing visit. Dosing is 1 capsule orally per day.

Each bottle of O/E investigational study medication will be labeled with a single or multi-lingual label containing pertinent study information and country-specific regulatory caution statement.

≥50 kg

Losartan 50 mg and 100 mg tablets will be O/E in Swedish orange opaque, size B- DB capsules. Matching placebo capsules will be manufactured. The capsules will be packaged in 75 cc wide-mouth, pharmaceutical-grade, round, white, HDPE bottles with a 38 mm child-resistant cap with 75M induction seal.

Each bottle for the Run-in segment will contain 20 placebo capsules. Each bottle for the Double-Blind and Withdrawal segments of the study will contain 20 O/E losartan 50 mg, 100 mg, or matching placebo capsules. One bottle will be provided at each dispensing visit. Dosing is 1 capsule orally per day.

Each bottle of O/E investigational study medication will be labeled with a single or multi-lingual label containing pertinent study information and country-specific regulatory caution statement.

An IVRS/IWRS program will be used to manage inventory, assist the site in dispensing the proper investigational drug to the subjects, record accountability and support the return to Arbor or designee of these investigational drugs after study completion.

8.1.1.3 Ancillary Materials

The following nondrug materials will be provided to the sites by Arbor or designee:

- ABPM devices: Devices will be returned to the site by the subject after each use. After study completion the site will return the devices to Arbor or designee.
- Clinic BP monitoring devices: Instructions on final disposition of the devices will be provided to the sites during the study.
- HBPM devices: Instructions on final disposition of the devices will be provided to the sites during the study.
- BP diary: Diary should be returned to the site by the subject at each OL study visit.

8.1.1.4 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

- AZM 10 mg, 20 mg, 40 mg, 80 mg, or matching placebo orally administered tablets.
- O/E losartan 25 mg, 50 mg, 100 mg, or matching placebo orally administered capsules.

8.1.2 Storage

AZM and matching placebo investigational study drugs should be stored at 25°C (77°F); with excursions permitted to 15°C to 30°C (59°F-86°F). Study medication is to remain stored in the original container until time of dosing.

O/E losartan and matching placebo study drug should be stored at 25°C (77°F); with excursions permitted to 15°C to 30°C (59°F-86°F). Keep container tightly closed. Protect from light. Study medication is to remain stored in the original container until time of dosing.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All sponsor-supplied drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day. Temperature excursions must be reported to sponsor or designee.

8.1.3 Dose and Regimen

Each subject who qualifies following the initial screening visit will enter the 2-week, single-blind placebo Run-in/Washout at Day -14 (Visit 2) and will be dispensed 1 blister card containing AZM placebo tablets and 1 bottle containing losartan placebo capsules. Subjects will receive their first dose of investigational study medication in the clinic. For currently treated subjects, if seDBP remains below inclusion criterion #4 after the Run-in/Washout, it can be extended in 1-week increments up to 2 times, for a maximum washout of 4 weeks. The date of the first dose of single-blind, placebo run-in investigational medication should be recorded in the subject's source document and eCRF.

The investigator or designee will instruct the subject or parent/legal guardian on the dosing procedures and study medication storage requirements. Subjects should return their unused study medication at each study visit to allow the opportunity for the investigator or designee to evaluate subjects' compliance with the dosing instructions.

For subjects that choose to participate in the ABPM procedure, the final dose of single-blind placebo run-in investigational medication will be administered in the clinic on Day -1 immediately prior to the Baseline ABPM start. For subjects who do not participate in the ABPM procedure, the final dose of single-blind placebo run-in investigational medication will be administered at home on Day -1.

Eligible subjects will be randomized into 1 of 4 double-blind treatment arms using an IVRS/IWRS. The 3 treatment groups include (1) AZM-L, (2) AZM-M, (3) AZM-H or (4) losartan (Figure 8.a).

The 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 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 or additional medication 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.

Figure 8.a 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.

Table 8.a describes the dose and tablet count that will be provided to each group.

Table 8.a Sponsor-Supplied Drug

≥25 to <50 kg – Run-in and Double-Blind Phase (2 tablets+ 1 capsule)

Treatment Group	Dose QD	Treatment Description		
		Active wk 0-2	**Active wk 2-6**	**Placebo(a)**
NA	Run-in	NA	NA	One placebo for 20 mg AZM tablet, one placebo for 40 mg AZM tablet, one placebo for O/E losartan capsule
B	AZM Low Dose	One 10 mg AZM tablet	One 10 mg AZM tablet	One placebo for 40 mg AZM tablet, one placebo for O/E losartan capsule
C	AZM Med Dose	One 10 mg AZM tablet	One 20 mg AZM tablet	One placebo for 40 mg AZM tablet, one placebo for O/E losartan capsule
D	AZM High Dose	One 10 mg AZM tablet	NA	One placebo for 40 mg AZM tablet, one placebo for O/E losartan capsule
		NA	One 40 mg AZM tablet	One placebo for 20 mg AZM tablet, one placebo for O/E losartan capsule
E	Comparator	One 25 mg O/E losartan capsule	One 50 mg O/E losartan capsule	One placebo for 20 mg AZM tablet, one placebo for 40 mg AZM tablet

(a) The placebo for AZM 20 mg is being used to blind both the AZM 10 mg and AZM 20 mg doses as they are the same shape and size.

Table 8.a Sponsor-Supplied Drug (continued)

≥25 to <50 kg – Withdrawal Phase (2 tablets+ 1 capsule)

Treatment Group	Dose QD	Treatment Description	
		Active wk 6-8	**Placebo(a)**
A	AZM Low Dose Placebo	N/A	One placebo for 20 mg AZM tablet, one placebo for 40 mg AZM. one placebo for O/E losartan capsule
B	AZM Low Dose	One 10 mg AZM tablet	One placebo for 40 mg AZM tablet. one placebo for O/E losartan capsule
A	AZM Med Dose Placebo	N/A	One placebo for 20 mg AZM tablet; one placebo for 40 mg AZM. one placebo for O/E losartan capsule
C	AZM Med Dose	One 20 mg AZM tablet	One placebo for 40 mg AZM tablet. one placebo for O/E losartan capsule
A	AZM High Dose Placebo	N/A	One placebo for 20 mg AZM tablet, one placebo for 40 mg AZM. one placebo for O/E losartan capsule
D	AZM High Dose	One 40 mg AZM tablet	One placebo for 20 mg AZM tablet. one placebo for O/E losartan capsule
A	Comparator Placebo	N/A	One placebo for 20 mg AZM tablet, one placebo for 40 mg AZM. one placebo for O/E losartan capsule
E	Comparator	One 50 mg O/E losartan capsule	One placebo for 20 mg AZM tablet, one placebo for 40 mg AZM tablet

(a) The placebo for AZM 20 mg is being used to blind both the AZM 10 mg and AZM 20 mg doses as they are the same shape and size.

Table 8.a Sponsor-Supplied Drug (continued)

≥50 kg – Run-in and Double-Blind Phase (2 tablets)

Treatment Group	Dose QD	Treatment Description		
		Active wk 0-2	**Active wk 2-6**	**Placebo(a)**
NA	Run-in	NA	NA	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet. one placebo for O/E losartan capsule
B	AZM Low Dose	One 10 mg AZM tablet	One 10 mg AZM tablet	One placebo for 80 mg AZM tablet. one placebo for O/E losartan capsule
C	AZM Med Dose	One 10 mg AZM tablet	One 20 mg AZM tablet	One placebo for 80 mg AZM tablet. one placebo for O/E losartan capsule
D	AZM High Dose	One 10 mg AZM tablet	NA	One placebo for 80 mg AZM tablet. one placebo for O/E losartan capsule
		NA	One 80 mg AZM tablet	One placebo for 20 mg AZM tablet. one placebo for O/E losartan capsule
E	Comparator	One 50 mg O/E losartan capsule	One 100 mg O/E losartan capsule	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet

(a) The placebo for AZM 20 mg is being used to blind both the AZM 10 mg and AZM 20 mg doses as they are the same shape and size.

Table 8.a Sponsor-Supplied Drug (continued)

≥50 kg – Withdrawal Phase (2 tablets)

Treatment Group	Dose QD	Treatment Description	
		Active wk 6-8	**Placebo(a)**
A	AZM Low Dose Placebo	NA	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet, one placebo for O/E losartan capsule
B	AZM Low Dose	One 10 mg AZM tablet	One placebo for 80 mg AZM tablet, one placebo for O/E losartan capsule
A	AZM Med Dose Placebo	N/A	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet, one placebo for O/E losartan capsule
C	AZM Med Dose	One 20 mg AZM tablet	One placebo for 80 mg AZM tablet, one placebo for O/E losartan capsule
A	AZM High Dose Placebo	N/A	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet, one placebo for O/E losartan capsule
D	AZM High Dose	One 80 mg AZM tablet	One placebo for 20 mg AZM tablet, one placebo for O/E losartan capsule
A	Comparator Placebo	N/A	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet, one placebo for O/E losartan capsule
E	Compartor	One 100 mg O/E losartan capsule	One placebo for 20 mg AZM tablet, one placebo for 80 mg AZM tablet

(a) The placebo for AZM 20 mg is being used to blind both the AZM 10 mg and AZM 20 mg doses as they are the same shape and size.

Table 8.a Sponsor-Supplied Drug (continued)

– 44 week OL Phase (1 tablet)

Treatment Group	Dose	Treatment Description	
		Active	
≥25 to <50 kg	Treat to Target Blood Pressure	One 10 mg AZM tablet	or
		One 20 mg AZM tablet	or
		One 40 mg AZM tablet	
≥50 kg	Treat to Target Blood Pressure	One 10 mg AZM tablet	or
		One 20 mg AZM tablet	or
		One 40 mg AZM tablet	or
		One 80 mg AZM tablet	

8.1.4 Overdose

An overdose is defined as a **known** deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Adverse events associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs of overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically. AZM is not dialyzable.

8.2 Investigational Drug Assignment and Dispensing Procedures

A sufficient number of subjects will be screened to randomize at least 213 eligible subjects. A 2-digit number (01, 02, etc.) will be assigned to each subject who signs the informed consent. Throughout the study, the subject's identification number (subject ID) will consist of the 2-digit subject number preceded by a 3-digit site number.

The investigator or investigator's designee will access the IVRS/IWRS at Screening to obtain the subject number, and will use this number as an identifier for the subject in all future contacts with the IVRS/IWRS. The investigator or designee will utilize the IVRS/IWRS to dispense run-in placebo. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. The medication identification (MED ID) numbers of the placebo run-in medication will then be provided by the IVRS/IWRS. One single-blind blister card will be dispensed to the subject for this run-in visit. The MED ID numbers will be entered onto the eCRF.

The investigator or the investigator's designee will utilize the IVRS/IWRS to randomize the subject into the DB and Withdrawal Phases of the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The IVRS/IWRS will associate and assign the randomization number to the subject. The MED ID numbers of the investigational drugs to be dispensed will then be provided by the IVRS/IWRS. The MED ID numbers of the dispensed investigational drug will be entered onto the eCRF.

At subsequent drug-dispensing visits, the investigator or designee will again contact the IVRS/IWRS to request additional investigational drug for a subject. The MED ID number of the investigational drugs to be dispensed will be provided by the IVRS/IWRS. The MED ID numbers will be entered onto the eCRF.

Subjects will be dispensed one OL label blister card for a 4 week visit or 2 blister cards for an 8-week visit during the OL extension phase of the study. The IVRS/IWRS will provide the investigator or designee with the MED ID number(s) for dispensing.

If sponsor supplied drug (AZM, O/E losartan or placebo) is lost or damaged, the site can request a replacement from the IVRS/IWRS (refer to the system manual that will be provided separately). The MED ID numbers will be entered onto the eCRF.

Throughout all treatment phases, including the Placebo Run-in, study drug will be administered once daily, orally, with water, with or without food. Individual subjects or parents/legal guardians will be instructed to administer the medication at approximately the same time every day. In order to ensure that clinic BP measures are recorded at trough (ie, approximately 24 hours after the previous dose of study medication), clinic visits should be scheduled at approximately the same time as the medication is dosed. Subject will take their first dose of study medication in clinic.

The subjects or parents/legal guardians should be instructed by the investigator or designee that the AZM study medications are plain, white tablets in appearance. The desiccant is also white in appearance and that it should not be removed from the blister card and they are not to ingest the desiccants. The AZM tablets and O/E losartan capsules are to be swallowed whole. They are not to be chewed, crushed, or opened. Subjects or parents/legal guardians should also be instructed on the dosing procedures, dispensing instructions, and study medication storage requirements. They should also be instructed to withhold study medication on days that a clinic visit is scheduled. The study drug should be administered in the clinic after trough vital signs (BP and pulse rate) and other applicable procedures are recorded. All sponsor-supplied drug is to remain in original container until dose is to be dispensed.

Subjects or parents/legal guardians should be informed as follows if they miss a scheduled dose. If it is almost time for the next dose (within 12 hours), skip the missed dose and take the next dose when it is due. Otherwise, take the missed dose as soon as it is remembered, and then go back to taking the investigational drug as usual. Do not take a double dose to make up for a missed dose.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel. For 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). Enrollment caps will also be applied to ensure a percentage of subjects with secondary hypertension of at least 20% and to ensure that no more than ≈25% of subjects are post-renal transplant patients and no more than ≈80% 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 (ie, AZM-L, AZM-M, AZM-H or losartan).

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IVRS/IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IVRS/IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel is unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (AZM 10 mg, 20 mg, 40 mg, 80 mg or matching placebo and O/E losartan 25 mg, 50 mg, 100 mg or matching placebo), the investigator must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and that the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording it in the IVRS/IWRS. If there are any discrepancies between the packing list versus the actual product received, Arbor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must maintain 100% accountability for all sponsor-supplied drugs and ancillary materials received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or MED ID or job number) used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Current inventory of all sponsor-supplied drugs (AZM, O/E losartan and placebo) will be recorded in the IVRS/IWRS. The following information will be recorded at a minimum: protocol number, subject number, name of investigator, site number, description of sponsor-supplied drugs, date and amount dispensed, date and amount returned to the site by the subject, and the name of the person making each IWRS transaction. The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction. The investigator will retain a copy of the documentation regarding clinical study material accountability, return, and/or destruction, and a copy will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Table 9.b.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Assent and informed consent (either from parent/legal guardian or subject, if of an appropriate age) must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject ID number (subject number) will be assigned to each subject at the time that informed consent and assent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (US only), race as described by the subject or parent/legal guardian, and smoking status of the subject at Screening.

Medical history to be obtained will include congenital heart disease and renal transplant as well as determining whether the subject has any other significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 30 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the pretreatment assessment immediately prior to the start of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (12) other. All subsequent physical examinations should assess clinically significant changes from the baseline examination.

Tanner stage will be documented. Previous medical history documentation is acceptable if assessment was performed within the previous 6 months.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing light-weight clothing and with shoes off. This is to minimize weight variation in summer/winter as dosing is weight sensitive. Height will be collected in centimeters without decimal places and weight will be collected in kilograms to 1 decimal place. Height percentile will be determined using the US Centers for Disease Control and Prevention Stature-for-Age charts [43]. Height percentiles will be used to determine BP percentiles for study qualification and target BP.

The BMI will be calculated by Arbor or designee using metric units with the formula provided below:

Metric: $BMI = weight\ (kg)/height\ (m)^2$

9.1.5 Vital Sign Procedure

Vital signs will include sitting and standing BP and pulse (bpm).

Sitting and standing BP will be measured at each study visit. As pediatric normative charts are based on measurements taken from the right arm, study BP measurements will be taken from the right arm throughout the study, unless there is a medical reason that the right arm cannot be used.

At each visit, 3 serial BP measurements will be obtained while the subject is seated using a calibrated oscillometric automated device provided by the sponsor and validated for use in pediatric subjects. The average (arithmetic mean) of the 3 serial measurements will be used for determination of subject eligibility and in the analyses of seated clinic trough systolic/diastolic BP. The measurements should be a minimum of 2 minutes apart with the cuff fully deflated between each reading. A single sitting pulse measurement should also be taken. Prior to measuring sitting BP, the subject should be seated quietly in a chair, not an examination table, for at least 5 minutes with feet on the floor and arm supported at heart level. The time the subject began sitting should be recorded in the source documents. BP will be measured using an appropriately sized cuff, according to arm width (40% of the arm circumference). The cuff will be applied to the upper arm at heart level. The right arm and same cuff size should be used for each measurement at all visits. Every effort should be made to standardize the conditions of clinic BP measurements, including the time of day, and BP should be measured by the same investigator or site personnel (whenever possible), with the same equipment. All readings will be entered into the source document and eCRF for all subjects. However, if any of the 3 SBP measurements differ by more than 8 mm Hg or DBP measurements differ by more than 5 mm Hg, a second set of 3 sitting BP measurements should be obtained and only the second set of readings should be entered into the eCRF (even if these still differ by >8 mm Hg for SBP or 5 mm Hg for DBP). Original and repeat readings must all be recorded in the source documents with an explanation.

Standing blood pressure will also be measured at each visit to evaluate orthostatic vital signs. After blood pressure is measured in the seated position as described above, a single blood pressure measurement will be obtained after 2 minutes of standing. Standing blood pressure will be measured using the same equipment and the same arm that was used for the seated measurements.

For standing blood pressure measurements, the arm should be supported and extended such that the cuff is at heart level. A single pulse measurement should also be taken while the subject is standing.

Trough BP measurements should be performed approximately 24 hours after the previous day's dosing, but before blood collection and before the next dose of study drug is administered. In order to ensure that clinic BP measures are recorded at trough, clinic visits should be scheduled at approximately the same time as medication is dosed each day. Subjects or parents/legal guardians will be contacted regularly (by phone-calls) to remind them not to take/administer study drug at home on days of clinic visits. If a subject takes a dose in error before their clinic visit, the subject or parent/legal guardian should be re-instructed. The date and time of the dose prior to the clinic BP measurement should be captured in the subject source document and eCRF.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject or subject's parent/legal guardian over the counter. Concomitant medication is not provided by Arbor. At each study visit, subjects or parents/legal guardians will be asked whether they have taken or administered any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases including CKD and diabetes mellitus that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at Screening examination. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 11.5 mL, and the approximate total volume of blood for the study is 59 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry		Urinalysis
RBCs WBCs (with differential) Hemoglobin Hematocrit Platelets Mean Corpuscular Volume (MCV) Mean Corpuscular Haemoglobin (MCH) Mean Corpuscular Haemoglobin Concentration (MCHC) Red Cell Distribution Width (RDW)	HbA1c for diabetic subjects only (a) ALT Albumin Alkaline phosphatase AST Bicarbonate Bilirubin (total, if increased measure direct) BUN (b) Calcium Chloride (b) Creatinine (b)	Creatine kinase Cystatin C (b) eGFR by the Schwartz formula [45] (b) γ-Glutamyl transferase Glucose Lipid panel (total cholesterol, LDL-C, HDL-C, and triglycerides) Phosphate Potassium (b) Sodium (b) Total protein	Glucose Specific gravity pH Protein Blood Ketones RBCs WBCs Creatinine Urinary albumin Albumin/creatinine ratio

Other:

Blood	Urine
Serum hCG (c): Only female subjects ≥12 years old and younger females deemed to be of reproductive potential. Pharmacokinetics sample (d)	Urine hCG (e): Only female subjects ≥12 years old and younger females deemed by the principal investigator to be of reproductive potential. Drug and alcohol screens (f): Only subjects ≥12 years of age; however, testing may be completed for younger subjects if deemed appropriate by the principal investigator.

hCG=human chorionic gonadotropin, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, RBC=red blood cell, WBC=white blood cell.
(a) Screening/Visit 1, Week 8/Visit 9, Week 20/Visit11, Week 36/Visit 13 and Week 52/Visit 16.
(b) Lab is part of the renal subpanel. The renal subpanel will be completed at Week 4/Visit 6 instead of the full clinical laboratory testing. The renal subpanel may also be requested by the investigator at unscheduled visits after study drug is titrated.
(c) Screening only.
(d) Collected on Day 1/Visit 4, Week 4/Visit 6, and Week 6/Visit 8.
(e) At all visits.
(f) Screening/Visit 1 and Week 8/Visit 9.

The central laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, lipid panel and other safety tests.

eGFR will be calculated by the central laboratory using the Schwartz formula [42].

The urine pregnancy tests will be performed at the site. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results with the source documents.

If subjects experience ALT or AST >3 × upper limit of normal (ULN) or ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN, clinical follow-up should take place (including repeat laboratory tests within a maximum of 7 days and preferably within 48-72 hours after the abnormality was found) until a subject's laboratory profile has stabilized at a level that is deemed clinically non-significant/acceptable by the investigator. If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies.

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.8.1 Withdrawal and Follow-up of Subjects with Acute Decreases in Renal Function

Acute increases of creatinine have been described in some patients receiving agents that block the RAAS, including ACE inhibitors and ARBs. This effect is caused by inhibition of AII-mediated vasoconstriction of efferent glomerular arterioles, resulting in decreased intraglomerular pressure, and thus an acute decrease of GFR. The acute creatinine increases observed with RAAS blockade may be exacerbated under certain conditions, such as hypovolemia. Subjects who experience acute decreases in renal function (creatinine elevation of 0.5 mg/dL/44.2 umol/L from Baseline) should be evaluated by repeat testing(s) within approximately one week until resolution or stabilization. Subjects whose eGFR decreases by more than 50% or to below 20 mL/min/1.73m^2 (as confirmed by repeat measurement) should be withdrawn. All discontinued subjects should be followed to resolution or stabilization.

9.1.9 Contraception and Pregnancy Avoidance Procedure for Pediatric Subjects

This protocol does not condone or endorse under-age sexual activity. Female participants will be asked to use contraception if they are going to be sexually active. Age appropriate contraceptive pill or condom plus spermicide are advised. It is noted that investigators will neither prescribe contraceptives, nor provide contraceptive advice beyond the protocol requirements; subjects must take responsibility for obtaining advice from the appropriate family doctor or family planning provider and preferably after discussion with their parents/legal guardians. Contraception use must be practiced if sexually active, from the date of the Screening visit until the last dose of study medication intake. Parents/legal guardians and children will be advised of this during the informed consent and assent process, and subjects will be asked to sign an informed assent form or consent form (as appropriate) stating that they understand the requirements for avoidance of pregnancy during the course of the study.

All female subjects aged ≥12 years old and younger females who the investigator deems to be of reproductive potential must have a negative serum hCG pregnancy test at Screening, and a negative urine hCG pregnancy test on Day 1 prior to the first dose of study drug.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Visit 4 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed-up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded at Day D-28/Visit 1, Week 8/Visit 9 and Week 52/Visit 16. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, PR interval, QT interval, and QRS interval. Corrected QT interval will be calculated by Arbor or designee and will not be recorded on the CRF. One copy of each 12-lead ECG and the physician's assessment will be filed with the source documents. ECGs on thermal paper must be photocopied and the copy should be kept in the subjects' source documents.

9.1.12 Pharmacokinetic Sample Collection and Analysis

All pharmacokinetic samples should be collected at the designated time intervals stated in Section 9.1.12.1 and Table 9.b. Refer to Section 14.2 for deviations for pharmacokinetic sample collection times. To minimize discomfort and distress, butterfly needles or indwelling catheters will be used when appropriate for the collection of the pharmacokinetic blood samples. In addition, topical local anesthetics such as EMLA and "Cold Spray" will be offered to all subjects, and will be documented appropriately. To minimize the risk and distress the number and volume of blood draws has been kept to an absolute minimum.

9.1.12.1 Collection of Blood for Plasma Pharmacokinetic Sampling

A total of 4 blood samples (2 mL each) will be collected during the DB Phase at Day 1/Visit 4; Week 4/Visit 6; and Week 6/Visit 8 for quantitation of azilsartan in plasma. All of these

pharmacokinetic samples will be collected into chilled tubes containing K2EDTA placed on ice (wet) until centrifuged at 4°C. Within 60 minutes of the blood collection, plasma samples are to be stored at -20°C. Refer to the study manual for detailed instructions regarding the collection, processing and shipping of these samples for pharmacokinetic analysis.

At Day 1/Visit 4, one post-dose sample will be obtained approximately 1 to 2 hours after administration of the study medication. At Week 4/Visit 6, one pre-dose trough sample will be obtained approximately 24 to 36 hours after the previous dose of study medication and one post-dose sample will be obtained at approximately 3 to 5 hours after administration of the in-clinic dose of study medication. Predose trough samples will be obtained at Week 6/Visit 8 approximately 24 to 36 hours after the previous dose of study medication.

The exact timing of the post-dose sample may vary based on subject preferences for scheduling. If subject's schedule does not allow for collection of a post-dose sample, it will be recorded in the eCRF. However, every effort should be made to collect post-dose samples at different times within the designated intervals. For each sample, the actual date and the actual clock time when the blood samples are drawn will be recorded in the eCRF as well as the date and time of drug administration at the clinic visit and of the prior dose.

Pharmacokinetic blood samples will be collected at 3 study visits during the DB Phase, and collection of these samples will be limited to days when blood draws are already scheduled for other purposes (ie, clinical safety laboratory tests). The data collected during this trial will be used to explore the relationship between pharmacokinetic parameters and covariates, such as body weight, age, and other factors as appropriate. Because pharmacodynamic endpoints are also being measured during the study, concentration-response relationships may also be investigated.

9.1.12.2 Bioanalytical Methods

Plasma concentrations of azilsartan and M-II will be measured using a high-performance liquid chromatography with tandem mass spectrometry method with a validated range of 10.0 to 5000 ng/mL and 2.00 to 1000 ng/mL for azilsartan and M-II, respectively.

9.1.13 Documentation of Screen Failure

Investigators must account for all subjects for whom an informed consent has been signed.

If the subject is found to be not eligible at the Screening Visit, the investigator should complete the appropriate eCRF pages. The IVRS/IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Major protocol deviation.
- Lost to follow-up.

- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.14 Documentation of Randomization and Run-in Failure

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. The IVRS/IWRS will be contacted for treatment assignment and this information should be captured on the appropriate eCRF.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF. If the subject has begun the single-blind placebo run-in study medication, they are considered a run-in failure. The investigator should complete the appropriate eCRFs and register the subject as a run-in failure in the IVRS/IWRS.

9.1.15 Ambulatory Blood Pressure Monitoring

ABPM is a noninvasive technology to measure ambulatory BP during at least 24 hours. The device is programmed by the investigator or designee to measure BP and heart rate at set intervals during the day and night. The subject wears a compact and lightweight (about 1 pound/500 g or less) device that does not interfere with daily activities. Measurements are stored in the device and later uploaded onto a computer.

An Arbor-selected vendor will provide oscillometric ABPM units. The proper cuff size will be selected according to the circumference of the non-dominant arm. ABPM will be performed while subjects participate in their regular daily activities; however, each subject will be advised against participating in excessively vigorous physical activities or contact sports during the ABPM procedure. Recording will begin immediately after dosing. The reading frequency will be programmed for pre-set intervals that are more frequent during the daytime. When interference or error in the reading occurs, the process will be automatically repeated.

All subjects will have the opportunity to participate in serial 24-hour ABPM recordings. The baseline ABPM will be performed on Day -1/Visit 3 after subject eligibility has been verified but before randomization. Subjects who have a baseline ABPM procedure that meets predefined quality criteria will undergo a second recording for the 24 hours preceding the Week 6 visit (ie, Week 6 -1Day/Visit 7). An optional ABPM may also be conducted one day prior to the last day of the OL Phase (ie Week 52 -1 Day/Visit 15) for subjects with a baseline ABPM that meets quality criteria. Subjects who do not wish to participate in the ABPM procedure but otherwise qualify for the study will be allowed to enroll.

Subjects should be instructed to withhold their dose of study medication on the morning when an ABPM recording is scheduled to begin, and that day's dose of study medication will be administered in the clinic. The ABPM measurement should begin immediately after dosing, and every effort should be made to initiate all ABPM recordings at the same time of day. Subjects will

be instructed to return to the clinic on the following day approximately 24 hours after the device is fitted so that the quality of the ABPM measurement can be verified and the device can be removed. If the ABPM does not meet quality criteria but study entry criteria are met, the subject may be enrolled.

If the subject terminates early from the study and the subject (a) had a baseline ABPM that met quality criteria, (b) has not been without study medication, and (c) has completed at least 4 weeks of active treatment, the site should attempt to complete the early termination ABPM prior to discontinuing study medication (subject safety permitting).

See study manual for additional ABPM guidelines.

9.1.16 Home Blood Pressure Monitoring

Upon initiation of the OL Phase (Week 8/Visit 9), subjects and their parents/legal guardians, will be provided with an automated HBPM device which has been validated according ESH International Protocol standards. Subjects and their parents/legal guardians will be instructed to measure the subject's BP at home at least once daily for the remainder of the study, preferably immediately before dosing. The subject should be seated for at least 5 minutes with the BP cuff applied to the same arm (right) as used to measure BP at the clinic visits. A blood pressure diary will be provided so that the daily measurements can be recorded and reviewed by the investigator. At each visit, the investigator will provide the subject (and parent/legal guardian) with a BP threshold and instructions to contact the investigative site if BP is at or above this threshold. The recommended threshold that would prompt contact with the site is an SBP and/or DBP by HBPM that is 15 or 10 mm Hg, respectively, above the 99th percentile for age, gender, and height [5]. The subject should be asked to return to the site for BP assessment. If the elevated BP is confirmed by repeat clinic measurements (as provided in Section 7.5) the subject is to be discontinued from the study and referred back to the treating physician and provided with treatment according to the physician`s decision.

The home BP data will not be recorded in the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication blister cards to each clinic visit, regardless of whether the study medication blister card is empty.

If a subject is persistently noncompliant with the study medication (<70% or >130% of the allocated medication for the period since the last visit), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in the schedule of study procedures (Table 9.b). Assessments should be completed at the designated visit/time point(s).

Table 9.b Schedule of Study Procedures

Washout/Placebo Run-in ↓			RZ ↓				RZ ↓								Follow-up ↓	
Screening			DB Phase				WD Phase		OL Phase							
Study Day/Week (y):	D-28	D-14	D-1	D1	W2	W4	W6 -1D	W6	W8 (a)	W12 (b,c)	W20	W28	W36	W44	W52 -1D	W52 (d)	W54
Visit Windows (Days):	-	(e)	(e)		±2	±2	-	±2	±2	±5	±5	±5	±5	±5	-	±5	±2
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent/assent	X																
Inclusion/exclusion criteria	X	X	X_1 (f,g)	X_0 (f,g)													
Randomization				X				X									
Demographics and medical history	X																
Concurrent medical conditions	X																
Medication history	X																
Concomitant medications	X	X	X_1	X	X	X	X_1	X	X	X	X	X	X	X	X_1	X	X
Vital signs (h,i)	X	X	X_1	X	X	X	X_1	X	X	X	X	X	X	X	X_1	X	X
Weight and height	X		X_1	X_0					X	X	X	X	X	X		X	
Physical examination	X								X							X	
Document Tanner stage (j)	X																
PTE or AE assessment (k,l)	X	X	X_1	X	X	X	X_1	X	X	X	X	X	X	X	X_1	X	X
Clinical laboratory tests (m)	X			X		X (n)		X	X		X		X			X	
HbA1c (o)	X								X		X		X			X	
PK sampling (p)				X		X		X									
Pregnancy test (q,r)	X	X		X	X	X		X	X	X	X	X	X	X		X	X
Pregnancy avoidance counseling (q)	X	X		X	X	X		X	X	X	X	X	X	X			
Urine alcohol/drug screen (s)	X								X								
ABPM fitting			X_1				X_1 (t)								X_1 (t)		
ABPM removal				X_1				X_1								X_1	
ECG	X								X							X	
Contact IVRS/IWRS	X	X		X	X	X		X	X	X	X	X	X	X		X	
Discontinue or taper off anti-HTN medications		X (u)															
Dispense/redispense SB placebo		X	X_1	X (v)													
Dispense/redispense DB medication				X	X	X	X_1	X									
Dispense/redispense OL medication									X	X	X	X	X	X	X_1		
Assess need for titration/add-on medication										X	X	X	X	X			
Clinic dosing		X	X_1	X	X	X	X_1	X	X	X	X	X	X	X	X_1		
Drug accountability and compliance check (w)			X_1	X	X	X	X_1	X	X	X	X	X	X	X	X_1	X	
Issue HBPM device (x)									X								
Issue/review/collect BP diary									X	X	X	X	X	X		X	

Footnotes for Schedule of Study Procedures are on the following page.

Note: X=all subjects, X_1=subjects who participate in ABPM, and X_0=subjects who do not participate in ABPM. Only subjects undergoing ABPM should attend visits D-1, W6-1D, and W52-1D (shaded columns).
RZ=Randomization, WD=Withdrawal, OL=Open-Label, D=Day, W=Week, PTE=pretreatment event, AE=adverse event, PK=pharmacokinetics, ICF=informed consent form, HTN=hypertension, SB=single-blind, DB=double-blind.
(a) Conduct W8 procedures for subjects who prematurely discontinue DB treatment in the DB Phase or WD Phase.
(b) An additional unscheduled visit may be requested before Week 12 at the investigator's discretion.
(c) For subjects whose BP is controlled and medications remain unchanged at Week 12, subsequent visits will be scheduled at 8-week intervals. If further medication adjustment is needed, the subject will be required to return to the site for a vital sign evaluation at an unscheduled visit 2 to 4 weeks after each change until medications are stable; a renal subpanel may be requested and/or the visits may occur earlier if deemed necessary. Other unscheduled visits may be requested by the investigator at any time for other reasons; however, if the visit results in a medication change, the up- or down-titration must be registered in IVRS/IWRS.
(d) Conduct W52 procedures for subjects who prematurely discontinue open-label treatment in the OL Phase.
(e) Washout/Placebo Run-in visits should be timed so that a subject receives placebo for 14 (±5) days, unless an extended washout is needed as described in footnote (g).
(f) Inclusion criterion #4 (ie, seDBP ≥95th percentile for age, gender, and height or ≥90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present) and exclusion criterion #6 (compliance >130% or <70%) must be confirmed.
(g) If seDBP remains below inclusion criterion #4, the washout can be extended in 1-week increments up to 2 times (currently treated subjects only), for a maximum washout of 4 weeks. Placebo should be re-dispensed and continued during the extension(s).
(h) Includes sitting and standing BP and pulse. Obtain a second set of 3 seated measurements if any of the initial BP readings differ by >8 mm Hg for SBP or >5 mm Hg for DBP; if clinic BP at any visit exceeds the 99th percentile for age, gender, and height by 15 mm Hg for SBP or 10 mm Hg for DBP, a repeat measurement should be obtained within 48 hrs and the subject withdrawn if BP remains elevated.
(i) In the OL Phase, if BP is above the target (ie, seDBP and/or seSBP are not <90th percentile for age, gender, and height), titrate study medication or add additional medication according to the recommended treatment algorithm provided in Figure 6.b. A lower BP target may be employed for subjects with CKD at the investigator's discretion.
(j) Previous medical history documentation is acceptable if assessment was performed within the previous 6 months.
(k) Spontaneous reports of PTEs should be collected from the time that informed consent is acquired until the first dose of study drug.
(l) Spontaneous reports of AEs and SAEs should be collected from the time of the first dose of study drug through 14 and 30 days, respectively, after the last dose.
(m) Includes the following listed in Table 9.a- hematology, urinalysis and all serum chemistry except for HgA1c; fasting is not required.
(n) Renal subpanel only; the renal subpanel may be may also be requested by the investigator at unscheduled visits after study drug is titrated.
(o) For diabetic subjects only
(p) One PK sample will be obtained 1 to 2 hrs post-dose on D1/V4. At W4/V6, 1 sample will be collected at trough (ie, 24 to 36 hours after the previous dose) and 1 at 3 to 5 hrs post-dose. At W6/V8, a sample will be obtained at trough.
(q) Only female subjects ≥12 years old and younger girls deemed by the investigator to be of reproductive potential.
(r) Includes serum and urine pregnancy test at Screening and urine pregnancy test at all other visits.
(s) Required only for subjects ≥12 years old; may be performed for younger children if deemed appropriate by the investigator. Results must be negative for the subject to continue in the study.
(t) The Week 6 ABPM should be completed only for subjects with a baseline ABPM that met quality criteria. The Week 52 ABPM is optional for subjects with a baseline ABPM that met quality criteria; participating subjects should return to the clinic ≈24 hours after the fitting for device removal.
(u) After applicable inclusion/exclusion criteria are verified, instruct currently treated subjects to stop their antihypertensive treatment(s); β-blocker use should be tapered off during the first week of the washout.
(v) Placebo will be re-dispensed only for subjects who require an extended washout as described in footnote (g).
(w) Instruct subjects to return drug supplies to the clinic at each visit for compliance check.
(x) Instruct subjects to contact and return to the clinic if home BP readings are above thresholds provided by the investigator.
(y) Study days/weeks and visit windows should be calculated after Randomization and should be calculated from the day of first dose treatment (Day 1).

9.3.1 Screening (Visit 1)

Subjects will be screened for enrollment prior to discontinuing previous antihypertensive treatment or initiating the placebo run-in. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.13 for procedures for documenting screening failures.

Procedures to be completed at Screening/Visit 1 include:

- Informed consent/assent.
- Demographics, medical history, and medication history.
- Physical examination.
- Tanner stage documentation. Previous medical history documentation is acceptable if assessment was performed within the previous 6 months.
- Vital signs (including standing measurements).
- Weight, height.
- Concomitant medications.
- Concurrent medical conditions.
- PTE assessment.
- Screening clinical laboratory tests.
- Urine alcohol drug screen (required only for subjects ≥12 years old; may be performed for younger children if deemed appropriate by the investigator).
- Serum and urine (performed at the site) pregnancy tests (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- 12-Lead ECG procedure.
- IVRS/IWRS access to obtain subject number.
- Inclusion/exclusion criteria.

Subjects who are ineligible for the study will be contacted by the Investigator or designee and informed that they did not meet study criteria. See Section 9.1.13 for procedures for documenting screening failures.

9.3.2 Washout (Day -14 through Day -1)

If the subject is currently taking antihypertensive medication, the subject will require a 14-day washout. Subjects should not begin washout until all applicable inclusion and exclusion criteria,

including laboratory results, have been verified. β-blockers should be tapered off gradually during the first week of the washout. Therefore, all currently treated subjects will have a minimum of 7 drug-free days prior to their qualifying clinic seDBP assessment and subsequent randomization.

The washout will coincide with the Placebo Run-in.

9.3.3 Run-in (Day -14 through Day -1)

After clinical laboratory tests results are available and eligibility criteria have been verified (except inclusion criterion #4 and exclusion criterion #6) qualified subjects will enter a 2-week, single-blind placebo run-in. For currently treated subjects, the Run-in will coincide with the Washout. Subjects should take single-blind study medication for 14 days (±5 days), unless an extended washout is needed.

If the subject fails to meet the inclusion and exclusion criteria after starting single-blind placebo run-in study medication, including during the optional extension(s) (washout/run-in may be extended in 1 week increments up to 2 times for currently treated subjects only), they are considered a run-in failure. The procedure for documenting run-in failures is provided in Section 9.1.14.

Run-in will consist of the following 2 visits.

9.3.3.1 Run-in, Day -14 (Visit 2)

Procedures to be completed at Day -14/Visit 2 include:

- Vital signs (including standing measurements).
- Inclusion/exclusion criteria.
- Concomitant medications.
- PTE assessment.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- IVRS/IWRS access for single-blind placebo run-in medication assignment and to register study visit.
- Discontinuation/tapering of antihypertensive medications (currently treated subjects).
- Dispensing of single-blind placebo run-in medication with dosing instructions.
- Administration of the first dose of single-blind placebo run-in medication in the clinic.

9.3.3.2 Run-in, Day -1 (Visit 3)

This visit will only be required for subjects participating in the ABPM procedure. All other subjects will be assessed at Visit 4. See Section 9.3.4.

Procedures to be completed at Day -1/Visit 3 include:

- Vital signs (including standing measurements) (mean clinic seated DBP must be ≥95th percentile by age, gender, and height or ≥90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present for the ABPM to be initiated).
- Weight and height.
- Concomitant medications.
- AE assessment.
- Collection of single-blind placebo run-in study medication and assessment of subject compliance with dosing. If required, counsel subject or parent/legal guardian on compliance. (See Exclusion Criterion 6)
- Inclusion/exclusion criteria.
- In-clinic dose with single-blind placebo run-in study medication.
- Initiation of 24-hour ABPM immediately after dosing.
- Re-dispensing of placebo single-blind study medication.

If a subject's seDBP remains <95th percentile for age, gender, and height or <90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present after Washout/Placebo Run-in (ie, does not satisfy inclusion criterion #4 on Day -1), the washout may be extended in 1-week increments up to 2 times, for a maximum possible washout of 4 weeks (currently treated subjects only), as long as SBP also remains below this threshold. Placebo should be continued during the extension(s). Subjects whose seDBP remains <95th percentile or <90th percentile if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present after the extensions will not be eligible for randomization to the DB Phase and shall be discontinued from the study and referred back to their treating physicians to resume appropriate antihypertensive treatment.

9.3.4 Double-Blind Phase

9.3.4.1 Randomization/Visit 4

Randomization to the DB Phase will take place on Day 1. The following procedures will be performed and documented during randomization:

- ABPM removal (subjects who participated in this procedure).

- Vital signs (including standing measurements).
- Height and weight (only for subjects who did not complete Visit 3).
- Concomitant medications. If the subject received excluded medications listed in Section 7.3 during the placebo run-in phase, the subject cannot be randomized and will be classified as a run-in failure. The procedure for documenting run-in failure is provided in Section 9.1.14.
- AE assessment.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential). Test must be negative before the subject can be randomized.
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Collection of single-blind placebo run-in study medication and assessment of subject compliance with dosing (See Exclusion Criterion 6). If required, counsel subject or parent/legal guardian on compliance.
- Inclusion and exclusion criteria assessment (before randomization to treatment).
- Clinical laboratory tests.
- Pharmacokinetic sampling.
- IVRS/IWRS access to randomize the subject to the DB Phase and to dispense double-blind study medication.
- Dispensing of double-blind study medication with dosing instructions.
- Administration of in-clinic first dose of double-blind study medication.

For subjects who did not participate in the ABPM procedure, if the subject's seDBP remains <95th percentile for age, gender, and height or <90th percentile by age, gender, height if chronic renal disease, diabetes, heart failure or hypertensive target organ damage is present after the Washout/Placebo Run-in Phase (ie, does not satisfy inclusion criterion #4 on Day 1), the washout may be extended in 1-week increments up to 2 times (currently treated subjects only), for a maximum possible washout of 4 weeks, as long SBP also remains below this threshold. Placebo should be continued during the extension(s). Subjects whose seDBP remains below the entry criteria after the extensions will not be eligible for randomization to the DB Phase and shall be discontinued from the study and referred back to their treating physicians to resume appropriate antihypertensive treatment.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS system, as described in Section 8.3. The procedure for documenting run-in failures is provided in Section 9.1.14.

9.3.4.2 Double-Blind Phase-Week 2/Visit 5

Visit can occur within a ± 2 day window. The following procedures will be performed.

- Vital signs (including standing measurements).
- Concomitant medications.
- AE assessment.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Collection of double-blind study medication and compliance assessment. If required, counsel subject or parent/legal guardian on compliance.
- IVRS/IWRS access to dispense double-blind study medication and register study visit.
- Administration of the first dose of the newly assigned double-blind study medication in the clinic.
- Dispensing of new supply of double-blind study medication with dosing instructions.

9.3.4.3 Double-Blind Phase-Week 4/Visit 6

Visit can occur within a ± 2 day window. The following procedures will be performed.

- Vital signs (including standing measurements).
- Concomitant medications.
- AE assessment.
- Clinical laboratory tests (renal subpanel).
- Pharmacokinetic sampling.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Collection of double-blind study medication and compliance assessment. If required, counsel subject or parent/legal guardian on compliance.
- IVRS/IWRS access to dispense double-blind study medication and register study visit.
- Administration of the first dose of the newly assigned double-blind study medication in the clinic.

- Dispensing of new supply of double-blind study medication with dosing instructions.

9.3.4.4 Double-Blind Phase – Week 6 -1Day/Visit 7

Visit 7 is only required for subjects who had a Baseline ABPM that met quality criteria. The following procedures will be performed.

- Vital signs (including standing measurements).
- Concomitant medications.
- AE assessment.
- Collection of double-blind study medication and compliance assessment. If required, counsel subject or parent/legal guardian on compliance.
- In-clinic dose with double-blind study medication.
- Initiation of 24-hour ABPM immediately after dosing.
- Re-dispensing of double-blind study medication.

9.3.4.5 Double-Blind Phase- Week 6/Visit 8

Randomization to the Withdrawal Phase will take place at this visit. Visit can occur within a ± 2 day window. The following procedures will be performed:

- 24-hour ABPM removal (subjects who had ABPM initiated at Visit 7).
- Vital signs (including standing measurements).
- Concomitant medications.
- AE assessment.
- Clinical laboratory tests.
- Pharmacokinetic sampling.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Collection of double-blind study medication and compliance assessment. If required, counsel subject or parent/legal guardian on compliance.
- IVRS/IWRS access to randomize the subject to the Withdrawal Phase and to dispense double-blind study medication.
- Dispensing of double-blind study medication with dosing instructions.

- Administration of in-clinic dose of double-blind study medication.

9.3.5 Withdrawal Phase – Week 8/Visit 9

Assessments scheduled for Visit 9 should be completed for all subjects who are randomized and (safety permitting) for those who withdraw early from the DB Phase or Withdrawal Phase. Visit can occur within a ± 2 day window. The following procedures will be performed:

- Vital signs (including standing measurements).
- Weight and height.
- Concomitant medications.
- AE assessment.
- Clinical laboratory tests.
- Physical exam.
- 12-lead ECG.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Urine alcohol drug screen (required only for subjects ≥12 years old; may be performed for younger children if deemed appropriate by the investigator). Results must be negative for the subject to continue in the study.
- Collection of double-blind study medication and compliance assessment. If required, counsel subject or parent/legal guardian on compliance.
- IVRS/IWRS access to dispense OL study medication and register study visit (or to record early termination for subjects being terminated).
- Dispensing of OL study medication with dosing instructions.
- Administration of in-clinic first dose of OL study medication.
- Dispensing of HBPM device.
- Dispensing of BP diary.

If a subject participating in the ABPM procedure terminates early from the study and the subject (a) had a passing baseline ABPM, (b) has not been without study medication and (c) has completed at least 4 weeks of active treatment, the site should attempt to complete the early termination ABPM prior to discontinuing study medication (subject safety permitting).

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page upon completion or early termination.

9.3.6 Open-Label Phase

9.3.6.1 Open-Label Phase-Week 12/Visit 10, Week 20/Visit 11, Week 28/Visit 12, Week 36/Visit13 and Week 44/Visit 14

Visits can occur within a ± 5 day window. The following procedures will be performed.

- Vital signs (including standing measurements).
- Weight and height.
- Concomitant medications.
- AE assessment.
- Clinical laboratory tests (Visits 11 and 13 only).
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Pregnancy avoidance counseling (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Collection of OL study medication and assess compliance. If required, counsel subject or parent/legal guardian on compliance.
- Assess need for titration of study medication or addition of other antihypertensive medications.
- IVRS/IWRS access to dispense OL study medication and register study visit.
- Dispensing of new supply of OL study medication with dosing instructions.
- Administration of the first dose of the newly dispensed OL study medication in the clinic.
- Diary review for BP measurements and re-dispensing of diary.

9.3.6.2 Open-Label Phase-Week 52 -1 Day/Visit 15

Visit 15 is optional and only for subjects who had a Baseline ABPM that met quality criteria. The following procedures will be performed.

- Vital signs (including standing measurements).
- Concomitant medications.
- AE assessment.
- Collection of OL study medication and compliance assessment. If required, counsel subject or parent/legal guardian on compliance.

- In-clinic dose with OL study medication.
- Initiation of 24-hour ABPM immediately after dosing.
- Re-dispensing of OL study medication.

9.3.6.3 Open-Label Phase-Week 52/Visit 16 (Final Visit of the Open-Label Phase or Early Termination)

Visit can occur within a ±5-day window.

Assessments scheduled for Visit 16 should be completed for all subjects who are randomized and (safety permitting) for those who withdraw early from the OL Phase. The following procedures will be performed:

- 24-hour ABPM removal (subjects who had ABPM initiated at Visit 15).
- Vital signs (including standing measurements).
- Weight and height.
- Concomitant medications.
- AE assessment.
- Clinical laboratory tests.
- Physical exam.
- 12-lead ECG.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).
- Review diary for BP measurements and collect diary.
- Access IVRS/IWRS to record study completion or early termination.
- Collect OL study medication and assess compliance

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.7 Follow-up (Week 54/Visit 17 or Follow-up visit after Early Termination Visit)

For subjects who complete the study, follow-up will begin the first day after the Final Visit and will continue until Week 54.

Early-terminated subjects who received study medication (single-blind placebo or active study medication) should return to the clinic approximately 2 weeks after the last dose of study medication. The visit can occur within a ±2-day window.

If a subject participating in the ABPM procedure terminates early from the study and the subject (a) had a passing baseline ABPM, (b) has not been without study medication and (c) has completed at least 4 weeks of active treatment, the site should attempt to complete the early termination ABPM prior to discontinuing study medication (subject safety permitting).

The following procedures will be performed for Followup (Week 54/Visit 17) or Follow-up Visit after Early Termination.

- Vital signs (including standing measurements).
- Concomitant medications.
- AE assessment.
- Urine pregnancy test performed at the site (female subjects ≥12 years old and younger females deemed by the investigator to be of reproductive potential).

9.3.8 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies to be provided as deemed appropriate by the treating physician immediately after the Final Visit (Week 52)/Early Termination.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for preexisting conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as adverse events.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as adverse events.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The principal investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with study medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Arbor Medically Significant AE List (Table 10.a).

Table 10.a Arbor Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizures	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Definitely: The AE is clearly related to the study drug. A "Definitely" assessment means there is evidence to suggest there is clear, causal relationship between the study drug and the AE.

Probably: The AE is likely to be related to the study drug. A "Probably" assessment suggests that a reasonable temporal sequence of the AE with drug administration exists, that in the investigator's clinical judgment, it is likely that a causal relationship exists between the study drug administration and the AE, and that other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

Possibly: The AE may be related to study drug. A "Possibly" assessment suggests that the association of the AE with the study medication is unknown; however, the AE is

not reasonably supported by other conditions.

Unlikely: The AE is doubtfully related to study drug. "Unlikely" suggests other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear more likely to explain the reported AE.

Unrelated: The AE is clearly not related to the study drug.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

10.1.8 The relationship should be assessed according to causality scale in Section 10.1.6. Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/ PTEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/serious PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/serious PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject or parent/legal guardian signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day -14/Visit 2) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day -14/Visit 2). Routine collection of AEs will continue until the follow-up visit (Week 54/Visit 17). If the subject is early terminated after study drug administration, AE collection will continue until the follow-up visit. Spontaneous reporting of SAEs will be collected for 30 days after the final dose of study medication.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects and parents/legal guardians may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (yes or no) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.

All AEs should be followed up until resolution or stabilization.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An Arbor SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator for 30 days following the AE collection period should be reported to the sponsor.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, a Liver Function Test (LFT) Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Arbor SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to monitor the conduct of the study. The DMC will consist of independent statistical and clinical consultants with expertise in the evaluation and analysis of pediatric clinical safety data. One member will serve as the chairperson. The DMC will periodically monitor safety data and AEs, and determine whether there is a sufficient cause to recommend modification or termination of the trial. Details pertaining to the DMC composition, requirements and responsibilities will be specified in the DMC Charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Arbor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent/assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being

investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement. Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The analysis populations are defined as follows:

Safety Analysis Set	All subjects who receive at least one dose of active study medication. Subjects will be analyzed according to the study medication they received for the study phase being summarized.
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 double-blind study medication for the respective study phase. Subjects will be analyzed according to the treatment group to which they are randomized.
Per Protocol Set (PPS)	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.
Pharmacokinetic Set	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 in plasma.

The FAS will be the primary data set used for efficacy analyses of the DB Phase and the Withdrawal Phase, unless otherwise specified. Efficacy analyses using the PPS will also be performed where appropriate. All routine safety analysis will be based on the Safety Analysis Set. All analysis of data (ie, efficacy and safety) from the OL Phase will use the Safety Analysis Set and subjects will be summarized overall (ie, all subjects together) and by status of additional antihypertensive use (ie, AZM alone versus AZM plus additional antihypertensives).

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (eg, age, race, gender, height, weight, kidney function, and hypertension diagnosis) will be summarized using descriptive statistics for each study phase by treatment group and overall (eg, mean, SD, median, minimum and maximum values, and the number and percentage of subjects in specified categories). Unless otherwise specified, baseline

values used to summarize all 3 phases (DB, withdrawal and open-label) will be the last obtained value prior to treatment in the DB phase.

13.1.3 Efficacy Analysis

Unless otherwise specified all statistical tests will be 2-sided, and p-values will be rounded to 3 significant digits prior to accessing for statistical significance at the 0.05 level

The primary analysis for the primary endpoint, change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase in clinic seDBP, will be an analysis of covariance (ANCOVA) model with treatment (AZM low, med, high and placebo), age (Tanner stage <3, ≥3) and weight (<50 kg, ≥50 kg) as fixed effects, and Week 6/Final Visit of the DB Phase seDBP as covariate. For the primary analysis the placebo group will exclude subjects that were treated with losartan during the DB Phase. The primary comparison, mean (ie, pooled) AZM effect versus placebo, will be made using 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 following sequential testing procedure will be employed in the analysis of the primary endpoint using the above described ANCOVA model and contrast 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 .

The primary analysis will use multiple imputations for missing data, supported by sensitivity analysis using observed data. Multiple imputations 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 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.

Secondary endpoints, change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the Withdrawal Phase for clinic seSBP and MAP, will be analyzed using an ANCOVA model and contrast statements similar to what was used for the primary endpoint analysis, except the relevant baseline covariate term will be used in the analysis. These analyses will be performed without using the sequential testing procedure.

The analysis for the secondary endpoint, change from baseline to Week 6/Final Visit of the DB Phase, will be mixed models for repeated measure (MMRM) with treatment (AZM low, med, high dose and losartan), age (Tanner stage <3, ≥3) and weight (<50 kg, ≥50 kg) as fixed effects, and baseline seDBP as covariate. An unstructured covariance matrix will be used to model the within-subject variation-covariance errors. The primary comparison, mean (ie, 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. Additional sensitivity

analyses will be performed including ANCOVA using observed case data and last observation carried forward (LOCF). Similar analyses will be performed for the secondary endpoints change from baseline in seSBP and MAP at Week 6/Final Visit of the DB Phase and each other visit of the DB Phase. Additional analyses, e.g, similar MMRM models with different factors, for the above endpoints may be performed where appropriate.

Exploratory dose response analysis using only AZM low, med and high dose groups, for change from Baseline to Week 6/ Final Visit of the DB Phase in clinic seDBP will be performed using linear regression model with weight adjusted dose (mg/kg) as the continuous covariate. Additionally, an ANCOVA with treatment, age and weight as fixed effects, and baseline seDBP as covariate will be performed to assess between-group comparisons. Similar analyses may be performed on change from Baseline in seSBP and MAP at Week 6/Final Visit of the DB Phase and each other visit of the DB Phase.

A logistic model with treatment, age and weight as fixed effects and baseline clinic BP as covariate will be used to analyze the percent of subjects achieving target BP at Week 8/Final Visit of the Withdrawal Phase. The odds ratio and associated 95% confidence interval (CI) will be estimated. Similar logistic regression may be performed on percent of subjects achieving target BP at Week 6/Final Visit of the DB Phase. The target blood pressures (percentiles by age, gender and height) evaluated as secondary or additional endpoints include the following (at Week 6/Final Visit of the DB Phase and at Week 8/Final Visit of the Withdrawal Phase):

- seDBP <90th percentile.
- seSBP <90th percentile.
- Both seDBP<90th percentile and seSBP< 90th percentile.

Additional BP target endpoints to be tabulated (for seDBP, seSBP, and both) include:

  – <90th percentile at Week 6/Final Visit of the DB Phase and Week 8/Final Visit of the Withdrawal Phase, for subjects with CKD.
  – <50th percentile at Week 6/Final Visit of the DB Phase and Week 8/Final Visit of the Withdrawal Phase, for subjects with CKD.
  – <90th percentile at Final Visit of OL Phase, for all subjects.
  – <90th percentile at Final Visit of OL Phase, for subjects with CKD.
  – <50th percentile at Final Visit of OL Phase, for subjects with CKD.

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. Additional analysis of the SBP/DBP by ABPM will be performed where appropriate.

The efficacy analysis on DB Phase will be based on last-observation-carried-forward (LOCF) data set, unless otherwise specified. In the LOCF analysis data set, the last postbaseline double-blind observed value will be carried forward and used for all subsequent scheduled time points in the DB

Phase where data are missing (eg, the subject has missing data or has dropped out of the study). The efficacy analysis for the target BP will also be based on the LOCF data set. Sensitivity analyses on trough seDBP, seSBP, and MAP will be performed on observed values and using multiple imputation for missing trough BP data to assess the impact of LOCF methodology and drop-outs.

Subgroup analyses such as gender, race, region, diagnosis (primary versus secondary hypertension), and other important baseline factors may be performed on the primary endpoint and secondary endpoints as appropriate.

For the 44-week, OL extension phase descriptive statistics will be presented on subjects overall (ie, all subjects) and by status of additional antihypertensive use for the endpoints collected during the extension phase as follows: (a) Change from Baseline at each study visit and at the Final/End-of-Study Visit in trough clinic seSBP, seDBP, and MAP and (b) The number and percent of subjects achieving target BP at the end of the 44-week open-label extension period. Baseline for the OL Phase will be the last value prior to the first dose of study drug in the DB Phase.

13.1.4 Pharmacokinetic Analysis

A separate analysis plan will be prepared for population modeling analysis. Plasma concentration of TAK-536 at different time points will be listed for each subject by treatment and dose level and analyzed using population pharmacokinetic modeling as appropriate and reported separately. The relationship between pharmacokinetic parameters and covariates such as body weight, age, and other factors will be explored as appropriate. A pharmacokinetic-pharmacodynamic model may also be developed to assess concentration and blood pressure response.

13.1.5 Safety Analysis

Safety analyses will be presented separately for the different study phases (ie, DB, Withdrawal, and OL Phases) and where applicable, phases may be pooled together. Summaries for the DB and Withdrawal Phases will be by Overall (ie, 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 (ie, AZM alone and AZM plus additional antihypertensive). 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.

AEs will be summarized using the safety analysis set. Coding of all AEs will be performed using MedDRA. Data will be summarized using preferred term and primary system organ class. TEAEs will be defined as any AEs, regardless of relationship to study drug, that occur after the first dose of study drug and no more than 14 days (30 days for SAEs) after the last dose of study drug. TEAEs will be displayed in summary tables. Drug-related AEs will be defined as any AEs that are considered by the investigator to be related to study drug. TEAEs will also be presented by

causality (relationship to study drug) and intensity (mild, moderate, and severe). Serious TEAEs, TEAEs leading to study drug discontinuation; and all AEs leading to death will also be summarized using preferred term and system organ class.

For each laboratory parameter, at each scheduled time point over the course of the study (eg, at each visit), the following will be displayed for the absolute values and for the change from Baseline values: number of subjects, mean, SD, minimum, median, maximum. Markedly abnormal laboratory values will be tabulated (n and %). The number and percent of subjects with marked abnormality in each of the laboratory parameters will be presented. In addition, shift tables will be presented showing the number of subjects with low, normal, or high values according to the central laboratory reference ranges at Baseline and at the scheduled time points. The number of subjects in each of the combinations of shifts will be presented. Laboratory data collected more than 7 days after the last dose of study medication will be excluded from the summaries but will be listed. A listing of all laboratory data will be provided.

The other safety variables will be summarized by descriptive statistics (eg, number of subjects, mean, SD, median, minimum and maximum values, and the number and percentage of subjects in specified categories).

13.2 Interim Analysis and Criteria for Early Termination

A formal interim analysis will be performed after all subjects have completed the Withdrawal Phase and after complete and final data (ie, 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 Withdrawal and DB Phases. Since this interim analysis will be performed on final data for the Withdrawal and DB Phases no alpha spending correction will be needed.

13.3 Determination of Sample Size

Prior to study start:

Assuming an SD of 10.5 mm Hg and an overall 10% dropout rate (ie, 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:

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 (ie, 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).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent/assent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator or designee should consult with the regional medical monitor or CRA (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements. In addition, the responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be complete and signed before the investigator may participate in this study.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the informed consent and assent forms, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent and assent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor or designee will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent and assent forms, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, Subject Assent and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent and assent forms and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent and assent is given. The informed consent and assent forms will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent and assent forms and, if applicable, the subject authorization form. The informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form, whenever possible, and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and assent form (if applicable) and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent/assent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent and assent forms and subject authorization (if applicable) at the time of consent/assent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject/parent/legal guardian signs the informed consent/assent in the subject's medical record. Copies of the signed informed consent and assent

forms, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent and assent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent and assent. The date the revised consent and assent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent and assent forms.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and

review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Arbor will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. Arbor contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

Any investigator who objects to Arbor providing this information to callers must provide Arbor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Arbor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. Edarbi (azilsartan medoxomil) Tablets. Full Prescribing Information. Takeda Pharmaceuticals America, Inc., Revised October 2012.
2. Edarbi (azilsartan medoxomil) Tablets. Full Prescribing Information. Mexico City, Mexico: Takeda Pharmaceuticals Mexico, S.A de C.V Revised June 2011.
3. Edarbi 20, 40, and 80 mg tablets. Summary of Product Characteristics. London, UK: Takeda Global Research and Development Centre (Europe), Ltd., Revised 04/2012.
4. Edarbi (azilsartan medoxomil). Product Monograph. Mississauga, Ontario, Canada: Takeda Canada, Inc., Revised March 2012.
5. National High Blood Pressure Education Program The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 Suppl 4th Report):555-76.
6. Chiolero A, Paccaud F, Bovet P. Pre-hypertension and hypertension among adolescents of Switzerland. J Pediatr 2007;151(6):e24-5.
7. Genovesi S, Giussani M, Pieruzzi F, Vigorita F, Arcovio C, Cavuto S, et al. Results of blood pressure screening in a population of school-aged children in the province of Milan: role of overweight. J Hypertens 2005;23(3):493-7.
8. Nawrot TS, Hoppenbrouwers K, Den Hond E, Fagard RH, Staessen JA. Prevalence of hypertension, hypercholesterolemia, smoking and overweight in older Belgian adolescents. Eur J Public Health 2004;14(4):361-5.
9. Kardas P, Kufelnicka M, Herczynski D. Prevalence of arterial hypertension in children aged 9-14 years, residents of the city of Lodz. Kardiol Pol 2005;62(3):211-6; discussion 6-7.
10. Portman RJ, McNiece KL, Swinford RD, Braun MC, Samuels JA. Pediatric hypertension: diagnosis, evaluation, management, and treatment for the primary care physician. Curr Probl Pediatr Adolesc Health Care 2005;35(7):262-94.
11. Luma GB, Spiotta RT. Hypertension in children and adolescents. Am Fam Physician 2006;73(9):1558-68.
12. Falkner B. Hypertension in children. Pediatr Ann 2006;35(11):795-801.
13. Temple ME, Nahata MC. Treatment of pediatric hypertension. Pharmacotherapy 2000;20(2):140-50.
14. Cromwell PF, Munn N, Zolkowski-Wynne J. Evaluation and management of hypertension in children and adolescents (part two): evaluation and management. J Pediatr Health Care 2005;19(5):309-13.
15. Pappadis SL, Somers MJ. Hypertension in adolescents: a review of diagnosis and management. Curr Opin Pediatr 2003;15(4):370-8.

16. Blowey DL. Safety of the newer antihypertensive agents in children. Expert Opin Drug Saf 2002;1(1):39-43.

17. Sinaiko AR. Hypertension in children. N Engl J Med 1996;335(26):1968-73.

18. TAK-491 Investigator's Brochure. 8th Edition. Takeda Global Research & Development Center, Inc., 18 November 2013 or current edition.

19. An open-label, parallel-group comparison study of single-dose pharmacokinetics of TAK 491 in subjects with varying degrees of renal impairment and their healthy matched subjects. Takeda Global Research & Development Center, Inc., Report No. TAK-491_103, 11 February 2010.

20. A phase 1, randomized, double-blind, placebo-controlled, sequential-panel, ascending, multiple-dose study of the safety, tolerability, and pharmacokinetics of high doses of TAK-491 in healthy volunteers. Takeda Global Research & Development Center, Inc., Report No. 01-06-TL-491-017, 13 November 2007.

21. A comparative single-dose pharmacokinetic and safety study of TAK-491 between infants, children, and adolescents with hypertension and healthy adults. Takeda Global Research & Development, Inc., Report No. TAK-491-109, in progress.

22. Smith PB, Li JS, Murphy MD, Califf RM, Benjamin DK, Jr. Safety of placebo controls in pediatric hypertension trials. Hypertension 2008;51(4):829-33.

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

24. Cozaar (losartan potassium) Tablets. Full Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc., Revised September 2012.

25. Cozaar Comp 50 mg/12.5, 100 mg/12.5, and 100 mg/25 mg film-coated tables. Summary of Product Characteristics. Hertfordshire, UK: Merck Sharp & Dohme Limited, June 2012.

26. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360(9349):1903-13.

27. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338(23):1650-6.

28. McGill HC, Jr., McMahan CA, Gidding SS. Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. Circulation 2008;117(9):1216-27.

29. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003;290(17):2277-83.

30. Daniels SR, Loggie JM, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. Circulation 1998;97(19):1907-11.

31. Hanevold C, Waller J, Daniels S, Portman R, Sorof J. The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. Pediatrics 2004;113(2):328-33.

32. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med 2010;362(6):485-93.

33. Benjamin DK, Jr., Smith PB, Jadhav P, Gobburu JV, Murphy MD, Hasselblad V, et al. Pediatric antihypertensive trial failures: analysis of end points and dose range. Hypertension 2008;51(4):834-40.

34. Kikuya M, Hansen TW, Thijs L, Bjorklund-Bodegard K, Kuznetsova T, Ohkubo T, et al. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. Circulation 2007;115(16):2145-52.

35. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure monitoring and risk of cardiovascular disease: a population based study. Am J Hypertens 2006;19(3):243-50.

36. Mancia G, Omboni S, Parati G. Twenty-four hour ambulatory blood pressure in the International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT). J Hypertens 2002;20(3):545-53.

37. Mancia G, Omboni S, Parati G, Clement DL, Haley WE, Rahman SN, et al. Twenty-four hour ambulatory blood pressure in the Hypertension Optimal Treatment (HOT) study. J Hypertens 2001;19(10):1755-63.

38. Pedersen OL, Mancia G, Pickering T, Hoegholm A, Julius S, Kjeldsen SE, et al. Ambulatory blood pressure monitoring after 1 year on valsartan or amlodipine-based treatment: a VALUE substudy. J Hypertens 2007;25(3):707-12.

39. Lurbe E, Cifkova R, Cruickshank JK, Dillon MJ, Ferreira I, Invitti C, et al. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens 2009;27(9):1719-42.

40. Urbina E, Alpert B, Flynn J, Hayman L, Harshfield GA, Jacobson M, et al. Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the council on cardiovascular disease in the young and the council for high blood pressure research. Hypertension 2008;52(3):433-51.

41. Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med 2009;361(17):1639-50.

42. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20(3):629-37.

43. 2001 CDC Growth Charts: Data Table of Stature-for-age Charts. Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Examination Statistics. 24 August 2001.