Title: A Phase 3, Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 with Valsartan in Chinese Subjects with Essential Hypertension

NCT Number: NCT02480764

Protocol Approve Date: 09 May 2016

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Phase 3, Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 with Valsartan in Chinese Subjects with Essential Hypertension

TAK-491 Compared to Valsartan in Chinese Subjects with Hypertension

Sponsor:	Takeda Development Center Asia, Pte. Ltd. 21 Biopolis Road, Nucleos North Tower, Level 4, Singapore 138567
Study Number:	TAK-491_305
IND Number:	N/A **EudraCT Number:** N/A
Compound:	TAK-491 (azilsartan medoxomil)
Date:	09 May 2016 **Amendment Number: 4**

Amendment History:

Date	Amendment Number	Amendment Type	Region
27 April 2011	Initial Protocol	Not applicable	China
26 March 2013	1	Non-Substantial	China
27 January 2014	2	Substantial	China
11 December 2014	3	Substantial	China
09 May 2016	4	Substantial	China

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda sponsored Asian Pacific 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 is given in Section 3.1 and relevant guidelines will be provided to the site.

Issue	China Contact
Serious adverse event and pregnancy reporting	Quintiles Integrated Safety Management Lifecycle Safety Contact details: See Study Reference Materials
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	Quintiles Medical Services Department Contact details: See Study Reference Materials
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

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.

SIGNATURES

Electronic Signatures may be found on the last page of this document.

PPD Date

PPD Date

PPD Date

PPD Date

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.
- Appendix B - Responsibilities of the Investigator.
- I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

China

Location of Facility (Country)

1.3 Protocol Amendment 4 Summary of Changes

This document describes the changes in reference to Protocol Amendment No. 3 dated 11 December 2014.

The primary purpose of this amendment is to add Week 2 clinical laboratory tests. Minor grammatical and editorial changes are included for clarification proposes only. Full details on changes of text are given in Appendix F including detailed rationale. The following is a summary of the changes made in the amendment:

- Clinical chemistry tests, hematology tests, urinalysis, and estimated GFR were added at Week 2 (Visit 6).

  Justification: Clinical laboratory tests were added at Week 2 (Visit 6) to be consistent with the current Takeda standard. Week 2 blood draw will allow full characterization of possible early postdose laboratory parameter changes that are considered relevant for monitoring with use of an ARB class of drug, including serum creatinine, electrolytes, liver enzyme tests, CPK, and hemoglobin. Mild ALT and AST elevations above ULN (but not exceeding 3×ULN) were observed in 7 of 16 subjects on Day 11 of a phase 1 study of TAK-491 in healthy Chinese subjects.

- Testing of serum lipids was added at Week 2 (Visit 6) and Week 4 (Visit 7).

  Justification: Lipids were added to the list of serum chemistry tests and are now tested at the same time points as other serum chemistry tests.

- The definition of "trough" in the primary endpoint was changed from "22-24 hours after the previous dose" to "approximately 24 hours after the previous dose".

  Justification: For consistency with the required timing for blood pressure measurements stated in Section 9.1.5 (Vital Sign Procedures).

- The maximum volume of blood drawn at any single Visit was changed from 40 mL to 15 mL, and the approximate total amount of blood drawn for the study was changed from 185 mL for all subjects to 75 mL for male subjects and 80 mL for female subjects.

  Justification: The central laboratory only requires 15 mL of blood per Visit. Blood for all clinical laboratory tests will now be drawn at 5 Visits with the addition of Week 2 (Visit 6). An additional 5 mL of blood will be drawn on Day -14 (Visit 2) for serum pregnancy testing in female subjects only.

- A serum pregnancy test was added to Day -14 (Visit 2), and urine pregnancy tests were removed from Day -7 (Visit 3) and Week 4 (Visit 7), such that serum pregnancy tests will be performed at Screening (Visit 1), on Day -14 (Visit 2), on Day 1 (Visit 5), at Week 4 (Visit 7), and at Week 8/ET (Visit 9), and urine pregnancy tests will only be performed on Day 1 (Visit 5).

Justification: For consistency with the current Takeda standard as serum pregnancy tests are more sensitive than urine pregnancy tests.

- Treatment information for overdose of TAK-491 was updated to include the results from the TAK-491 phase 1 renal impairment study.

  Justification: It was concluded from the TAK-491 phase 1 renal impairment study that hemodialysis does not significantly remove TAK-536 or TAK-536 M-II from the systemic circulation.

- The definition of "postmenopausal" in the Contraception and Pregnancy Avoidance Procedure section (Section 9.1.9) was updated.

  Justification: To make the definition consistent with the current Takeda standard.

- The definition for an SAE of congenital anomaly was corrected in Section 10.1.4.

  Justification: To align Takeda's definition with ICH and the USFDA definitions.

Administrative and Other Changes

- The name of the responsible medical officer was updated in Section 1.1.
- The names of the signatories and/or job titles were updated in Section 1.2.
- The List of Abbreviations was updated (Section 3.3).
- "TDC" was changed to "Takeda" throughout where applicable.
- References were updated/added, including the current US prescribing information and EU Summary of Product Characteristics (SmPC).

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:
Takeda Development Center Asia, Pte. Ltd.</td><td colspan="2">Compound:
TAK-491 (azilsartan medoxomil)</td></tr>
<tr><td>Title of Protocol: A Phase 3, Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 with Valsartan in Chinese Subjects with Essential Hypertension</td><td>IND No.: Not Applicable</td><td colspan="2">EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Number: TAK-491_305</td><td colspan="3">Phase: 3</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 3, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of TAK-491 compared with valsartan over an 8 week treatment period in Chinese subjects with essential hypertension (mean, sitting clinic systolic blood pressure (SBP) ≥150 and ≤180 mm Hg on Day 1).
A subgroup of approximately 60 subjects/arm from selected sites will undergo 24-hour ABPM 2 times during the study.</td></tr>
<tr><td colspan="4">Primary Objective:
To evaluate the antihypertensive effect of TAK-491 compared with valsartan in Chinese subjects with essential hypertension.</td></tr>
<tr><td colspan="4">Secondary Objective:
To evaluate safety and tolerability of TAK-491 compared with valsartan.</td></tr>
<tr><td colspan="4">Subject Population: Subjects aged 18 and older with essential hypertension</td></tr>
<tr><td colspan="2">Number of Subjects:
Estimated total: 600 randomized
200 subjects in each treatment arm</td><td colspan="2">Number of Sites:
Approximately 20-25 sites in China</td></tr>
<tr><td colspan="2">Dose Levels:
TAK-491 40 mg QD
TAK-491 80 mg QD
Valsartan 160 mg QD</td><td colspan="2">Route of Administration:
Oral</td></tr>
<tr><td colspan="2">Duration of Treatment:
8 week double-blind treatment period</td><td colspan="2">Period of Evaluation:
7 to 14 day Screening period
14 day Single-Blind Run-in period
8 week Double-Blind Treatment period
14 day Follow-up period</td></tr>
<tr><td colspan="4">Main Criteria for Inclusion:
• The subject is treated with antihypertensive therapy and has a post-washout mean sitting clinic SBP ≥150 and ≤180 mm Hg on Day 1; or the subject has not received antihypertensive treatment within 28 days prior to Screening and has a mean sitting clinic SBP ≥150 and ≤180 mm Hg at the Screening Visit and on Day 1.
• The subject is a man or woman aged 18 years or older.
• In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.</td></tr>
</table>

- The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
- A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent through 30 days after last study drug dose**.**
- The subject has clinical laboratory test results (clinical chemistry, hematology, and complete urinalysis) within the reference range for the testing laboratory or the investigator does not consider the results to be clinically significant.
- The subject is willing to discontinue current antihypertensive medications on Day -21 or on Day -28 if the subject is on amlodipine or chlorthalidone.

Main Criteria for Exclusion:

- The subject has a mean sitting, clinic diastolic blood pressure (DBP) greater than 110 mm Hg at Day 1(after placebo run in).
- The subject is non-compliant (less than 70% or greater than 130%) with study medication during placebo run-in period.
- The subject has secondary hypertension of any etiology (eg, renovascular disease documented as the cause of hypertension, pheochromocytoma, Cushing's syndrome).
- The subject has a history of myocardial infarction, heart failure, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, hypertensive encephalopathy, cerebrovascular accident, or transient ischemic attack.
- The subject has clinically significant cardiac conduction defects (eg, third-degree atrioventricular block, sick sinus syndrome).
- The subject has hemodynamically significant left ventricular outflow obstruction due to aortic valvular disease or hypertrophic obstructive cardiomyopathy.
- The subject has severe renal dysfunction or disease (based on estimated glomerular filtration rate <30 mL/min/1.73 m^2) at Screening.
- Subject has known or suspected unilateral or bilateral renal artery stenosis.
- The subject has a history of cancer that has not been in remission for at least 5 years prior to the first dose of study drug. (This criterion does not apply to those subjects with basal cell or Stage 1 squamous cell carcinoma of the skin).
- The subject has type 1 or poorly controlled type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.5%) at Screening.
- The subject has hyperkalemia (defined as serum potassium above the normal reference range of the central laboratory) at Screening.
- The subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level of greater than 2.5 times the upper limit of normal (ULN), active liver disease, or jaundice at Screening.
- The subject has any other known serious disease or condition at Screening (or Randomization) that would compromise subject safety, might affect life expectancy, or make it difficult to successfully manage and follow the subject according to the protocol.
- The subject has a history of hypersensitivity or allergies to hypersensitivity to TAK-491 (azilsartan medoxomil), any of its excipients or other angiotension II (AII) receptor blockers (ARBs).
- If female, the subject is pregnant or lactating or intending to become pregnant during the participation in this study; or intending to donate ova during such time period.

- The subject currently is participating in another investigational study or is receiving or has received any investigational compound within 30 days prior to the first dose of the study medication.

  Note: This criterion does not apply to subjects who participated in observational studies that lacked an intervention or invasive procedure.
- The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
- The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within the past 2 years.
- The subject is taking or expected to take an excluded medication listed in Section 7.3 of the protocol.
- The subject works a night (third) shift (defined as 11 PM [2300] to 7 AM [0700]). (Only for subjects with ambulatory blood pressure monitoring (ABPM).
- The subject has an upper arm circumference <24 cm or >42 cm. (Only for subjects with ABPM.)

Main Criteria for Evaluation and Analyses:

The primary endpoint is change from baseline to Week 8 in trough (approximately 24 hours after the previous dose) sitting clinic SBP.

Secondary endpoints are:

- The change from baseline to Week 8 in trough sitting clinic DBP.
- Percentage of responders at Week 8, as defined by the following:
  a) Clinic SBP <140 mm Hg and/or reduction of ≥20 mm Hg from baseline.
  b) Clinic DBP <90 mm Hg and/or reduction of ≥10 mm Hg from baseline.
  c) a and b.
- Percentage of subjects achieving target blood pressure at Week 8, as defined by the following:
  a) Clinic SBP <140 mm Hg.
  b) Clinic DBP <90 mm Hg.
  c) Clinic SBP <140 mm Hg and DBP <90 mm Hg.
  d) Clinic SBP <130 mm Hg.
  e) Clinic DBP <80 mm Hg.
  f) Clinic SBP <130 mm Hg and DBP <80 mm Hg.

Additional endpoints are:

CCI

Statistical Considerations:

Analysis Sets:

Safety Analysis Set: All subjects who receive at least 1 dose of double-blind study medication. Subjects will be analyzed according to the study medication they received.

Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the treatment group to which they were randomized.

Subjects who were randomized more than once will be excluded from both the safety analysis set and the FAS.

Efficacy Analysis:

Unless otherwise specified, efficacy analyses will be performed using the FAS and all statistical inference will use a 2-sided 0.05 significance level. A subject will be included in the primary analyses only when there is both a baseline value and at least 1 value during the double-blind treatment period. Missing values will be imputed using last observation carried forward (LOCF) methodology. In the LOCF analysis data set, the last post-baseline double-blind observed value will be carried forward and used for all subsequent scheduled time points where data are missing (eg, the subject has missing data or has dropped out of the study).

The primary analysis will be based on an analysis of covariance (ANCOVA) model for change in clinic SBP from baseline to week 8. The model will include treatment as a fixed effect and baseline clinic SBP as a covariate. From the framework of the ANCOVA the following will be determined: treatment LS mean, LS mean for the difference between TAK-491 and valsartan, p-value and 2-sided 95% confidence intervals for the treatment difference. For the primary analysis the overall type 1 error rate of 0.05 will be controlled using the 4 step sequential test described below.

- Step 1: A test for noninferiority of TAK-491 80 mg to valsartan 160 mg will be performed using a noninferiority margin of 1.5 mm Hg. If the upper limit of the 2-sided 95% CI of the treatment difference (TAK-491 – valsartan) is not greater than 1.5 then proceed to Step 2.
- Step 2: A test for noninferiority of TAK-491 40 mg to valsartan 160 mg will be performed using a noninferiority margin of 1.5 mm Hg. If the upper limit of the 2-sided 95% CI of the treatment difference (TAK-491 – valsartan) is not greater than 1.5 then proceed to Step 3.
- Step 3: A test for significant difference between TAK-491 80 mg versus valsartan 160 mg will be performed at the 5% level. If the p-value is not greater than 0.05 then proceed to Step 4.
- Step 4: A test for significant difference between TAK-491 40 mg versus valsartan 160 mg will be performed at the 5% level.

Based on historical data, the observed placebo-corrected treatment effects on change from Baseline in clinic SBP for valsartan 160 mg once daily was -8.6 mm Hg. Therefore, the noninferiority margin was set conservatively at 1.5 mm Hg, which is less than one-third of the valsartan treatment effect. Accordingly, TAK-491 will be considered noninferior to valsartan when the upper limit of the 2-sided 95% CI of the treatment difference (TAK-491-comparator) is ≤1.5 mm Hg. The secondary endpoint, change from baseline to Week 8 in trough sitting clinic DBP will be analyzed similar to the primary endpoint, excluding the sequential testing. Change from baseline for both SBP and DBP at other visits will be summarized similar to the primary endpoint.

Additionally, similar analyses will be performed for both SBP and DBP for selected subgroups where appropriate, eg, age, sex.

The categorical secondary efficacy endpoints, percentage of subjects responding to treatment and percentage of subjects reaching blood pressure target at Week 8 will be tabulated for each of the following definitions:

- Response criteria.
  a) Clinic SBP <140 mm Hg and/or a reduction of ≥20 mm Hg from baseline.
  b) Clinic DBP <90 mm Hg and/or a reduction of ≥10 mm Hg from baseline.
  c) a and b (ie, joint criteria).
- Target blood pressure.

a) Clinic SBP <140 mm Hg.
b) Clinic DBP <90 mm Hg.
c) Clinic SBP<140 mm Hg and DBP<90 mm Hg.
d) Clinic SBP<130 mm Hg.
e) Clinic DBP<80 mm Hg.
f) Clinic SBP<130 mm Hg and DBP<80 mm Hg.

A logistic model with treatment as fixed effect and baseline clinic SBP as a covariate will be used to analyze response for clinic SBP. The odds ratio and its 95% confidence will be estimated. Similarly, a logistic model with treatment as fixed and baseline clinic DBP as a covariate will be used to analyze the response for clinic DBP. The joint response for both clinic SBP and DBP will be analyzed using a logistic model with treatment as fixed effect and baseline clinic SBP as a covariate. A similar analysis and model will be used to analyze the percentage of subjects reaching target blood pressure at Week 8. The percentage of subjects responding to treatment, as well as reaching blood pressure target, will also be presented for other visits, using the above methods.

Subgroups (eg, age, sex) analyses may be performed if data permit.

Sensitivity analyses to be performed on the primary endpoint (and other endpoints where appropriate) include: multiple imputation for missing values; analyses using the per protocol set; and analyses using observed values only.

Safety Analysis:

All safety assessments, including AEs, clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be presented in the data listings. Treatment-emergent AEs will be summarized by treatment group. Laboratory values, pulse rate, and 12-lead ECG results will be summarized with descriptive statistics and/or shift tables.

Sample Size Justification:

Assuming an SD of 17 mm Hg and a 10% dropout rate, a sample size of 200 subjects per treatment group (total of 600 subjects) is sufficient to achieve at least 90% power to detect a difference of 6 mm Hg between TAK-491 dose and valsartan by a 2-sample t-test on the mean change from baseline to Week 8 in mean sitting clinic SBP at 0.05 2-sided significance level. This sample size will also provide, for the above assumptions, at least 90% power for demonstrating noninferiority with a margin of 1.5 mm Hg between TAK-491 and valsartan.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda 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.

3.3 List of Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
AE	adverse event
AII	angiotensin II
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AT1	angiotensin II type 1 receptor
AT2	angiotensin II type 2 receptor
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CCB	calcium channel blocker
CFDA	China Food and Drug Administration
COX-2	Cyclooxygenase-2
CPAP	continuous positive airway pressure
eCRF	case report form (electronic)
CRO	contract research organization
CYP	cytochrome P-450
DBP	diastolic blood pressure
ECG	Electrocardiogram
eGFR	estimated GFR
EMA	European Medicines Agency
ESRD	end-stage renal disease
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	γ-glutamyl transferase
HbA1c	Hemoglobin A1c
hCG	human chorionic gonadotropin
HDL-C	high-density lipoprotein cholesterol
HOCM	hypertrophic obstructive cardiomyopathy
HTN	hypertension
ICH	International Conference on Harmonisation
IEC	independent ethics committee

IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
JNC	Joint National Committee
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LOCF	last observation carried forward
MAO	monamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	nonsteroidal anti-inflammatory drugs
O/E	over-encapsulated
PDE5	phosphodiesterase type 5
PPS	per-protocol analysis set
PTE	pretreatment event
QD	once daily
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half life
TAK-491	azilsartan medoxomil
TAK-536	azilsartan
TEAE	treatment-emergent adverse events
UACR	urinary albumin creatinine ratio
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

TDC Asia	Takeda Development Center Asia, Pte. Ltd.
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Asia, TDC Europe and/or TDC Americas, as applicable
TPC	Takeda Pharmaceutical Company Limited
Takeda	TDC Asia, TDC Americas, TDC Europe, and/or TPC, as applicable

4.0 INTRODUCTION

4.1 Background

According to the World Health Organization (WHO), hypertension is the most common attributable cause of preventable death in developed nations and is increasing in importance in developing countries [1], as uncontrolled hypertension greatly increases the risk of cardiovascular disease, cerebrovascular disease, and renal failure [2,3]. As the population ages, the prevalence of hypertension will continue to increase if broad and effective preventive and treatment measures are not implemented [2]. According to the current Chinese guideline for the management of hypertension, there are more than 200 million Chinese with hypertension. Despite the availability of antihypertensive agents, hypertension remains inadequately controlled. There is about 50% awareness of hypertension, the percentage of patients with hypertension receiving treatment is only 30% with only 10% with high BP controlled to below 140/90 mmHg in China [4].

Angiotensin Receptor Blockers (ARBs), such as olmesartan medoxomil and valsartan, are widely used for the treatment of hypertension and have well-established safety profiles [5]. ARBs modulate the renin-angiotensin-aldosterone system (RAAS), a system of hormone-mediated feedback interactions that results in the relaxation or constriction of blood vessels in response to various stimuli. Renin, an enzyme produced in the kidney, acts on angiotensinogen, to form angiotensin I, which is converted to angiotensin II (AII) in a reaction catalyzed by angiotensin-converting enzyme (ACE). AII is the principal pressor agent of the RAAS with effects on the cardiovascular system and electrolyte homeostasis [6]. Two receptor subtypes have been identified for AII, the angiotensin II type 1 receptor (AT1) and the angiotensin II type 2 receptor (AT2), which often have opposing actions when activated. Activation of the AT1 receptor results in vasoconstriction, hypertrophic proliferation, and inflammation, while activation of the AT2 receptor results in vasodilation and antiproliferative effects [7]. Blocking the AT1 receptor allows blood vessels to dilate, resulting in blood pressure (BP) reduction [8].

Drugs that modulate the RAAS are used globally for the treatment of hypertension (eg, ACE inhibitors, ARBs, and more recently the direct renin inhibitor, aliskiren) [8]. These and other antihypertensive agents are often effective, but many have side effects that limit their use. ACE inhibitors are associated with cough and, more rarely, with angioedema; β-blockers, with fatigue and erectile dysfunction; calcium-channel blockers (CCBs), with peripheral edema; and diuretics, with metabolic complications [9].

ARBs are generally considered to be more tolerable than other classes of antihypertensive agents and are often used to treat hypertension in patients who are intolerant of ACE inhibitors [10]. Cough and angioedema occur less frequently with ARBs than with ACE inhibitors, and common side effects such as symptomatic hypotension, flushing, tachycardia, palpitations, and dizziness, along with headache and lightheadedness, are generally mild and well tolerated [5].

There is still a need for compounds which improve tolerability and efficacy for the treatment of hypertension and therefore, TAK-491 (azilsartan medoxomil), a prodrug that is rapidly hydrolyzed

to the active moiety, TAK-536 (azilsartan), which is a highly potent, long-acting ARB is being evaluated by Takeda to treat subjects with essential hypertension.

4.2 Summary of Nonclinical Data

Nonclinical studies have indicated that TAK-491 reduces BP in rats and dogs after single or multiple daily dosing without tachycardia and without rebound hypertension after withdrawal of treatment. TAK-491 also demonstrated antiproteinuric effects in Wistar fatty rats with overt nephropathy and increased insulin sensitivity in spontaneously hypertensive rats. TAK-491 is not expected to have any untoward effects on the central nervous system or respiratory system. Its effect on the cardiovascular system in conscious dogs was limited to a reduction in systolic blood pressure (SBP), an observation consistent with the pharmacodynamic profile of the compound.

4.3 Summary of Clinical Data

After oral administration, TAK-491 is converted to the active moiety TAK-536 by ester hydrolysis in the gut and/or during the process of absorption. Conversion is rapid, as the salt free form of TAK-491 (TAK-491F) is undetectable in human plasma at the earliest time points examined (5 minutes following administration of single oral doses of TAK-491 at 40 and 80 mg and 15 minutes following multiple oral doses of TAK-491 at 320 mg). TAK-536 undergoes extensive metabolism to TAK-536 M-I and TAK-536 M-II. Following both single and multiple dosing of TAK-491 tablets, dose proportionality was established for TAK-536 and TAK-536 M-II area under the plasma concentration-time curve and maximum observed plasma concentration values over the dose range of 20 to 320 mg.

TAK-491 has been evaluated in 17 phase 1 studies and 1 phase 2 study. The phase 3 program consisted of 5 randomized, controlled, monotherapy studies of 6 weeks or 6 months duration; 2 randomized, controlled, 6-week studies in which TAK-491 was coadministered with the thiazide-like diuretic chlorthalidone or the calcium channel blocker (CCB) amlodipine; and 2 open-label studies of up to 56 weeks duration.

Dose adjustment is not needed based on age, gender, or race.

Steady-state total exposures to TAK-536 after multiple doses of TAK-491 in a phase 1 hepatic impairment study were approximately 28% and 64% greater in subjects with mild and moderate hepatic impairment, respectively, than in healthy subjects. Subjects with severe hepatic impairment were not studied. The increases in exposure to TAK-536 in the phase 1 hepatic impairment study are not considered to be clinically meaningful as TAK-491 was well-tolerated in other pharmacokinetic studies in which exposures to TAK-536 were greater than those observed in subjects with hepatic impairment. Therefore, TAK-491 dose reduction is not necessary for subjects with mild or moderate hepatic impairment, although subjects with any degree of hepatic impairment are excluded from the present study.

The single dose phase 1 study in renal impaired subjects showed that after 40 mg TAK-491 dosing, total exposure to TAK-536 tended to be higher in subjects with renal impairment than in healthy subjects with increases of 30%, 25%, 95%, and 4% in subjects with mild, moderate, or severe renal

impairment, and end-stage renal disease (ESRD), respectively. These increases in exposure to TAK-536 are not considered to be clinically meaningful, as TAK-491 was well-tolerated in a high-dose (160 to 320 mg) study in healthy subjects (01-06-TL-491-017). The mean terminal elimination half-life ($t_{1/2z}$) of TAK-536 was not substantially different in subjects with renal impairment than in healthy subjects. Therefore, no dose adjustment of TAK-491 is required for subjects with any degree of renal impairment or ESRD, although subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 (mL/min/1.73 m^2) are excluded from this study.

No clinically significant interactions have been observed with drugs that are metabolized by cytochrome P-450 (CYP) isozymes (eg, pioglitazone, glyburide, caffeine, tolbutamide, midazolam, dextromethorphan, and warfarin), with the potent CYP inhibitors (ketoconazole and fluconazole), with drugs that are excreted unchanged in urine (metformin, digoxin, and chlorthalidone), or with the P-glycoprotein substrates (fexofenadine and digoxin). There was no clinically significant interaction between TAK-491 and an aluminum-magnesium hydroxide antacid. In a study evaluating the potential effects of TAK-491 on the QT interval, TAK-491 320 mg was not associated with evidence of QT prolongation based on analyses of multiple QT interval correction formulae.

Results of the phase 3 program demonstrated that, relative to placebo, the TAK-491 20, 40, and 80 mg doses produce clinically and statistically significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP), as assessed by both ambulatory blood pressure monitoring (ABPM) and clinic blood pressure measurements. The differences between doses were greater for subgroups of subjects characterized by more severe and/or resistant hypertension, including black subjects, subjects with renal impairment, and subjects with Grade 2 hypertension. In each study, most of the blood pressure-lowering effect of TAK-491 was observed within 2 weeks of treatment; a plateau of effect was generally reached by week 4 and reductions were maintained through week 6 in short-term studies and over the long-term in two 6-month studies (and up to 1 year in open-label studies). In replicate studies, TAK-491 at 80 mg was shown to reduce systolic blood pressure more effectively than olmesartan medoxomil 40 mg and valsartan 320 mg, the highest approved doses in the US.

In two controlled studies, coadministration of TAK-491 with chlorthalidone (491-009) and amlodipine (491-010) provided additional blood pressure reduction compared with chlorthalidone or amlodipine monotherapy. In open-label studies, addition of diuretic therapy to treatment with TAK-491 led to additional blood pressure reductions in subjects who did not reach blood pressure targets after initiation of TAK-491.

In clinical trials with hypertensive subjects, treatment with TAK-491 was well-tolerated with an overall incidence of adverse reactions and withdrawals due to adverse events similar to that of placebo. Generally, adverse reactions were mild, not dose related and similar regardless of age, gender and race. The safety and tolerability profile of TAK-491 was similar to that of other agents of the ARB class. Commonly reported adverse events included headache, dizziness, urinary tract infection (UTI), nasopharyngitis and dyslipidemia; diarrhea was reported more frequently with TAK-491 than placebo. As compared with other ARBs, a higher incidence of mechanism-based

side effects of dizziness and reversible serum creatinine elevations were observed with TAK-491, which is consistent with the greater antihypertensive effect of the drug.

In summary, TAK-491 was well tolerated at doses up to 320 mg in healthy subjects and up to 80 mg in hypertensive subjects (maximal dose evaluated in this population). TAK-491 has been shown to have a strong antihypertensive effect, predictable pharmacokinetic and metabolic profiles, a prolonged duration of action, and good safety and tolerability profiles when administered as a monotherapy to hypertensive subjects. As of February 2016, TAK-491 (azilsartan medoxomil [Edarbi]) has been approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents, in a total of 59 countries worldwide, including approval in the United States by the Food and Drug Administration (FDA) in February 2011 and in the European Union by the European Medicines Agency (EMA) in December 2011.

Please refer to the TAK-491 monotherapy Investigator's Brochure [11] and Edarbi package insert [12,13] for additional information.

4.4 Rationale for the Proposed Study

Phase 3 studies have demonstrated that TAK-491 treatment at a dose of 40 mg once daily and 80 mg once daily are effective and safe in hypertensive subjects evaluated in the United States, Latin America, and Europe. This 8-week study is being conducted to compare the efficacy and safety profile of TAK-491 40 mg once daily and 80 mg once daily to that of valsartan 160 mg once daily in Chinese subjects with essential hypertension. Valsartan is a marketed, widely used ARB with well documented efficacy and safety in treatment of hypertension; the highest approved dose in China is 160 mg once daily (QD).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To evaluate the antihypertensive effect of TAK-491 compared with valsartan in Chinese subjects with essential hypertension.

5.1.2 Secondary Objective

To evaluate safety and tolerability of TAK-491 compared with valsartan.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is change from baseline to Week 8 in trough (approximately 24 hours after the previous dose) sitting clinic SBP.

5.2.2 Secondary Endpoints

- The change from baseline to Week 8 in trough sitting clinic DBP.
- Percentage of responders at Week 8, as defined by the following:
  a) Clinic SBP <140 mm Hg and/or reduction of ≥20 mm Hg from baseline.
  b) Clinic DBP <90 mm Hg and/or reduction of ≥10 mm Hg from baseline.
  c) a and b.
- Percentage of subjects achieving target blood pressure at Week 8, as defined by the following:
  a) Clinic SBP <140 mm Hg.
  b) Clinic DBP <90 mm Hg.
  c) Clinic SBP <140 mm Hg and DBP <90 mm Hg.
  d) Clinic SBP <130 mm Hg.
  e) Clinic DBP <80 mm Hg.
  f) Clinic SBP <130 mm Hg and DBP <80 mm Hg.

5.2.3 Additional Endpoints

Efficacy

- CCI [redacted]

- CCI
- [redacted]

5.2.4 Safety

AEs, safety laboratory tests, 12-lead ECG findings and vital signs (including orthostatic vital signs).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of TAK-491 compared with valsartan over an 8 week treatment period in Chinese subjects with essential hypertension (trough, sitting clinic SBP ≥150 and ≤180 mm Hg on Day 1). This study will be conducted in China at approximately 20 to 25 sites and will include approximately 600 randomized subjects.

Before initiation of treatment, all subjects will participate in a 2-week, single-blind, placebo run-in period (Days -14 to -1). Subjects who have not received antihypertensive treatment within 28 days before screening can be entered into the run-in period as soon as all inclusion and exclusion criteria, including laboratory results, have been verified. Subjects taking previous antihypertensive agents will be required to participate in a 3-week washout/placebo run-in period (Days -21 to -1). If the subject's previous antihypertensive treatment includes amlodipine or chlorthalidone, then the washout/placebo run-in must be extended to 4 weeks (Days -28 to -1). Screening (Visit 1) will be scheduled before the washout/run-in period begins so that laboratory test results can be reviewed and subject eligibility can be confirmed before other treatments are stopped or placebo is initiated. At Day -14 (Visit 2), subjects will receive the first dose of single-blind placebo in clinic.

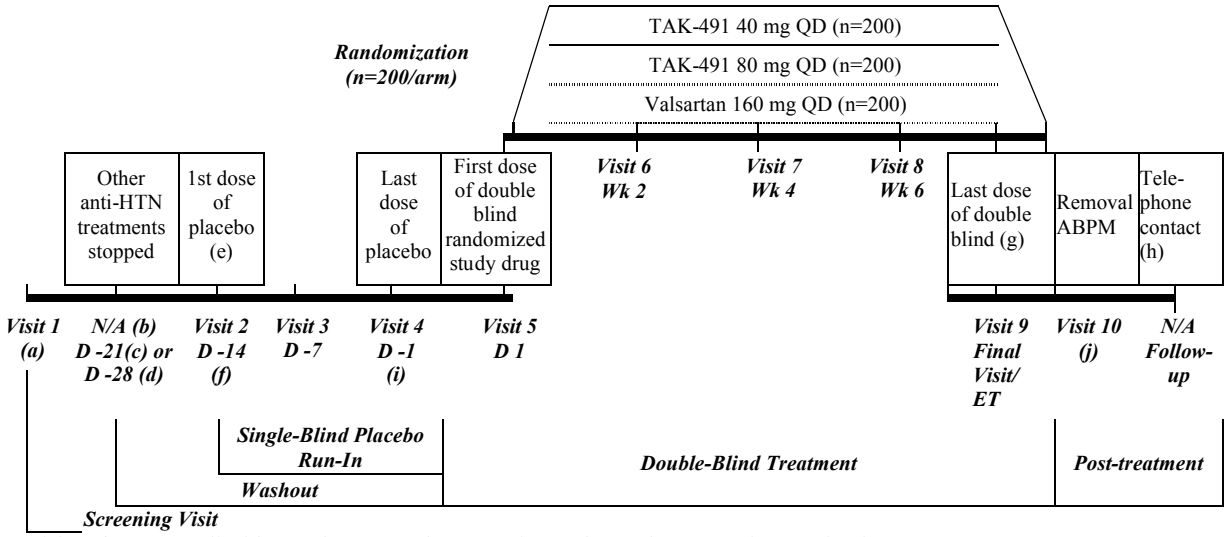
At Day 1 (Visit 5), eligible subjects will be randomly assigned to one of the following 3 groups with a 1:1:1 ratio:

- TAK-491 40 mg QD.
- TAK-491 80 mg QD.
- Valsartan 160 mg QD.

Subjects will be given the first dose of randomized study drug in the clinic at Day 1 (Visit 5). The last dose of randomized study drug will be taken the day of Week 8 visit (Visit 9). End of study assessment will be taken at Week 8/Early Termination (Visit 9). All subjects who receive study drug (placebo or double-blind) will be required to have a follow-up telephone call at approximately 14 days after the last dose.

A schematic of the study design is included as Figure 6.a.

Figure 6.a Schematic of Study Design



V=visit, N/A=not applicable, D=day, HTN=hypertension, Wk=week, ET=Early Termination.
(a) The Screening Visit should be scheduled before the washout/run-in period begins so that laboratory tests results can be reviewed and subject eligibility can be confirmed before other treatments are stopped or placebo is initiated.
(b) Subjects may be notified by telephone to begin the washout period.
(c) Subjects taking previous antihypertensive agents are required to participate in a 3-week washout/run-in period (Days -21 to -1).
(d) If the subject's previous antihypertensive treatment includes amlodipine or chlorthalidone, then the washout must be extended to 4 weeks (Days -28 to -1).
(e) The first dose of placebo will be taken at the clinic on Day -14 (Visit 2).
(f) Subjects who have not received antihypertensive treatment within 28 days prior to Screening can be entered into the run-in period as soon as all inclusion and exclusion criteria, including laboratory results, have been verified.
(g) Last dose of double-blind is the day of Week 8/Final clinic visit or ET (Visit 9). And, in subgroup of ABPM subjects will start 24-hour ABPM measurement.
(h) The follow-up telephone contact should be made approximately 14 days after the last dose.
(i) Visit 4 only applies to ABPM subgroup subjects; start 24-hour ABPM measurement.
(j) Visit 10 only applies to ABPM subgroup subjects.

A schedule of assessments is provided in Appendix A.

6.2 Justification for Study Design, Dose, and Endpoints

TAK-491 is a prodrug that is rapidly hydrolyzed to the active moiety, TAK-536, which is a long-acting, angiotensin II AT1 receptor blocker (ARB). TAK-491 has been shown to have a strong antihypertensive effect, predictable pharmacokinetic and metabolic profiles, a prolonged duration of action, and good safety and tolerability profiles when administered as a monotherapy to hypertensive subjects. The phase 3 TAK-491 studies have shown that TAK-491 80 mg reduced blood pressure more effectively than olmesartan medoxomil 40 mg and valsartan 320 mg, the highest approved doses in the US. As of February 2016, TAK-491 has been approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents, in a total of 59 countries worldwide, including approval in the United States by the Food and Drug Administration (FDA) in February 2011 and in the European Union by the European Medicines Agency (EMA) in December 2011.

The objective of this phase 3, randomized, double-blind, parallel-group study of 8 weeks duration is to examine the efficacy and safety of TAK-491 compared to valsartan in Chinese subjects with mild to moderate essential hypertension. Since the intended registration doses for TAK-491 in China will be 40 mg and 80 mg, these were the TAK-491 doses selected for this study. Valsartan is a marketed, widely used ARB with known efficacy in mild to moderate essential hypertension and the highest approved dose in China is 160 mg, with 320 mg as the highest approved dose in other regions (United States, European Union, etc).In addition in Takeda's global studies (TAK-491-019 and 301), TAK-491 40 mg and 80 mg were evaluated in comparison with 320 mg of valsartan. Based on these considerations, and to reflect standard of care practices in China, 40 mg and 80 mg TAK-491 were selected for comparison with 160 mg of valsartan in this study.

The 8 week duration is sufficient to evaluate the efficacy because in all previous studies, a plateau in blood pressure reduction was observed after 4 weeks of treatment for both TAK-491 and valsartan. The study design employs a 3 to 4 week washout period to establish a true drug-free baseline blood pressure and to determine severity of hypertension in enrolled population at randomization. A coincident 2-week, single-blind, placebo run-in period is to evaluate study drug compliance. This short-term washout/placebo treatment period is not associated with increased risk of major irreversible cardiovascular events in a hypertensive population [14,15].

Frequent visits and withdrawal criteria for elevated BP during the study as defined in Section 7.5 will further ensure the safety of the study subjects.

The primary endpoint of this study is sitting, clinic SBP, which is a well-established measure for assessing antihypertensive effect and is a better predictor of cardiovascular outcomes than DBP. Clinic SBP is an appropriate primary endpoint because it is validated as a surrogate endpoint in observational and interventional clinical studies [16-18].

ABPM parameters will also be evaluated in a subset of approximately 60 patients per arm. ABPM parameters are clinically more predictive of cardiovascular outcome than clinic BP measurements, as demonstrated by numerous studies. In particular, mean 24-hour SBP is the best predictor of cardiovascular risk, even after adjustment for risk factors including clinic BP [19-21].

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.
- 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 Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (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.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is treated with antihypertensive therapy and has a post-washout mean sitting clinic SBP ≥150 and ≤180 mm Hg on Day 1; or the subject has not received antihypertensive treatment within 28 days prior to Screening and has a mean sitting clinic SBP ≥150 and ≤180 mm Hg at the Screening Visit and on Day 1.
2. The subject is a man or woman aged 18 years or older.
3. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
4. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent through 30 days after last study drug dose.

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

6. The subject has clinical laboratory test results (clinical chemistry, hematology, and complete urinalysis) within the reference range for the testing laboratory or the investigator does not consider the results to be clinically significant.
7. The subject is willing to discontinue current antihypertensive medications on Day -21 or on Day -28 if the subject is on amlodipine or chlorthalidone.

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 mean, sitting clinic DBP greater than 110 mm Hg at Day 1 (after placebo run in).
2. The subject is non-compliant (less than 70% or greater than 130%) with study medication during placebo run-in period.
3. The subject has secondary hypertension of any etiology (eg, renovascular disease documented as the cause of hypertension, pheochromocytoma, Cushing's syndrome).

4. The subject has a history of myocardial infarction, heart failure, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, hypertensive encephalopathy, cerebrovascular accident, or transient ischemic attack.
5. The subject has clinically significant cardiac conduction defects (eg, third-degree atrioventricular block, sick sinus syndrome).
6. The subject has hemodynamically significant left ventricular outflow obstruction due to aortic valvular disease and hypertrophic obstructive cardiomyopathy (HOCM).
7. The subject has severe renal dysfunction or disease (based on estimated glomerular filtration rate [GFR] <30 mL/min/1.73 m^2) at Screening.
8. The subject has known or suspected unilateral or bilateral renal artery stenosis.
9. The subject has a history of cancer that has not been in remission for at least 5 years prior to the first dose of study drug. (This criterion does not apply to those subjects with basal cell or Stage 1 squamous cell carcinoma of the skin).
10. The subject has type 1 or poorly controlled type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.5%) at Screening.
11. The subject has hyperkalemia (defined as serum potassium above the normal reference range of the central laboratory) at Screening.
12. The subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level of greater than 2.5 times the upper limit of normal (ULN), active liver disease, or jaundice at Screening.
13. The subject has any other known serious disease or condition at Screening (or Randomization) that would compromise subject safety, might affect life expectancy, or make it difficult to successfully manage and follow the subject according to the protocol.
14. The subject has a history of hypersensitivity or allergies to TAK-491 (azilsartan medoxomil), any of its excipients or other angiotension II (AII) receptor blockers (ARBs).
15. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study; or intending to donate ova during such time period.
16. The subject currently is participating in another investigational study or is receiving or has received any investigational compound within 30 days prior to the first dose of study medication.

    Note: This criterion does not apply to subjects who participated in observational studies that lacked an intervention or invasive procedure.
17. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

18. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within the past 2 years.
19. The subject is taking or expected to take an excluded medication listed in Section 7.3 of the protocol.
20. The subject works a night (third) shift (defined as 11 PM [2300] to 7 AM [0700]). (Only for subjects with ABPM)
21. The subject has an upper arm circumference <24 cm or >42 cm. (Only for subjects with ABPM)

7.3 Excluded Medications and Treatments

- Antihypertensive agents, including those used for treatment of other conditions, such as benign prostatic hyperplasia (α-blockers) or edema (diuretics). Those used at screening must be discontinued for the washout/run-in period through the completion of final in-clinic procedures at Week 8/Early Termination (Visit 9). Amlodipine and chlorthalidone should be discontinued on Day -28, while all other antihypertensive medications should be discontinued on Day -21. If necessary, medications that need to be stopped gradually may be tapered in the first week of screening, but must be discontinued completely by Day -14.
- Other agents that alter BP are excluded from the beginning of the run-in period through the remainder of the study. These include:
  - Tricyclic antidepressants.
  - Monoamine oxidase (MAO) inhibitors.
  - Central nervous system stimulants.
  - Amphetamines or their derivatives.
  - Dopamine agonists.
  - Atypical antipsychotic agents.
  - Trazodone.
  - Lithium.
  - Diet medications (except orlistat).
  - Nitrates.
  - Thiazolidinediones.
- Conditionally excluded medications as specified:
  - Phosphodiesterase type 5 (PDE5) inhibitors within 72 hours of a clinic visit.

  - Chronically used (defined as more than 3 doses per week) common cold medications with pseudoephedrine or phenylephrine, or nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin >325 mg/day or cyclooxygenase-2 (COX-2) inhibitors.
  - Systemic use of corticosteroids (topical or inhaled is acceptable).
- Subjects will be instructed not to take any medications, including over-the-counter products, without first consulting the investigator.

7.4 Diet, Fluid, Activity Control

Subjects should be encouraged to avoid foods high in sodium and avoid adding extra salt to food since excessive sodium consumption may elevate blood pressure in certain individuals. Otherwise, subjects should maintain their usual diet prior to, and during the study.

For a subject with signs of volume depletion, such as weight loss or orthostatic hypotension (BP decreases by ≥20 mm Hg systolic or ≥10 mm Hg diastolic after standing for 2 minutes), inquire about other sources of volume loss (eg, diarrhea, vomiting, poor oral intake). If there is evidence of volume depletion, consider temporarily liberalizing salt intake and encouraging increased hydration. If these measures do not alleviate the orthostatic hypotension, the case should be discussed with the medical monitor and the subject considered for withdrawal.

After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period, and will be instructed to fast for at least 8 hours prior to returning to the study site for Day 1 (Visit 5), Week 2 (Visit 6), Week 4 (Visit 7), and Week 8/ET (Visit 9).

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 case report form (electronic) (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.12.

1. Pretreatment event or adverse event (AE). The subject has experienced a pretreatment event 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 pretreatment event or AE.
2. Major protocol deviation. The discovery post randomization 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 (e)CRF.

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 mean blood pressure exceeds 180 mm Hg systolic and/or 110 mm Hg diastolic at any time after screening or randomization, the blood pressure measurement should be repeated within 48 hours. If blood pressure remains elevated, the subject should be considered for withdrawal.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

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.

- TAK-491 40 mg and matching placebo tablets.
- TAK-491 80 mg and matching placebo tablets.
- Valsartan 80 mg and matching placebo capsules.

8.1.1.1 Investigational Drug

TAK-491 and Matching Placebo Tablets

TAK-491 study medication is manufactured by Takeda Pharmaceutical Company, Osaka, Japan and will be supplied as white, round 40 mg or 80 mg tablets with matching placebo tablets.

TAK-491 study medication will be foil/foil blistered and packaged in 20-day (2 week plus 6 additional spare daily doses) child resistant, blister cards containing 40 tablets with 40 desiccants. Each tablet is connected to a desiccant through a linked channel during the blistering process. Each blister card for the single blind treatment period will contain twenty placebo for TAK-491 40 mg tablets and twenty placebo for TAK-491 80 mg tablets. Each blister card for the blinded treatment periods will contain twenty TAK-491 40 mg, twenty TAK-491 80 mg or matching placebo tablets. The daily dose will be 2 tablets.

Each blister card label will be compliant with requirements of the China Food and Drug Administration, P.R., China (CFDA).

Valsartan and Matching Placebo Capsules

Valsartan 80 mg capsules will be manufactured by Novartis Pharmaceuticals Corp., China

Valsartan capsules will be over-encapsulated (O/E) and placebo capsules will be manufactured by Fisher Clinical Services. The capsules will be Swedish Orange Opaque, Size AAeL, DBcaps. The capsules will be packaged in 120 cc wide-mouth, pharmaceutical-grade, round, white, high-density polyethylene bottles with a 38 mm child-resistant cap with 75M induction seal.

Each bottle for the single blind placebo run-in period will contain 40 placebo capsules. Each bottle for the treatment period will contain 40 O/E valsartan 80 mg or matching placebo capsules. The daily dose will be 2 capsules (160 mg) to support the study design.

Each bottle label will be compliant with requirements of the China Food and Drug Administration, P.R, China (CFDA).

8.1.1.2 Sponsor-Supplied Drug

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

- TAK-491 40 mg and matching placebo tablets.
- TAK-491 80 mg and matching placebo tablets.
- Valsartan 80 mg and matching placebo capsules.

8.1.1.3 Ancillary Materials

ABPM devices will be supplied to the designated sites by the sponsor.

The investigator or designee must ensure that the sponsor-supplied device is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. The investigator must maintain records of all sponsor-supplied device delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee after the subjects complete the study.

8.1.2 Storage

TAK-491 investigational study drugs should be stored at 25°C (77°F); with excursions permitted to 15-30°C (59-86°F). Study medication is to remain stored in the original container until time of dosing.

Valsartan and matching placebo study drug should be stored at 25°C (77°F); with excursions permitted to 15-30°C (59-86°F). Protect from moisture.

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.

8.1.3 Dose and Regimen

This is a phase 3, multicenter, randomized, double-blind, parallel-group, 8-week efficacy and safety study comparing TAK-491 and valsartan.

Subjects will be randomized to 1 of the following 3 therapy treatment groups as follows:

- TAK-491 40 mg QD (N=200).
- TAK-491 80 mg QD (N=200).
- Valsartan 160 mg QD (N=200).

Study medication will be packaged in a manner to maintain the blind.

Placebo Run-in Period (Day-14 [Visit 2] to Day -1)

- Subjects will be dispensed one 2-week blister card and one bottle.
- Subjects will receive single-blind placebo tablets and placebo capsules.
- First dose will be given in-clinic at Day -14 (Visit 2).
- The daily oral administered dose will be two tablets from a blister card and two capsules from the bottle.

Treatment Period (Day 1 [Visit 5] through Week 8 / Early Termination [Visit 9])

- Subjects will receive blinded study medication and will be instructed to take their blinded study medication prior to their first meal of the day. Subjects will be dispensed one 2-week carton and one bottle at day 1 (Visit 5), at week 2 (Visit 6), week 4 (Visit 7), and week 6 (Visit 8).
- First dose will be given in-clinic at Day 1 (Visit 5).
- The daily oral administered dose will be two tablets from a blister card and two capsules from the bottle.

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

Table 8.a Sponsor-Supplied Drug

Treatment Group	Dose	Treatment Description	
		Active	Placebo
	Run-in QD	Zero active tablets/capsules	One placebo for 40 mg TAK-491 tablet, one placebo for 80 mg TAK-491 tablet, two placebo for 80 mg valsartan capsules
A	40 mg TAK-491 QD	One 40 mg TAK-491 tablet	One placebo for 80 mg TAK-491 tablet, two placebo for 80 mg valsartan capsules
B	80 mg TAK-491 QD	One 80 mg TAK-491 tablet	One placebo for 40 mg TAK-491 tablet, two placebo for 80 mg valsartan capsules
C	160 mg valsartan QD	Two 80 mg valsartan O/E capsules	One placebo for 40 mg TAK-491 tablet, one placebo for 80 mg TAK-491 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 adverse events) will be documented on an Overdose page of the (e)CRF, 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.

Serious 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. Hemodialysis does not significantly remove TAK-536 or M-II from the systemic circulation. Valsartan cannot be removed from plasma by hemodialysis [22].

8.2 Investigational drug Assignment and Dispensing Procedures

The investigator or investigator's designee will access the interactive voice/web response system (IVRS/IWRS) at Screening (Visit 1) to obtain the subject study number. The IVRS/IWRS will be accessed at Day -14 (Visit 2) to enroll the subject into the single-blind run-in period of the study and to randomize the subject into the study at Day 1 (Visit 5). During each of these contacts, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication identification (ID) number of the investigational drug and other sponsor-supplied drug(s) to be dispensed will then be provided by the IVRS/IWRS. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IVRS/IWRS. (Refer to IVRS/IWRS manual provided separately.). The Medication ID number will be entered onto the (e)CRF. At subsequent drug-dispensing visits, the investigator or designee will again contact the IVRS/IWRS to request additional investigational drug and other sponsor-supplied drug(s) for a subject. The medication ID number of the investigational drug and other sponsor-supplied drug(s) to be dispensed will be provided by the IVRS/IWRS. The Medication ID number will be entered onto the (e)CRF.

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.

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 (e)CRF.

If any site personnel are 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 (TAK-491 40 mg, TAK-491 80 mg and OE Valsartan 80 mg and matching placebo) 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, 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 is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IVRS/IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda 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 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 Medication 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.

The investigator must record the current inventory of all sponsor-supplied on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should 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 originals 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.

In the event of expiry date extension of supplies already at the study site, supplies may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

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 Appendix A.

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent 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, sex, race as described by the subject, and smoking status of the subject at Screening (Visit 1).

Medical history to be obtained will include determining whether the subject has any 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 28 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 (11) other. All subsequent physical examinations should assess clinically significant changes from the baseline examination.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The body mass index (BMI) is calculated by Takeda or designee using metric units with the formula provided below:

$$BMI = \text{weight (kg)}/\text{height (m)}^2$$

Height will be collected in centimeters without decimal places and weight will be collected in kilograms to 1 decimal place, results for BMI will be expressed with 1 decimal place.

Example:
-Height=176 cm (or 1.76 m), weight=79.2 kg; BMI=79.2/1.76^2=25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will be measured at the visits indicated in the Schedule of Study Procedures (see Appendix A), and will include sitting and standing BP and pulse, along with time of collection.

At each visit, 3 serial BP measurements should be taken while the subject is seated, with a semi-automated BP device, which will be provided by the sponsor. The measurements should be a minimum of 2 minutes apart with the cuff fully deflated between each reading [2,23]. A single sitting pulse measurement also should be taken manually. 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 (cuff bladder encircling at least 80% of the arm) that is applied on the upper non-dominant arm at heart level. The same arm should be used for each measurement at all visits. Every effort should be made to standardize the conditions of clinic BP measurements, and blood pressure levels are to be assessed by the same investigator or site personnel (whenever possible), with the same equipment [2]. All readings are entered into the source document and (e)CRF for all subjects.

BP levels should be measured in the morning approximately 24 hours after the previous day's dosing but before blood collection and before the next dose of study drug is administered. The date and time of the dose prior to the clinic BP measurement should be captured in the subject source document and (e)CRF. If any of the 3 SBP measurements differ by more than 8 mm Hg or any of the 3 DBP measurements differ by more than 5 mm Hg, a second set of 3 BP measurements should be obtained. The second set of readings should be entered into the (e)CRF. Original and repeat readings all must be recorded in the source documents with an explanation. The mean of the 3 serial blood pressure measurements will be used to determine subject eligibility.

Standing blood pressure will also be measured at each visit to evaluate orthostatic vital signs. After BP is measured in the seated position as described above, a single BP measurement will be obtained after 2 minutes of standing. Standing BP will be measured using the same equipment and the same (non-dominant) arm that was used for the seated measurements. For standing BP measurements, the arm should be supported and extended such that the cuff is at heart level. A single pulse measurement also should be taken while the subject is standing.

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 over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken 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 (e)CRF.

9.1.7 Documentation of Concurrent Medical Conditions

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

Data on medical conditions that require Continuous Positive Airway Pressure (CPAP) will be collected during the study. If CPAP is ongoing at the time of informed consent, the medical condition that required CPAP will be captured on the concurrent medical conditions (e)CRF. If CPAP is administered after first dose of study drug, then the medical condition will be captured as an AE.

9.1.8 Procedures for Clinical Laboratory Samples

9.1.8.1 Clinical Laboratory Tests

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 15 mL. The approximate total volume of blood for the study is 75 mL for male subjects, and 80 mL for female subjects (including an additional 5 mL of blood drawn for a serum pregnancy test on Day -14 [Visit 2]). After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period, and will be instructed to fast for at least 8 hours prior to blood draws on Day 1 (Visit 5), Week 2 (Visit 6), Week 4 (Visit 7), and Week 8/ET (Visit 9). 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
Hemoglobin Hematocrit Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate Bilirubin, total Bilirubin, direct (only if total is about ULN) Blood urea nitrogen (BUN) Calcium Chloride Creatinine Creatine kinase (CK) γ-Glutamyl transferase (GGT) Glucose Magnesium Potassium Protein, total Sodium Uric Acid High-density lipoprotein cholesterol (HDL-C) Low-density lipoprotein cholesterol (LDL-C) Total cholesterol Triglycerides	Specific gravity pH Qualitative Protein Blood Ketones Bilirubin Glucose Microscopy RBCs WBCs

Other	
HbA1c	Urine albumin
Female subjects of childbearing potential only:	Urine creatinine
Serum human chorionic gonadotropin (hCG) for pregnancy	Albumin:creatinine ratio (UACR)
Urine hCG for pregnancy (a)	eGFR
	Plasma renin concentration and activity
	Plasma and urine aldosterone

(a) Urine hCG will be performed at the site on Day 1 (Visit 5) prior to randomization.

The central laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, and other tests listed above. Estimated GFR will be calculated by the central laboratory using the Modification of Diet in Renal Disease equation [24,25]. Urinary albumin creatinine ratio (UACR) will also be calculated by the central laboratory. The urine pregnancy test on Day 1 (Visit 5) will be performed at the site. The results of laboratory tests will be sent to the investigator, who is responsible for reviewing and filing these results.

Clinical follow-up should take place (including repeat laboratory tests) until a subject's laboratory profile has returned to normal/baseline status. If at any time during treatment the subject's laboratory test meets the following criteria, the event must be reported as SAE:

- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN.

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

As a reminder, all abnormal laboratory results at final visit need to be followed until resolution to baseline levels or stabilization. Every effort should be made to obtain these follow-up tests from the central laboratory, and resolution or stabilization should be documented in the subject's source documents.

9.1.8.2 Management, Withdrawal, and Follow-up of Subjects with Creatinine Elevations

Acute, reversible increases of creatinine have been described in 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. If elevations in serum creatinine are observed, potential causes for the elevation should be investigated. If there is evidence for volume depletion such as body weight reduction or orthostatic hypotension, evaluate for sources of volume loss such as diarrhea, vomiting, low fluid or food intake, exercise-related water loss, etc. If there is evidence of volume depletion, consider temporarily liberalizing salt intake and encouraging increased hydration. The use of concomitant medications may be assessed, in particular nonsteroidal anti-inflammatory drugs (NSAIDs), that may worsen renal function or decrease renal creatinine secretion. Such medications may be discontinued if appropriate. Possible underlying causes of decreased renal function, such as bilateral arterial disease or heart failure also should be considered [25-27].

9.1.9 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.
- Progesterone T PLUS condom or spermicide.

Hormonal contraceptives:

- Implants.
- Hormone shot/injection.
- Combined pill.
- Minipill.
- Patch.
- Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening (Visit 1), subjects also must have a negative serum hCG pregnancy test at Day -14 (Visit 2) and a negative urine pregnancy test on the day of first dose of study drug (Day 1 [Visit 5]). Negative urine pregnancy test must be confirmed prior to receiving any dose of active study medication. A serum hCG pregnancy test will also be performed on Day 1 (Visit 5), at Week 4 (Visit 7), and at Week 8/ET (Visit 9). At any time during the study, a subject with a positive serum or urine pregnancy test will be discontinued immediately.

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, for example, after Day 1 (Visit 5) 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.

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. Results of the evaluation of the child after birth will also be collected.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. 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 (e)CRF from the subject's ECG trace: heart rate, PR interval, QT interval, QRS interval, and physician's assessment. Corrected QT interval will be calculated by Takeda or designee and will not be recorded on the (e)CRF.

Note: ECG traces recorded on thermal paper should be photocopied to avoid degradation of trace over time.

9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this visit, the investigator should complete the (e)CRF. The IVRS/IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- Pretreatment event/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.

9.1.13 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 (e)CRFs.

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

9.1.14 Ambulatory Blood Pressure Monitoring (for subset patients)

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 at 0800 (±2 hours).

The 24-hour ABPM reading will be started immediately after in-clinic dosing. ABPMs are performed only in a subset of subjects in selected sites at Baseline (Visit 4) and after the last dose of the double blind treatment (Visit 9).

An automated, portable ABPM device supplied by the sponsor will be used to record SBP and DBP over a 24-hour period on two occasions during the study; Baseline (Visit 4): Pre-randomization and Final (Visit 9): Week 8/Early termination visit. ABPM should be repeated within **3** days if pre defined quality control criteria are not met, as long as the subject has adequate supply of medication to stay on the current treatment.

The Baseline recording will begin on the last day of the single-blind placebo run-in period (Day -1), immediately after administration of the last dose of placebo.

The final ABPM will begin immediately after administration of the last dose of double-blind study drug at the Week 8 visit. If a subject wishes to withdraw early from the study and (a) has not been without study medication, (b) has completed at least 4 weeks of double-blind treatment, and (c) has not initiated other antihypertensive therapy, the site will attempt (safety permitting) to complete the final ABPM.

It is permitted for each scheduled ABPM to be repeated up to once only. In each instance, subjects will be instructed to return to the clinic on the morning after the device is fitted so that the ABPM measurement can be verified and the device removed.

See Appendix E for additional ABPM guidelines.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers to each clinic visit, regardless of whether the study medication container 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 Appendix A. Assessments should be completed at the designated visit/time point(s).

Study days/weeks and visit windows should be calculated after randomization and should be calculated from the day of the first dose of treatment (Day 1[Visit 5]). Visit windows are listed in Appendix A.

9.3.1 Screening (Visit 1)

Subjects will be screened for enrollment prior to discontinuing previous antihypertensive treatment or initiating the placebo run-in in accordance with the predefined entrance criteria described in Section 7.0. See Section 9.1.12 for procedures for documenting screen failures. After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period.

Procedures to be completed at the Screening (Visit 1) include:

- Informed consent.
- Inclusion and exclusion criteria.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs (including standing measurements). For subjects who have not received antihypertensive medications within 28 days, determine the mean sitting SBP for subject eligibility.
- Weight and height. BMI will be calculated during data analysis.
- 12-lead ECG.
- Concomitant medications.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, chemistry, urinalysis) and HbA1c. Estimated GFR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).
- Register subject in IVRS/IWRS to obtain subject number.
- Pretreatment event (PTE) assessment.

9.3.2 Washout, Day -28 or Day -21 through Day -1

If the subject is currently taking, or has taken antihypertensive medication within 28 days of screening, the subject will require washout. Subjects should not begin washout until all applicable inclusion and exclusion criteria, including laboratory results, have been verified.

- The subject may be notified by telephone to begin washout of current antihypertensive medication (if applicable) by Day -21 at the latest.

  Note: Subjects taking previous antihypertensive agents are required to participate in a 3-week washout period (Days -21 to -1). If the subject's previous antihypertensive treatment includes amlodipine or chlorthalidone, then the washout must be extended to 4 weeks (Days -28 to -1). Subjects who have not received antihypertensive medications within 28 days before screening can be entered into the run-in period as soon as all inclusion/exclusion criteria, including laboratory parameters, have been checked.

9.3.3 Placebo Run-in, Day -14 through Day -1 (Visits 2 and 3)

For subjects who were previously taking antihypertensive agents, the placebo run-in will coincide with the last two weeks of the washout period. Subjects who have not received antihypertensive treatment for 28 days before screening may begin the placebo run-in period after all inclusion criteria, including laboratory results, have been verified. The start of the placebo run-in period should occur approximately 14 days prior to randomization; however, this can be extended as long as the subject has an adequate amount of single-blind study medication. Subjects should take single-blind study medication (placebo) for a minimum of 10 days prior to randomization. The run-in period will consist of the 2 following visits:

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

The following procedures will be performed and documented during placebo Run-in, Day -14 (Visit 2):

- Inclusion and exclusion criteria.
- Vital signs (including standing measurements).
- Concomitant medications.
- PTE/Adverse event (AE) assessment.
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).
- Serum pregnancy test (female subjects of childbearing potential only).
- Access the IVRS/IWRS for single-blind placebo run-in study medication assignment.
- Dispense single-blind placebo run-in study medication with dosing instructions.
- In-clinic dose of single-blind placebo run-in study medication.

If the subject fails to meet the inclusion and exclusion criteria after starting single-blind placebo run-in study medication, they are considered a run-in failure. The procedure for documenting run-in failures is provided in Section 9.1.13.

9.3.3.2 Placebo Run-in, Day -7 (Visit 3)

The Placebo Run-in Day -7 visit should occur approximately 7 days from the Day -14 visit. Reminder: subjects should be on placebo run-in no less than 10 days prior to randomization.

The following procedures will be performed and documented during Run-in, Day -7 (Visit 3):

- Inclusion and exclusion criteria.
- Vital signs (including standing measurements).
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).
- Concomitant medications.
- AE assessment.
- Collect single-blind placebo run-in study medication and assess compliance, and counsel if on compliance if required.
- In-clinic dose with single-blind placebo run-in study medication (from the returned medication supply).
- Redispense single-blind placebo run-in study medication and instruct subject to withhold dose the morning of Day 1 (Visit 5). Last day of single-blind dosing is Day -1.
- Remind subjects to fast 8 hours before Day 1 Visit.

If the subject fails to meet the inclusion and exclusion criteria after starting single-blind placebo run-in study medication, they are considered a run-in failure. The procedure for documenting run-in failures is provided in Section 9.1.13.

9.3.4 Day -1 (Visit 4)

This visit only applies to the ABPM subgroup. Day -1 visit will take place 1 day prior to Day 1 visit. Reminder: the subject must be on placebo run-in medication a minimum of 10 days prior to randomization. The following procedures will be performed and documented during Visit 4:

- Update eligibility status (inclusion and exclusion criteria).
- Collect vital signs.
- Document changes to concomitant medications.
- Assess for AEs.

- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).
- Collect single-blind study medication and assess subject compliance with dosing regimen.

  Instruct subject to withhold dose the morning of the Day 1 (Randomization).
- Single-blind clinic dosing at 8:00 AM (±2 hours) and immediately prior to ABPM start.
- Start 24-hour ABPM.
- Remind subjects to fast 8 hours before Day 1 Visit.

If the subject does not meet the inclusion and exclusion criteria, the subject should be discontinued from the study. The procedure for documenting run-in failures is provided in Section 9.1.13.

9.3.5 Randomization, Day 1 (Visit 5)

Study randomization will take place on Day 1. Subjects should fast for at least 8 hours before this visit. The following procedures will be performed and documented during study randomization:

- Remove ABPM and ensure ABPM reading is successful (for subjects conduct ABPM only).

  Reminder: If the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current placebo treatment and ABPM should be repeated within **3** days.
- Inclusion and exclusion criteria (before randomized to treatment).
- Vital signs (including standing measurements) and weight. BP must meet inclusion #1 and must not meet exclusion #1.
- Urine pregnancy test (female subjects of childbearing potential only). Analysis is performed at the site. Test must be negative for subject before subject can be randomized.
- Collect single-blind placebo run-in study medication and assess subject compliance with dosing.
- Concomitant medications.
- AE assessment.
- 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 9.1.13. If subject does not meet all of the inclusion and none of the exclusion criteria, document the subject as a run-in failure and record the primary reason for failure on the applicable (e)CRF. The procedure for documenting run-in failures is provided in Section 9.1.13.
- Physical examination.
- 12-lead ECG.

- Clinical laboratory tests (hematology, chemistry, and urinalysis), HbA1c, plasma renin concentration and activity, plasma and urine aldosterone, urine albumin, and urine creatinine. Estimated GFR and UACR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).
- Dispense double-blind study medication with dosing instruction.
- In-clinic first dose of double-blind study medication.
- Instruct the subject to fast for at least 8 hours prior to Week 2 (Visit 6).

9.3.6 Treatment Visits, Week 2 through Week 6 (Visit 6 through Visit 8)

See Appendix A for windows for each visit. Subjects should fast for a minimum of 8 hours before Visits 6 and 7. The following procedures will be performed at these visits:

- Vital signs (including standing measurements) and weight.
- Laboratory tests: Clinical laboratory tests (hematology, chemistry, urinalysis) at Visits 6 and 7 only; plasma renin concentration and activity, and plasma and urine aldosterone at Visit 7 only. Estimated GFR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only) at Visit 7 only.
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).
- Concomitant medications.
- AE assessment.
- Collect double-blind study medication and assess subject compliance with dosing regimen. If required, counsel subject on compliance.
- Access the IVRS/IWRS and dispense double-blind study medication with dosing instructions.
- In-clinic first dose of the newly assigned double-blind medication in the clinic.
- Instruct subject to withhold dose of study medication the morning of all in-clinic study visits.
- Instruct the subject at Week 2 (Visit 6) to fast for at least 8 hours prior to Week 4 (Visit 7) and at Week 6 (Visit 8) to fast for Week 8 (Visit 9).

9.3.7 Week 8/Final Visit or Early Termination (Visit 9)

Subjects should fast for 8 hours before this visit. Assessments scheduled for Week 8/ET (Visit 9) should be completed (safety permitting) for subjects who were randomized and withdraw early. The following procedures will be performed and documented:

- Clinic dosing at 8:00 AM (±2 hours) and immediately prior to ABPM start (in subgroup only).
- Start 24-hour ABPM (in subgroup only).
- Vital signs (including standing measurements) and weight.
- Physical examination.
- 12-lead ECG.
- Concomitant medications.
- AE assessment.
- Collect double-blind study medication and assess subject compliance with dosing regimen.
- Access the IVRS/IWRS to register subject completion/early termination.
- Clinical laboratory tests (hematology, chemistry, and urinalysis), HbA1c, plasma renin concentration and activity, plasma and urine aldosterone, urine albumin and urine creatinine. Estimated GFR and UACR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).

9.3.8 ABPM Removal (Visit 10)

This visit only applies to the ABPM subgroup. Assessments scheduled for ABPM Removal Visit (Visit 10) should be completed (safety permitting) for subjects. The following procedures will be performed:

- Remove ABPM and ensure ABPM reading is successful.

  Reminder: If the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within **3** days
- Vital signs (including standing measurements) and weight.
- AE assessment.
- Concomitant medications.
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).

9.3.9 Follow-up

- Subjects should receive a follow-up telephone call to assess any new or ongoing AEs and changes to concomitant medications 14 days after the last dose of study medication (single-blind placebo or double-blind). Female subjects of childbearing potential should be

counseled on avoidance of pregnancy, ova donation, and use of acceptable methods of contraception through 30 days after the last dose of study medication.

- For all subjects receiving study medication, the investigator must complete the End of Study (e)CRF page.

9.3.10 Post Study Care

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 as required.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (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 AEs

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 pre existing 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 any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the (e)CRF.

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. Is 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 Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda 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:

Yes:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
No:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

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

The relationship should be assessed as Yes if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as No.

10.1.8 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/serious PTE (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 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 signs the informed consent to participate in the study and continue until the subject is first administered single-blind placebo run-in study medication (Day -14 [Visit 2]) or until screen failure. For subjects who discontinue prior to single-blind placebo run-in 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 single-blind placebo study medication (Day -14 [Visit 2]). Routine collection of AEs will continue until 14 days after the last dose of study medication, at which time a follow-up phone call will be made to the subject to query for any new AEs. Spontaneous reporting of AEs and SAEs will be collected from through 14 or 30 days, respectively, 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 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.

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:

A SAE eCRF must be completed, in English, in EDC 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 following the AE collection period should be reported to the sponsor if considered related to study participation.

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

10.2.3 Reporting of Abnormal Liver Function Tests (LFT)

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, a LFT Increases (e)CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

10.3.1 Safety Reporting of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should enter follow-up information via the SAE eCRF and/or provide other documentation (eg, ECGs, laboratory test results, diagnostic test results, discharge summary, death certificate, hospital notes etc.) and fax them immediately, within 24 hours of receipt to the contact provided (as per Section 1.1). 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.

10.3.2 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 to regulatory authorities, 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

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

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 (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

Completed (e)CRFs are required for each subject who signs an informed consent.

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

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 Takeda personnel (or designees) and will be answered by the site.

Corrections to (e)CRFs 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 (e)CRFs for completeness and accuracy and must sign and date the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

(e)CRFs 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 (e)CRFs. The completed (e)CRFs 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 forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of (e)CRFs, 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 between the investigator and sponsor.

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 further 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

All randomized subjects will comprise the randomized set. Analysis sets to be used include the following:

Safety Analysis Set: All subjects who receive at least 1 dose of double-blind study medication. Subjects will be analyzed according to the study medication they received.

Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the treatment group to which they were randomized.

Per-Protocol Set (PPS): All subjects in the FAS, excluding any subjects who had major protocol violations. Major violations from the protocol leading to exclusion from the Per Protocol Set will be identified prior to unblinding of subject's treatment assignment.

The FAS will be the primary data set used for efficacy analyses. Efficacy analysis based on the Per Protocol Set will also be performed where appropriate. All routine safety analysis will be based on the Safety Analysis Set.

All subjects who were randomized more than once will be excluded from the safety analysis set, the FAS, and the PPS.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (eg, age, race, gender, height, weight) will be summarized using descriptive statistics for each treatment group and overall (eg, mean, standard deviation, median, minimum and maximum values, and the number and percent of subjects in specified categories).

13.1.3 Efficacy Analysis

Unless otherwise specified, efficacy analyses will be performed using the FAS and all statistical inference will use a 2-sided 0.05 significance level. A subject will be included in the primary analyses only when there is both a baseline value and at least 1 value during the double-blind treatment period. Missing values will be imputed using last observation carried forward (LOCF) methodology. In the LOCF analysis data set, the last post-baseline double-blind observed value is

carried forward and used for all subsequent scheduled time points where data are missing (eg, the subject has missing data or has dropped out of the study).

The primary analysis will be based on an analysis of covariance (ANCOVA) model for change in clinic SBP from baseline to week 8. The model will include treatment as a fixed effect and baseline clinic SBP as a covariate. From the framework of the ANCOVA the following will be determined: treatment LS mean, LS mean for the difference between TAK-491 and valsartan, p-value and 2-sided 95% confidence intervals for the treatment difference. For the primary analysis the overall type 1 error rate of 0.05 will be controlled using the 4 step sequential test described below.

- Step 1: A test for noninferiority of TAK-491 80 mg to valsartan 160 mg will be performed using a noninferiority margin of 1.5 mm Hg. If the upper limit of the 2-sided 95% CI of the treatment difference (TAK-491 – valsartan) is not greater than 1.5 then proceed to Step 2.
- Step 2: A test for noninferiority of TAK-491 40 mg to valsartan 160 mg will be performed using a noninferiority margin of 1.5 mm Hg. If the upper limit of the 2-sided 95% CI of the treatment difference (TAK-491 – valsartan) is not greater than 1.5 then proceed to Step 3.
- Step 3: A test for significant difference between TAK-491 80 mg versus valsartan 160 mg will be performed at the 5% level. If the p-value is not greater than 0.05 then proceed to Step 4.
- Step 4: A test for significant difference between TAK-491 40 mg versus valsartan 160 mg will be performed at the 5% level.

Based on historical data, the observed placebo-corrected treatment effects on change from Baseline in clinic SBP for valsartan 160 mg once daily was -8.6 mm Hg [28]. Therefore, the noninferiority margin was set conservatively at 1.5 mm Hg, which is less than one-third of the valsartan treatment effect. Accordingly, TAK-491 will be considered noninferior to valsartan when the upper limit of the 2-sided 95% CI of the treatment difference (TAK 491 – comparator) is ≤1.5 mm Hg.

The secondary endpoint, change from baseline to Week 8 in trough sitting clinic DBP will be analyzed similar to the primary endpoint, excluding the sequential testing. Change from baseline for both SBP and DBP at other visits will be summarized similar to the primary endpoint. Additionally, similar analyses will be performed for both SBP and DBP for selected subgroups, where appropriate, eg, age, sex.

The categorical secondary efficacy endpoints, percentage of subjects responding to treatment and percentage of subjects reaching blood pressure target at Week 8 will be tabulated for each of the following definitions:

- Response criteria.
  a) Clinic SBP <140 mm Hg and/or a reduction of ≥20 mm Hg from baseline.
  b) Clinic DBP <90 mm Hg and/or a reduction of ≥10 mm Hg from baseline.
  c) a and b (ie, joint criteria).

- Target blood pressure.
  a) Clinic SBP <140 mm Hg.
  b) Clinic DBP <90 mm Hg.
  c) Clinic SBP<140 mm Hg and DBP<90 mm Hg.
  d) Clinic SBP<130 mm Hg.
  e) Clinic DBP<80 mm Hg.
  f) Clinic SBP<130 mm Hg and DBP<80 mm Hg.

A logistic model with treatment as fixed effect and baseline clinic SBP as a covariate will be used to analyze response for clinic SBP. The odds ratio and its 95% confidence will be estimated. Similarly, a logistic model with treatment as fixed and baseline clinic DBP as a covariate will be used to analyze the response for clinic DBP. The joint response for both clinic SBP and DBP will be analyzed using a logistic model with treatment as fixed effect and baseline clinic SBP as a covariate. A similar analysis and model will be used to analyze the percentage of subjects reaching target blood pressure at Week 8. The percentage of subjects responding to treatment, as well as reaching blood pressure target, will also be presented for other visits, using the above methods.

Change from baseline to Week 8 24-hour mean SBP by ABPM will be analyzed using an ANCOVA model with treatment as a fixed effect and baseline 24-hour mean SBP by ABPM as a covariate. Similar analyses will be performed for other ABPM parameters for both SBP and DBP determined and descriptive statistics calculated.

The peak effect and trough-to-peak ratio will also be calculated and summarized.

Subgroup (eg, age, sex) analyses may be performed if data permit.

Sensitivity analyses to be performed on the primary endpoint (and other endpoints where appropriate) include: multiple imputation for missing values; analyses using the per protocol set; and analyses using observed values only.

13.1.4 Safety Analysis

Safety and tolerability will be accessed via treatment emergent adverse events, laboratory results, and other safety variables. Unless otherwise specified safety analyses will be performed using the safety analysis set, and presented by treatment group. Results presented by study visit will also include the final visit; where final visit is defined as the last observation (post-baseline) carried forward no later than 7 days after the last dose of study drug.

13.1.4.1 Adverse Events

Adverse events will be coded using MedDRA. Treatment-emergent adverse events (TEAE) will be defined as any AEs, regardless of relationship to study drug, that occur after the first dose of double-blind study drug, no later than 14 days after the last dose of study drug for AEs, and no later than 30 days after the last dose of study drug for SAEs. TEAEs will be tabulated by system organ

class and preferred term. The TEAE summary tables will include count and percent of subjects reporting the event by treatment group. Therefore, if a subject experiences more than 1 episode of a particular AE, the subject will be counted only once for that event. If a subject has more than 1 AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than 1 AE within a system organ class, the subject will be counted only once in that system organ class. Adverse events with onset dates on or after the start of treatment and prior to 14 days (onset date – last date of dose ≤14) after the permanent discontinuation of the study medication, or continuing AEs diagnosed prior to the date of first dose of study medication and getting worse in severity or intensity after receiving study medication will be summarized.

Serious adverse events with onset dates on or after the start of treatment and prior to 30 days (onset date – last date of dose ≤30) after the last dose of study medication will be summarized. Specific decision will be made for inclusion of SAEs with onset dates 30 days after the final discontinuation of study medication.

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

13.1.4.2 Laboratory Analysis

Laboratory test variables will be summarized by treatment group and study visit using descriptive statistics for the observed and change from baseline values. Markedly abnormal laboratory values will be determined and listed by treatment group and study visit. The number and percentage of subjects with markedly abnormal laboratory values in each of the laboratory parameters will be presented. Shift tables displaying the change (number of subjects) relative to the normal range from Baseline to each study visit will also be presented by treatment for each laboratory test. Laboratory data collected more than 7 days after the last dose of study medication will be excluded from the summaries but will be listed.

13.1.4.3 Additional Safety Values

CCI

[redacted]

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Assuming an SD of 17 mm Hg and a 10% dropout rate, a sample size of 200 subjects per treatment group (total of 600 subjects) is sufficient to achieve at least 90% power to detect a difference of 6 mm Hg between TAK-491 dose and valsartan by a 2-sample t-test on the mean change from baseline to Week 8 in mean sitting clinic SBP at 0.05 2-sided significance level. This sample size will also provide, for the above assumptions, at least 90% power for demonstrating noninferiority with a margin of 1.5 mm Hg between TAK-491 and valsartan.

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 (e)CRFs. 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 [CRO]) 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 documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of (e)CRFs 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 should consult with the medical monitor (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 and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable 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.

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 Investigator's Brochure, a copy of the informed consent form, 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 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 will notify 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 form, 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, 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 form, 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 form 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 is given. The informed consent form 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 form and if applicable, the subject authorization form. The informed consent form, 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 form, 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 form, 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 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 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 form and subject authorization (if applicable) at the time of consent 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 form, 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 signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent 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. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

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 [e]CRF).

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, Takeda 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. Takeda contact information, along with investigator's information, country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda 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. Elliott WJ. Management of hypertension in the very elderly patient. Hypertension 2004;44(6):800-4.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289(19):2560-72.
3. World Health Organization. International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21(11):1983-92.
4. Chinese Guidelines. Chinese guidelines for management of hypertension - 2010. Chinese Journal of Hypertension 2011;19(8):701-43.
5. Shusterman N. Risk-benefit assessment of angiotensin II receptor antagonists. Expert Opin Drug Saf 2002;1(2):137-52.
6. Appel GB, Appel AS. Angiotensin II receptor antagonists: role in hypertension, cardiovascular disease, and renoprotection. Prog Cardiovasc Dis 2004;47(2):105-15.
7. Messerli FH, Weber MA, Brunner HR. Angiotensin II receptor inhibition. A new therapeutic principle. Arch Intern Med 1996;156(17):1957-65.
8. Weber MA. The angiotensin II receptor blockers: opportunities across the spectrum of cardiovascular disease. Rev Cardiovasc Med 2002;3(4):183-91.
9. Graettinger WF. Systemic hypertension. In: Crawford MH, editor. Current Diagnosis & Treatment in Cardiology. 2nd ed. New York, NY: McGraw-Hill Professional; 2003, p. 167-78.
10. Neutel JM. Choosing among renin-angiotensin system blockers for the management of hypertension: from pharmacology to clinical efficacy. Curr Med Res Opin 2010;26(1):213-22.
11. TAK-491 Global Investigator's Brochure. 10th Edition. Takeda Development Centre Europe Ltd., 22 April 2015.
12. Edarbi 20, 40, and 80 mg tablets. Summary of Product Characteristics. Taastrup, Denmark: Takeda Pharma A/S, Revised 09 September 2014.
13. Edarbi (azilsartan medoxomil) Tablets. Full Prescribing Information. Atlanta, GA: Arbor Pharmaceuticals, LLC, Revised May 2014.
14. 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.
15. Al-Khatib SM, Califf RM, Hasselblad V, Alexander JH, McCrory DC, Sugarman J. Medicine. Placebo-controls in short-term clinical trials of hypertension. Science 2001;292(5524):2013-5.

16. Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. Lancet 2008;371(9631):2219-21.

17. Duprez DA. Systolic hypertension in the elderly: addressing an unmet need. Am J Med 2008;121(3):179-84 e3.

18. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension 2001;37(3):869-74.

19. 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.

20. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 2003;348(24):2407-15.

21. 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.

22. Valsartan 80 mg capsules. Summary of Product Characteristics. Ruislip, United Kingdom: Milpharm Limited, Revised 09 August 2013.

23. Pan Americana Hypertension Initiative. Working meeting on blood pressure measurement: suggestions for measuring blood pressure to use in populations surveys. Rev Panam Salud Publica 2003;14(5):300-2, 3-5.

24. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

25. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Guideline 11: Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in CKD. Am J Kidney Dis 2004;43(5, Suppl 1):S183-S205.

26. Thorp ML, Ditmer DG, Nash MK, Wise R, Jaderholm PL, Smith JD, et al. A study of the prevalence of significant increases in serum creatinine following angiotension-converting enzyme inhibitor administration. J Hum Hypertens 2005;19(5):389-92.

27. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160(5):685-93.

28. Pool J, Oparil S, Hedner T, Glazer R, Oddou-Stock P, Hester A. Dose-responsive antihypertensive efficacy of valsartan, a new angiotensin II-receptor blocker. Clin Ther 1998;20(6):1106-14.

Appendix A Schedule of Study Procedures

		Washout				Double-Blind Treatment Period					Post-Treatment Period	
			Single-Blind Placebo Run-in									
Study Day or Week:	**Screening Visit (a)**	**D -21 (b) or D -28 (c)**	**D -14 (d,e)**	**D -7**	**D -1 (v)**	**D1**	**W2**	**W4**	**W6**	**Final clinic/ ET W8 (f)**	**ABPM Removal Visit (w)**	**Tele-phone Follow-up (g)**
Visit Window	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**N/A**	**N/A**
Visit Number:	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N/A**
Informed consent	X											
Inclusion/exclusion criteria	X		X	X	X	X						
Demographics and medical history	X											
Medication history	X											
Physical examination	X					X				X		
PTE assessment (h)	X		X									
AE assessment (i,j,r)			X	X	X	X	X	X	X	X	X	X
Vital signs (k)	X		X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (l)	X					X	X	X	X	X	X	
12-lead ECG	X					X				X		
Clinical laboratory tests (m)	X					X	X	X		X		
Urine albumin and creatinine and UACR (n)						X				X		
HbA1c	X					X				X		
Estimated GFR (n)	X					X	X	X		X		
Serum hCG (o)	X		X			X		X		X		
Urine pregnancy test (o,p)						X						
Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception	X		X	X	X	X	X	X	X	X	X	X
Notify subject to begin washout period (q)		X										
Plasma renin concentration and activity, plasma and urine aldosterone						X		X		X		
ABPM start (subgroup only)					X					X		
ABPM removal (subgroup only)						X					X	

		Washout			Double-Blind Treatment Period					Post-Treatment Period	
			Single-Blind Placebo Run-in								
Study Day or Week:	**Screening Visit (a)**	**D -21 (b) or D -28 (c)**	**D -14 (d,e)**	**D -7**	**D -1 (v)**	**D1**	**W2**	**W4**	**W6**	**Final clinic/ ET W8 (f)**	**ABPM Removal Visit (w)**	**Tele-phone Follow-up (g)**
Visit Window	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**N/A**	**N/A**
Visit Number:	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N/A**
Concurrent medical conditions (r)	X											
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X
Access IVRS/IWRS (s)	X		X			X	X	X	X	X		
Dispense single-blind study placebo for run-in and dose in-clinic (t)			X									
Redispense single-blind placebo for run-in				X								
Last dose of single-blind placebo (u)					X							
Dispense double blind study drug						X	X	X	X			
Last dose of double blind study drug										X		
Clinic dosing (u)			X	X	X	X	X	X	X	X		
Compliance assessment				X	X	X	X	X	X	X		

Footnotes for Appendix A are on the next page.

Footnotes for Appendix A
D=Day, W=Week.
(a) The Screening Visit should be scheduled before the washout/run-in period begins so that laboratory tests results can be reviewed and subject eligibility can be confirmed before other treatments are stopped or placebo is initiated.
(b) Subjects taking previous antihypertensive agents are required to participate in a 3-week washout period (Days -21 to -1).
(c) If the subject's previous antihypertensive treatment includes amlodipine or chlorthalidone, then the washout must be extended to 4 weeks (Days -28 to -1).
(d) Subjects who have not received antihypertensive treatment within 28 days before screening can be entered into the run-in period as soon as all inclusion and exclusion criteria, including laboratory results, have been verified.
(e) At minimum, the run-in should be 10 days but can extend to as long as the subject has an adequate supply of single-blind placebo run-in study medication.
(f) Conduct Final Visit procedures for subjects who are randomized and discontinued early per Section 7.6.
(g) Telephone contact for the follow-up AE and concomitant medication assessments should be made approximately 14 days after the last dose (single-blind placebo or double-blind).
(h) Reports of pretreatment events should be solicited at each visit from the time that informed consent is acquired until the first dose of placebo run-in study medication.
(i) AEs should be solicited at each visit from the time that single-blind placebo run-in study medication is started through 14 days after the last dose (via the telephone follow-up AE assessment).
(j) Spontaneous reports of AEs and SAEs should be collected from the time of the first dose of single-blind placebo run-in medication through 14 or 30 days, respectively, after the last dose.
(k) Includes sitting and standing BP and pulse rate. Pulse rate will be taken manually while sitting and standing.
(l) Collect height at the Screening (Visit 1) only; BMI will be calculated during data analysis at Screening (Visit 1).
(m) Hematology, serum chemistry, and urinalysis tests (as listed in Table 9.a). After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period, and will be instructed to fast for at least 8 hours prior to blood draws on Day 1 (Visit 5), Week 2 (Visit 6), Week 4 (Visit 7), and Week 8/ET (Visit 9).
(n) UACR and estimated GFR will be calculated by the central laboratory.
(o) Women of childbearing potential only.
(p) Urine pregnancy test is performed at the site and must be negative for subject prior to randomization on Day 1 (Visit 5).
(q) Subject can be notified by telephone to begin the washout period.
(r) Data on medical conditions that require Continuous Positive Airway Pressure (CPAP) will be collected during the study. If CPAP is ongoing at the time of informed consent, the medical condition that required CPAP will be captured on the concurrent medical conditions (e)CRF. If CPAP is administered after first dose of study drug, then the medical condition will be captured as an AE.
(s) If a subject withdraws early, contact IVRS/IWRS to document the ET.
(t) Subjects to take the first dose of single-blind placebo run-in study medication in-clinic.
(u) Instruct subjects to withhold their dose of study drug, if applicable so they can be dosed in-clinic. For ABPM subgroup subjects, clinic dosing at 8:00 AM (±2 hours) for Visits 4 and 9.
(v) Visit 4 is only applied to ABPM subgroup subjects; if the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within 3 days.
(w)Visit 10 is only applied to ABPM subgroup subjects; if the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within 3 days.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE/AESI, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures which are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Ambulatory Blood Pressure Monitoring

The ambulatory BP recording device provided by the sponsor has been validated independently by the American Association for the Advancement of Medical Instrumentation. The device is an automatic, portable monitor that will be used to record BP and heart rate over a 24-hour period on two occasions during the study per the Schedule of Assessments, Appendix A.

The ABPM studies should be performed under similar circumstances (eg, a working weekday) if possible, and the device should be applied on the same day of the week and as close to the same time of day as feasible on each occasion. The non-dominant arm should be used for all ABPM readings. For each evaluation, the subject should report to the clinic for ABPM placement by 0800 am (±2 hours). Calibration should be performed per the ABPM Training Manual.

The ABPM recorder will be manually initiated to indicate the beginning of the test and the start time will be recorded in the eCRF and source document. The time of the in-clinic dose of study medication will also be recorded in the eCRF and source document. The device will be set to obtain readings every 15 minutes during the interval of 0600 to 2200 (to coincide with the daytime, awake period) and every 20 minutes during the interval of 2200 to 0600 (to coincide with the night time, sleeping period). Refer to the ABPM Training Manual for specific set-up requirements.

The subject should engage in their usual physical activity levels, but should avoid strenuous exercise during the monitoring period. Additionally, sleeping during the daytime (eg, a siesta) should be avoided during the ABPM study period. During the actual BP measurements, the subject should be instructed to hold their arm still and remain in place once cuff inflation begins.

Following completion of the 24-hour collection period, subjects should be instructed to return to the clinic site to return the ABPM equipment. The data collected should be verified by the investigator or designee to ensure adequate data collection. An ABPM recording will be considered of sufficient quality (pass) if:

- The “Beginning of Test” time is between 0600 and 1000.
- The monitoring period is at least 24 hours in duration.
- A minimum of 80% of the BP readings expected during the 24-hour period is recorded.
- There are no more than 2 non-consecutive hours with less than 1 valid BP reading, and 0 consecutive hours with less than 1 valid BP reading.

If any of the ABPM measurements do not pass these quality control criteria, they may be repeated once as long as the subject has an adequate supply of medication (placebo run-in /double-blind treatment) to resume treatment until the repeat measure can be taken.

For the Baseline (pre-randomization) and Final (week 8/early termination) ABPM recordings it is preferable, but not mandatory, that recordings satisfy the predefined quality control criteria before moving on to the next study step. ABPM readings for the Baseline (pre-randomization) and Final (week 8/early termination) if repeated, must be completed within 3 days.

In all cases of repeat ABPM recordings, only 1 repeat is permitted. Clinic vital signs should be collected whenever repeat ABPM measurements are taken.

Appendix F Detailed Description of Amendments to Text

Page 2, Section 1.1: Contacts

Existing Text

Issue	China Contact
Serious adverse event and pregnancy reporting	Quintiles Integrated Safety Management Lifecycle Safety Contact details: See Study Reference Materials
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	Quintiles Medical Services Department Contact details: See Study Reference Materials
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

Revised Text

Issue	China Contact
Serious adverse event and pregnancy reporting	Quintiles Integrated Safety Management Lifecycle Safety Contact details: See Study Reference Materials
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	Quintiles Medical Services Department Contact details: See Study Reference Materials
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

Rational for Amendment

To update the name of and contact information for the Responsible Medical Officer.

Page 3, Section 1.2: Approval

Existing Text

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

Revised Text

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

Rationale for Amendment

To update the names and titles for the Takeda signatories.

Page 14, Study Summary (paragraph 1)

Existing Text

The primary endpoint is change from baseline to Week 8 in trough (*22-24 hour* after the previous dose) sitting clinic SBP.

Revised Text

The primary endpoint is change from baseline to Week 8 in trough (**approximately 24 hours** after the previous dose) sitting clinic SBP.

Rationale for Amendment

To be consistent with the required timing of blood pressure measurements stated in Section 9.1.5 (Vital Sign Procedures).

Page 14, Study Summary: Main Criteria for Evaluation and Analyses, Efficacy

Existing Text

Change from baseline in trough sitting clinic SBP and DBP; percentage of responders; and percentage of subjects achieving target blood pressure at other study visits.

CCI

Revised Text

Change from baseline in trough sitting clinic SBP and DBP; percentage of responders; and percentage of subjects achieving target blood pressure at other study visits.

Change from Baseline to Week 8 in the following ABPM parameters (in a subgroup): 24 hour mean SBP and DBP; trough (22-24 hours after dosing) SBP and DBP; mean daytime (6 AM-10 PM) SBP and DBP; mean nighttime (12 AM-6 AM) SBP and DBP; mean SBP and DBP at 0-12 hours after dosing; peak (SBP and DBP) effect.

Trough-to-peak ratios (SBP and DBP) as determined by ABPM (in a subgroup).

Rationale for Amendment

For clarity.

Page 15, Study Summary: Statistical Considerations, Analysis Sets

Existing Text

Safety Analysis Set: All subjects who receive at least 1 dose of double-blind study medication. Subjects will be analyzed according to the study medication they received.

Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the treatment group to which they were randomized.

Revised Text

Safety Analysis Set: All subjects who receive at least 1 dose of double-blind study medication. Subjects will be analyzed according to the study medication they received.

Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the treatment group to which they were randomized.

Subjects who were randomized more than once will be excluded from both the safety analysis set and the FAS.

Rational for Amendment

For clarity.

Page 21, Section 4.3: Summary of Clinical Data (paragraph 4)

Existing Text

TAK-491 dose reduction is not necessary for subjects with mild or moderate hepatic impairment, although *such* subjects are excluded from the present study.

Revised Text

Steady-state total exposures to TAK-536 after multiple doses of TAK-491 in a phase 1 hepatic impairment study were approximately 28% and 64% greater in subjects with mild and moderate hepatic impairment, respectively, than in healthy subjects. Subjects with severe hepatic impairment were not studied. The increases in exposure to TAK-536 in the phase 1 hepatic impairment study are not considered to be clinically meaningful as TAK-491 was well-tolerated in other pharmacokinetic studies in which exposures to TAK-536 were greater than those observed in subjects with hepatic impairment. Therefore, TAK-491 dose reduction is not necessary for subjects with mild or moderate hepatic impairment, although subjects **with any degree of hepatic impairment** are excluded from the present study**.**

Rational for Amendment

To add clinical data from the phase 1 hepatic impairment study to support the addition of Week 2 clinical laboratory tests.

Page 21, Section 4.3: Summary of Clinical Data (paragraph 5)

Existing Text

The single dose phase 1 study in renal impaired subjects showed that after 40 mg TAK-491 dosing, the total exposure to TAK-536 tended to be higher in subjects with renal impairment than in healthy subjects with increases of 30%, 25%, *96%, and 5%* in subjects with mild, moderate, or severe renal impairment, and end-stage renal disease (ESRD), respectively. These increases in exposure to TAK-536 are not considered to be clinically meaningful, as TAK-491 was well-tolerated in a high-dose (160 to 320 mg) study in healthy subjects. The mean terminal elimination half-life (*T1/2*) of TAK-536 was not substantially different in subjects with renal impairment than in healthy subjects. Therefore, no dose adjustment of TAK-491 is required for subjects with any degree of renal impairment or ESRD, although subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 (mL/min/1.73 m^2) are excluded from this study.

Revised Text

The single dose phase 1 study in renal impaired subjects showed that after 40 mg TAK-491 dosing, the total exposure to TAK-536 tended to be higher in subjects with renal impairment than in healthy subjects with increases of 30%, 25%, **95%, and 4%** in subjects with mild, moderate, or severe renal impairment, and end-stage renal disease (ESRD), respectively. These increases in

exposure to TAK-536 are not considered to be clinically meaningful, as TAK-491 was well-tolerated in a high-dose (160 to 320 mg) study in healthy subjects **(01-06-TL-491-017)**. The mean terminal elimination half-life ($t_{1/2z}$) of TAK-536 was not substantially different in subjects with renal impairment than in healthy subjects. Therefore, no dose adjustment of TAK-491 is required for subjects with any degree of renal impairment or ESRD, although subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 (mL/min/1.73 m^2) are excluded from this study.

Rationale for Amendment

To report total exposure for subjects with renal impairment as AUC_∞ instead of AUC_{last}. The abbreviation for half-life was updated to the current Takeda standard.

Page 22, Section 4.3: Summary of Clinical Data (paragraph 7)

Existing Text

Results of the phase 3 program demonstrated that, relative to placebo, the TAK-491 20, 40, and 80 mg doses produce clinically and statistically significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP), as assessed by both ambulatory blood pressure monitoring (ABPM) and clinic blood pressure measurements. The differences between doses were greater for subgroups of subjects characterized by more severe and/or resistant hypertension, including black subjects, subjects with renal impairment, and subjects with *essential* hypertension. In each study, most of the blood pressure-lowering effect of TAK-491 was observed within 2 weeks of treatment; a plateau of effect was generally reached by week 4 and reductions were maintained through week 6 in short-term studies and over the long-term in two 6-month studies (and up to 1 year in open-label studies). In replicate studies, TAK-491 at 80 mg was shown to reduce systolic blood pressure more effectively than olmesartan medoxomil 40 mg and valsartan 320 mg, the highest approved doses in the US.

Revised Text

Results of the phase 3 program demonstrated that, relative to placebo, the TAK-491 20, 40, and 80 mg doses produce clinically and statistically significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP), as assessed by both ambulatory blood pressure monitoring (ABPM) and clinic blood pressure measurements. The differences between doses were greater for subgroups of subjects characterized by more severe and/or resistant hypertension, including black subjects, subjects with renal impairment, and subjects with **Grade 2** hypertension. In each study, most of the blood pressure-lowering effect of TAK-491 was observed within 2 weeks of treatment; a plateau of effect was generally reached by week 4 and reductions were maintained through week 6 in short-term studies and over the long-term in two 6-month studies (and up to 1 year in open-label studies). In replicate studies, TAK-491 at 80 mg was shown to reduce systolic blood pressure more effectively than olmesartan medoxomil 40 mg and valsartan 320 mg, the highest approved doses in the US.

Rationale for Amendment

To correct the text.

Page 23, Section 4.3: Summary of Clinical Data (paragraph 10)

Existing Text

In summary, TAK-491 was well tolerated at doses up to 320 mg in healthy subjects and up to 80 mg in hypertensive subjects (maximal dose evaluated in this population). TAK-491 has been shown to have a strong antihypertensive effect, predictable pharmacokinetic and metabolic profiles, a prolonged duration of action, and good safety and tolerability profiles when administered as a monotherapy to hypertensive subjects. *TAK-491 has recently been approved in the United States (US) by the Food and Drug Administration (FDA), by the European Medicines Agency (EMA) in the European Union, and in other countries such as Canada, Switzerland, Mexico, Philippines for the treatment of hypertension, either alone or in combination with other antihypertensive agents.*

Revised Text

In summary, TAK-491 was well tolerated at doses up to 320 mg in healthy subjects and up to 80 mg in hypertensive subjects (maximal dose evaluated in this population). TAK-491 has been shown to have a strong antihypertensive effect, predictable pharmacokinetic and metabolic profiles, a prolonged duration of action, and good safety and tolerability profiles when administered as a monotherapy to hypertensive subjects. **As of February 2016, TAK-491 has been approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents, in a total of 59 countries worldwide, including approval in the United States by the Food and Drug Administration (FDA) in February 2011 and in the European Union by the European Medicines Agency (EMA) in December 2011.**

Rationale for Amendment

To present current registration information.

Page 24, Section 5.2.1: Primary Endpoint

Existing Text

The primary endpoint is change from baseline to Week 8 in trough (*22-24 hour* after the previous dose) sitting clinic SBP.

Revised Text

The primary endpoint is change from baseline to Week 8 in trough (**approximately 24 hours** after the previous dose) sitting clinic SBP.

Rationale for Amendment

To be consistent with the required timing of blood pressure measurements stated in Section 9.1.5 (Vital Sign Procedures).

Page 27, Section 6.1: Figure 6.a Schematic of Study Design (footnote [i])

Existing Text

(i) *In subgroup of ABPM subjects will* start 24-hour ABPM measurement.

Revised Text

(i) **Visit 4 only applies to ABPM subgroup subjects;** start 24-hour ABPM measurement.

Rationale for Amendment

To clarify that this visit applies only to the ABPM subgroup of subjects.

Page 27, Section 6.2: Justification for Study Design, Dose, and Endpoints

Existing Text

TAK-491 is a prodrug that is rapidly hydrolyzed to the active moiety, TAK-536, which is a long-acting, angiotensin II AT1 receptor blocker (ARB). TAK-491 has been shown to have a strong antihypertensive effect, predictable pharmacokinetic and metabolic profiles, a prolonged duration of action, and good safety and tolerability profiles when administered as a monotherapy to hypertensive subjects. The phase 3 TAK-491 studies have shown that TAK-491 80 mg reduced blood pressure more effectively than olmesartan medoxomil 40 mg and valsartan 320 mg, the highest approved doses in the US. *TAK-491 has recently been approved in the US by FDA, by the EMA in the European Union, and in other countries, such as Canada, Switzerland, Mexico, Philippines for the treatment of hypertension, either alone or in combination with other antihypertensive agents.*

Revised Text

TAK-491 is a prodrug that is rapidly hydrolyzed to the active moiety, TAK-536, which is a long-acting, angiotensin II AT1 receptor blocker (ARB). TAK-491 has been shown to have a strong antihypertensive effect, predictable pharmacokinetic and metabolic profiles, a prolonged duration of action, and good safety and tolerability profiles when administered as a monotherapy to hypertensive subjects. The phase 3 TAK-491 studies have shown that TAK-491 80 mg reduced blood pressure more effectively than olmesartan medoxomil 40 mg and valsartan 320 mg, the highest approved doses in the US. **As of February 2016, TAK-491 has been approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents, in a total of 59 countries worldwide, including approval in the United States by the Food and Drug Administration (FDA) in February 2011 and in the European Union by the European Medicines Agency (EMA) in December 2011.**

Rationale for Amendment

To present current registration information.

Page 33, Section 7.4: Diet, Fluid, and Activity Control (paragraph 3)

Existing Text

Subjects will be instructed to fast for at least 8 hours prior to returning to the study site for Day 1 (Visit 5), Week 4 (Visit 7), and Week 8/ET (Visit 9).

Revised Text

After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period and will be instructed to fast for at least 8 hours prior to returning to the study site for Day 1 (Visit 5), **Week 2 (Visit 6),** Week 4 (Visit 7), and Week 8/ET (Visit 9).

Rationale for Amendment

To state that after informed consent is provided, that subjects will be asked to fast prior to blood draws within the Screening Period as certain serum chemistry test results are not accurate unless the subject has fasted.

To add a fasting requirement for Week 2 (Visit 6); the fasting requirement for Week 2 (Visit 6) is due to the addition of clinical laboratory tests at this Visit.

Page 37, Section 8.1.3: Dose and Regimen (paragraphs 4 and 5)

Existing Text

Placebo Run-in Period (Day -14 [Visit 2] to Day -1)

- Subjects will be dispensed one 2-week blister card and one bottle.
- Subjects will receive single-blind placebo tablets and placebo capsules.
- First dose will be given in-clinic at Day -14 (Visit 2).
- The daily oral administered dose will be *one tablet* from a blister card and two capsules from the bottle.

Treatment Period (Day 1 [Visit 5] through Week 8 / Early Termination [Visit 9])

- Subjects will receive blinded study medication and will be instructed to take their blinded study medication prior to their first meal of the day. Subjects will be dispensed one 2-week carton and one bottle at day 1 (Visit 5), at week 2 (Visit 6), week 4 (Visit 7), and week 6 (Visit 8).
- First dose will be given in-clinic at Day 1 (Visit 5).
- The daily oral administered dose will be *one tablet* from a blister card and two capsules from the bottle.

Revised Text

Placebo Run-in Period (Day-14 [Visit 2] to Day -1)

- Subjects will be dispensed one 2-week blister card and one bottle.

- Subjects will receive single-blind placebo tablets and placebo capsules.
- First dose will be given in-clinic at Day -14 (Visit 2).
- The daily oral administered dose will be **two tablets** from a blister card and two capsules from the bottle.

Treatment Period (Day 1 [Visit 5] through Week 8 / Early Termination [Visit 9])

- Subjects will receive blinded study medication and will be instructed to take their blinded study medication prior to their first meal of the day. Subjects will be dispensed one 2-week carton and one bottle at day 1 (Visit 5), at week 2 (Visit 6), week 4 (Visit 7), and week 6 (Visit 8).
- First dose will be given in-clinic at Day 1 (Visit 5).
- The daily oral administered dose will be **two tablets** from a blister card and two capsules from the bottle.

Rationale of Amendment

To correct typographical errors.

Page 38, Section 8.1.4: Overdose (paragraph 3)

Existing Text

In the event of drug overdose, the subject should be treated symptomatically. *Elimination of TAK-491 by dialysis or hemoperfusion has not been examined.* Valsartan cannot be removed from the plasma by hemodialysis [22].

Revised Text

In the event of drug overdose, the subject should be treated symptomatically. **Hemodialysis does not significantly remove TAK-536 or M-II from the systemic circulation.** Valsartan cannot be removed from plasma by hemodialysis [22].

Rationale for Amendment

To add results from the TAK-491 phase 1 renal impairment study.

Page 43, Section 9.1.7: Documentation of Concurrent Medical Conditions (paragraph 2)

Existing Text

Continuous Positive Airway Pressure (CPAP) *data* will be collected during the study. If CPAP is ongoing at the time of informed consent, *this data* will be captured on the concurrent medical conditions (e)CRF. If CPAP is administered after first dose of study drug *administration*, then *this* will be captured as an AE.

Revised Text

Data on medical conditions that require Continuous Positive Airway Pressure (CPAP) will be collected during the study. If CPAP is ongoing at the time of informed consent, **the medical condition that required CPAP** will be captured on the concurrent medical conditions (e)CRF. If CPAP is administered after first dose of study drug, then **the medical condition** will be captured as an AE.

Rationale for Amendment

For clarity.

Pages 43-44, Section 9.1.8: Procedures for Clinical Laboratory Samples (paragraph 1, Table 9.a and paragraph 2)

Existing Text

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately *40 mL*, and The approximate total volume of blood for the study is *185 mL*. Subjects will be instructed to fast for at least 8 hours prior to blood draws on Day 1 (Visit 5), Week 4 (Visit 7), and Week 8/ET (Visit 9). 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**
Hemoglobin Hematocrit Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate Bilirubin, total Bilirubin, direct (only if total is about ULN) Blood urea nitrogen (BUN) Calcium Chloride Creatinine Creatine kinase (CK) γ-Glutamyl transferase (GGT) Glucose *(serum)* Magnesium Potassium Protein, total Sodium Uric Acid	Specific gravity pH *Creatinine* ** *Albumin* ** *Albumin:creatinine ratio (UACR)* ** *Microscopy* *RBCs* *WBCs* *Qualitative* *Protein* *Blood* *Ketones* *Bilirubin* *Glucose*

Other *(Performed as indicated on Schedule of Study Procedures)*

Lipid Panel	***Other Screening/Safety***	***Other***
High-density lipoprotein (HDL) cholesterol *Low-density lipoprotein (LDL) cholesterol* *Total cholesterol* *Triglycerides*	HbA1c Female subjects only Serum human chorionic gonadotropin (hCG)--for pregnancy *(female subjects of childbearing potential)* Urine hCG —for pregnancy *(female subjects of childbearing potential)**	eGFR Plasma renin concentration and activity Plasma and urine aldosterone

*Urine hCG will be performed at the site *at Day-7 (Visit 3) and* Day 1 (Visit 5) prior to randomization.
*** Performed as indicated on the Schedule of Study Procedures.*

The central laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, *lipid panel, other screening/safety parameters*, and other tests listed above. Estimated GFR will be calculated by the central laboratory using the Modification of Diet in Renal Disease equation [24,25]. Urinary albumin creatinine ratio (UACR) will also be calculated by the central laboratory. The urine pregnancy test *at Day -7 (Visit 3) and* Day 1 (Visit 5) 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.

Revised Text

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately **15 mL**. The approximate total volume of blood for the study is **75 mL for male subjects, and 80 mL for female subjects (including an additional 5 mL of blood drawn for a serum pregnancy test on Day -14 [Visit 2]). After**

informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period, and will be instructed to fast for at least 8 hours prior to blood draws on Day 1 (Visit 5), **Week 2 (Visit 6),** Week 4 (Visit 7), and Week 8/ET (Visit 9). 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**
Hemoglobin	Albumin	Specific gravity
Hematocrit	Alanine aminotransferase (ALT)	pH
Platelet count	Alkaline phosphatase	**Qualitative**
Red blood cell (RBC) count	Aspartate aminotransferase (AST)	**Protein**
White blood cell (WBC) count with differential	Bicarbonate	**Blood**
	Bilirubin, total	**Ketones**
	Bilirubin, direct (only if total is about ULN)	**Bilirubin**
	Blood urea nitrogen (BUN)	**Glucose**
	Calcium	**Microscopy**
	Chloride	**RBCs**
	Creatinine	**WBCs**
	Creatine kinase (CK)	
	γ-Glutamyl transferase (GGT)	
	Glucose	
	Magnesium	
	Potassium	
	Protein, total	
	Sodium	
	Uric Acid	
	High-density lipoprotein cholesterol (HDL-C)	
	Low-density lipoprotein cholesterol (LDL-C)	
	Total cholesterol	
	Triglycerides	

Other	
HbA1c	**Urine albumin**
Female subjects **of childbearing potential** only:	**Urine creatinine**
Serum human chorionic gonadotropin (hCG) for pregnancy	**Albumin:creatinine ratio (UACR)**
Urine hCG for pregnancy (a)	eGFR
	Plasma renin concentration and activity
	Plasma and urine aldosterone

(a) Urine hCG will be performed at the site on Day 1 (Visit 5) prior to randomization.

The central laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, and other tests listed above. Estimated GFR will be calculated by the central laboratory using the Modification of Diet in Renal Disease equation [24,25]. Urinary albumin creatinine ratio (UACR) will also be calculated by the central laboratory. The urine pregnancy test on Day 1 (Visit 5) will be performed at the site. The results of laboratory tests will be sent to the investigator, who is responsible for reviewing and filing these results.

Rationale for Amendment

To update the amount of blood needed at any single visit and for the study based on central laboratory blood volume requirements, to add a fasting requirement for Week 2 (Visit 6) due to the addition of clinical laboratory tests at this Visit, to state that after informed consent is provided, that subjects will be asked to fast prior to blood draws within the Screening Period as certain serum chemistry test results are not accurate unless the subject has fasted, to remove the urine pregnancy test on Day -7 (Visit 3) (replaced with a serum pregnancy test on Day -14 [Visit 2] per the current Takeda standard), to update the abbreviations for high- and low-density lipoprotein cholesterol for clarity, and to update Table 9.a for clarity.

Page 45, Section 9.1.9: Contraception and Pregnancy Avoidance Procedure (paragraphs 2 and 4)

Existing Text

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses).

During the course of the study, regular serum*/urine* human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening (Visit 1), subjects also must have a negative *urine* hCG pregnancy test at *Day -7 (Visit 3)* and on the day of first dose of study drug (Day 1 [Visit 5]), prior to receiving any dose of active study medication. A serum hCG pregnancy test will also be performed at Day 1. *The subject will start study drug based on a negative urine test, but will be contacted if the serum test is found to be positive.*

Revised Text

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses **with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).**

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening (Visit 1), subjects also must have a negative **serum** hCG pregnancy test **at Day -14 (Visit 2)** and **a negative urine pregnancy test** on the day of first dose of study drug (Day 1 [Visit 5]). **Negative urine pregnancy test must be confirmed** prior to receiving any dose of active study medication. A serum hCG pregnancy test will also be performed on Day 1 **(Visit 5), at Week 4 (Visit 7), and at Week 8/ET (Visit 9). At any time during the study, a subject with a positive serum or urine pregnancy test will be discontinued immediately.**

Rationale for Amendment

To update the definition of "postmenopausal" and the time points for serum and urine hCG tests to the current Takeda standard. To re-iterate that subjects with a positive pregnancy test will be immediately removed from the study.

Page 47, Section 9.1.10: Pregnancy (paragraph 4)

Existing Text

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.*

Revised Text

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. **Results of the evaluation of the child after birth will also be collected.**

Rationale for Amendment

The Sponsor will collect information from eligible subjects; however, does not provide this evaluation as part of the study.

Page 49, Section 9.3.1: Screening (Visit 1)

Existing Text

Subjects will be screened for enrollment prior to discontinuing previous antihypertensive treatment or initiating the placebo run-in in accordance with the predefined entrance criteria described in Section 7.0. See Section 9.1.12 for procedures for documenting screen failures.

Procedures to be completed at the Screening (Visit 1) include:

- Informed consent.
- Inclusion and exclusion criteria.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs (including standing measurements). For subjects who have not received antihypertensive medications within 28 days, determine the mean sitting SBP for subject eligibility.
- Weight and height. BMI will be calculated during data analysis.
- 12-lead ECG.
- Concomitant medications.
- Concurrent medical conditions.

- Clinical laboratory tests (hematology, chemistry, urinalysis), *lipid panel,* and HbA1c. Estimated GFR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy and acceptable methods of contraception*, if applicable*.
- Register subject in IVRS/IWRS to obtain subject number.
- Pretreatment event (PTE) assessment.

Revised Text

Subjects will be screened for enrollment prior to discontinuing previous antihypertensive treatment or initiating the placebo run-in in accordance with the predefined entrance criteria described in Section 7.0. See Section 9.1.12 for procedures for documenting screen failures. **After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period.**

Procedures to be completed at the Screening (Visit 1) include:

- Informed consent.
- Inclusion and exclusion criteria.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs (including standing measurements). For subjects who have not received antihypertensive medications within 28 days, determine the mean sitting SBP for subject eligibility.
- Weight and height. BMI will be calculated during data analysis.
- 12-lead ECG.
- Concomitant medications.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, chemistry, urinalysis) and HbA1c. Estimated GFR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy, **ova donation,** and acceptable methods of contraception **(female subjects of childbearing potential only).**
- Register subject in IVRS/IWRS to obtain subject number.
- Pretreatment event (PTE) assessment.

Rationale for Amendment

To state the requirement for fasting prior to Screening (Visit 1), and to clarify study procedures as follows: "lipid panel" is now part of the list of serum chemistry tests so is no longer stated separately; guidance regarding "ova donation" was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure), and "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9.

Page 50, Section 9.3.3.1: Placebo Run-in, Day -14 (Visit 2) (bullet points)

Existing Text

The following procedures will be performed and documented during placebo Run-in, Day -14 (Visit 2):

- Inclusion and exclusion criteria.
- Vital signs (including standing measurements).
- Concomitant medications.
- PTE/Adverse event (AE) assessment.
- Guidance on avoidance of pregnancy and acceptable methods of contraception*, if applicable*.
- Access the IVRS/IWRS for single-blind placebo run-in study medication assignment.
- Dispense single-blind placebo run-in study medication with dosing instructions.
- In-clinic dose of single-blind placebo run-in study medication.

Revised Text

The following procedures will be performed and documented during placebo Run-in, Day -14 (Visit 2):

- Inclusion and exclusion criteria.
- Vital signs (including standing measurements).
- Concomitant medications.
- PTE/Adverse event (AE) assessment.
- Guidance on avoidance of pregnancy, **ova donation**, and acceptable methods of contraception **(female subjects of childbearing potential only)**.
- **Serum pregnancy test (female subjects of childbearing potential only).**
- Access the IVRS/IWRS for single-blind placebo run-in study medication assignment.
- Dispense single-blind placebo run-in study medication with dosing instructions.

- In-clinic dose of single-blind placebo run-in study medication.

Rationale for Amendment

To add a serum pregnancy test at Day -14 (Visit 2) for consistency with the current Takeda standard. To clarify study procedures as follows: guidance regarding "ova donation" was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure), and "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9.

Page 51, Section 9.3.3.2: Placebo Run-in, Day -7 (Visit 3) (bullet points)

Existing Text

The following procedures will be performed and documented during Run-in, Day -7 (Visit 3):

- Inclusion and exclusion criteria.
- Vital signs (including standing measurements).
- *Urine pregnancy test (female subjects of childbearing potential only). Analysis is performed at the site. Test must be negative for subject to continue.*
- Guidance on avoidance of pregnancy and acceptable methods of contraception, *if applicable*.
- Concomitant medications.
- AE assessment.
- Collect single-blind placebo run-in study medication and assess compliance, and counsel if on compliance if required.
- In-clinic dose with single-blind placebo run-in study medication (from the returned medication supply).
- Redispense single-blind placebo run-in study medication and instruct subject to withhold dose the morning of Day 1 (Visit 5). Last day of single-blind dosing is Day -1.
- Remind subjects to fast 8 hours before Day 1 Visit.

Revised Text

The following procedures will be performed and documented during Run-in, Day -7 (Visit 3):

- Inclusion and exclusion criteria.
- Vital signs (including standing measurements).
- Guidance on avoidance of pregnancy, **ova donation**, and acceptable methods of contraception **(female subjects of childbearing potential only)**.
- Concomitant medications.

- AE assessment.
- Collect single-blind placebo run-in study medication and assess compliance, and counsel if on compliance if required.
- In-clinic dose with single-blind placebo run-in study medication (from the returned medication supply).
- Redispense single-blind placebo run-in study medication and instruct subject to withhold dose the morning of Day 1 (Visit 5). Last day of single-blind dosing is Day -1.
- Remind subjects to fast 8 hours before Day 1 Visit.

Rationale for Amendment

To remove urine pregnancy tests on Day -7 (Visit 3) to be consistent with the current Takeda standard. To clarify study procedures as follows: guidance regarding "ova donation" was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure), and "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9.

Pages 51-52, Section 9.3.4: Day -1 (Visit 4) (bullet points)

Existing Text

- Update eligibility status (inclusion and exclusion criteria).
- Collect vital signs.
- Document changes to concomitant medications.
- Assess for AEs.
- Guidance on avoidance of pregnancy and ova donation and acceptable methods of contraception*, if applicable*.
- Collect single-blind study medication and assess subject compliance with dosing regimen.

  Instruct subject to withhold dose the morning of the Day 1 (Randomization).
- Single-blind clinic dosing at 8:00 AM (±2 hours) and immediately prior to ABPM start.
- Start 24-hour ABPM.
- Remind subjects to fast 8 hours before Day 1 Visit.

Revised Text

- Update eligibility status (inclusion and exclusion criteria).
- Collect vital signs.
- Document changes to concomitant medications.

- Assess for AEs.
- Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception **(female subjects of childbearing potential only)**.
- Collect single-blind study medication and assess subject compliance with dosing regimen.

  Instruct subject to withhold dose the morning of the Day 1 (Randomization).
- Single-blind clinic dosing at 8:00 AM (±2 hours) and immediately prior to ABPM start.
- Start 24-hour ABPM.
- Remind subjects to fast 8 hours before Day 1 Visit.

Rationale for Amendment

To clarify study procedures as follows: "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure).

Pages 52-53, Section 9.3.5: Randomization, Day 1 (Visit 5) (bullet points)

Existing Text

Study randomization will take place on Day 1. Subjects should fast for at least 8 hours before this visit. The following procedures will be performed and documented during study randomization:

- Remove ABPM and ensure ABPM reading is successful.(for subjects conduct ABPM only).

  Reminder: If the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current placebo treatment and ABPM should be repeated within **3** days.
- Inclusion and exclusion criteria (before randomized to treatment).
- Vital signs (including standing measurements) and weight. BP must meet inclusion #1 and must not meet exclusion #1.
- Urine pregnancy test (female subjects of childbearing potential only). Analysis is performed at the site. Test must be negative for subject before subject can be randomized.
- Collect single-blind placebo run-in study medication and assess subject compliance with dosing.
- Concomitant medications.
- AE assessment.
- 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 9.1.13. If subject does not meet all of the inclusion and none of the exclusion criteria, document the subject as a run-in failure and record the primary reason for failure on

the applicable (e)CRF. The procedure for documenting run-in failures is provided in Section 9.1.13.

- Physical examination.
- 12-lead ECG.
- Clinical laboratory tests (hematology, chemistry, and urinalysis), HbA1c, *lipid panel*, *renin, aldosterone,* urine albumin, and urine creatinine. Estimated GFR and UACR will be calculated by the central laboratory.
- Serum/*urine* pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy and acceptable methods of contraception*, if applicable*.
- Dispense double-blind study medication with dosing instruction.
- In-clinic first dose of double-blind study medication.

Revised Text

Study randomization will take place on Day 1. Subjects should fast for at least 8 hours before this visit. The following procedures will be performed and documented during study randomization:

- Remove ABPM and ensure ABPM reading is successful (for subjects conduct ABPM only).

  Reminder: If the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current placebo treatment and ABPM should be repeated within **3** days.
- Inclusion and exclusion criteria (before randomized to treatment).
- Vital signs (including standing measurements) and weight. BP must meet inclusion #1 and must not meet exclusion #1.
- Urine pregnancy test (female subjects of childbearing potential only). Analysis is performed at the site. Test must be negative for subject before subject can be randomized.
- Collect single-blind placebo run-in study medication and assess subject compliance with dosing.
- Concomitant medications.
- AE assessment.
- 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 9.1.13. If subject does not meet all of the inclusion and none of the exclusion criteria, document the subject as a run-in failure and record the primary reason for failure on the applicable (e)CRF. The procedure for documenting run-in failures is provided in Section 9.1.13.
- Physical examination.

- 12-lead ECG.
- Clinical laboratory tests (hematology, chemistry, and urinalysis), HbA1c, **plasma renin concentration and activity, plasma and urine aldosterone,** urine albumin, and urine creatinine. Estimated GFR and UACR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy, **ova donation**, and acceptable methods of contraception **(female subjects of childbearing potential only).**
- Dispense double-blind study medication with dosing instruction.
- In-clinic first dose of double-blind study medication.
- **Instruct the subject to fast for at least 8 hours prior to Week 2 (Visit 6).**

Rationale for Amendment

To clarify that renin concentration and activity, and plasma and urine aldosterone will be measured, to add a fasting requirement for Week 2 (Visit 6) due to the addition of clinical laboratory tests at this Visit, and to remove duplication of urine pregnancy test instruction.

To clarify study procedures as follows: "lipid panel" is now part of the list of serum chemistry tests so is no longer stated separately; guidance regarding "ova donation" was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure), and "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9.

Page 53, Section 9.3.6: Treatment Visits, Week 2 through Week 6 (Visit 6 through Visit 8) (bullet points)

Existing Text

See Appendix A for windows for each visit. Subjects should fast for a minimum of 8 hours before *Visit 7*. The following procedures will be performed at these visits:

- Vital signs (including standing measurements) and weight.
- Laboratory tests *(Visit 7 only)*—Clinical laboratory tests (hematology, chemistry, and urinalysis), *renin, and aldosterone*. Estimated GFR will be calculated by the central lab.
- Serum/*urine* pregnancy test (female subjects of childbearing potential only) at Visit 7 only.
- Guidance on avoidance of pregnancy and acceptable methods of contraception*, if applicable*.
- Concomitant medications.
- AE assessment.
- Collect double-blind study medication and assess subject compliance with dosing regimen. If required, counsel subject on compliance.

- Access the IVRS/IWRS and dispense double-blind study medication with dosing instructions.
- In-clinic first dose of the newly assigned double-blind medication in the clinic.
- Instruct subject to withhold dose of study medication the morning of all in-clinic study visits.
- Instruct the subject to fast for at least 8 hours prior to Week 4 (Visit 7).

Revised Text

See Appendix A for windows for each visit. Subjects should fast for a minimum of 8 hours before **Visits 6 and 7**. The following procedures will be performed at these visits:

- Vital signs (including standing measurements) and weight.
- Laboratory tests: Clinical laboratory tests (hematology, chemistry, and urinalysis) **at Visits 6 and 7 only**; **plasma renin concentration and activity, and plasma and urine aldosterone at Visit 7 only**. Estimated GFR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only) at Visit 7 only.
- Guidance on avoidance of pregnancy, **ova donation**, and acceptable methods of contraception **(female subjects of childbearing potential only).**
- Concomitant medications.
- AE assessment.
- Collect double-blind study medication and assess subject compliance with dosing regimen. If required, counsel subject on compliance.
- Access the IVRS/IWRS and dispense double-blind study medication with dosing instructions.
- In-clinic first dose of the newly assigned double-blind medication in the clinic.
- Instruct subject to withhold dose of study medication the morning of all in-clinic study visits.
- Instruct the subject **at Week 2 (Visit 6)** to fast for at least 8 hours prior to Week 4 (Visit 7) **and at Week 6 (Visit 8) to fast for Week 8 (Visit 9).**

Rationale for Amendment

To add clinical laboratory tests (clinical chemistry, hematology, and urinalysis) and eGFR at Week 2 (Visit 6) to be consistent with the current Takeda standard. Week 2 blood draw will allow full characterization of possible early postdose laboratory parameter changes that are considered relevant for monitoring with use of an ARB class of drug, including serum creatinine, electrolytes, liver enzyme tests, CPK, and hemoglobin. Mild ALT and AST elevations above ULN (but not exceeding 3×ULN) were observed in 7 of 16 subjects on Day 11 of a phase 1 study of TAK-491 in healthy Chinese subjects.

To remove the urine pregnancy test from Week 4 (Visit 7) (replaced with a serum pregnancy test per current Takeda standard), to clarify that renin concentration and activity, and plasma and urine aldosterone will be measured, and to add a fasting requirement for Week 8 (Visit 9).

To clarify study procedures as follows: guidance regarding "ova donation" was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure), and "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9.

Page 53-54, Section 9.3.7: Week 8/Final Visit or Early Termination (Visit 9) (bullet points)

Existing Text

Subjects should fast for 8 hours before this visit. Assessments scheduled for Week 8/ET (Visit 9) should be completed (safety permitting) for subjects who were randomized and withdraw early. The following procedures will be performed and documented:

- Clinic dosing at 8:00 AM (±2 hours) and immediately prior to ABPM start. (in subgroup only).
- Start 24-hour ABPM. (in subgroup only).
- Vital signs (including standing measurements) and weight.
- Physical examination.
- 12-lead ECG.
- Concomitant medications.
- AE assessment.
- Collect double-blind study medication and assess subject compliance with dosing regimen.
- Access the IVRS/IWRS to register subject completion/early termination.
- Clinical laboratory tests (hematology, chemistry, and urinalysis), HbA1c, *lipid panel, renin, aldosterone*, urine albumin and urine creatinine. Estimated GFR and UACR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy and acceptable methods of contraception*, if applicable*.

Revised Text

Subjects should fast for 8 hours before this visit. Assessments scheduled for Week 8/ET (Visit 9) should be completed (safety permitting) for subjects who were randomized and withdraw early. The following procedures will be performed and documented:

- Clinic dosing at 8:00 AM (±2 hours) and immediately prior to ABPM start (in subgroup only).
- Start 24-hour ABPM (in subgroup only).

- Vital signs (including standing measurements) and weight.
- Physical examination.
- 12-lead ECG.
- Concomitant medications.
- AE assessment.
- Collect double-blind study medication and assess subject compliance with dosing regimen.
- Access the IVRS/IWRS to register subject completion/early termination.
- Clinical laboratory tests (hematology, chemistry, and urinalysis), HbA1c, **plasma renin concentration and activity, plasma and urine aldosterone**, urine albumin and urine creatinine. Estimated GFR and UACR will be calculated by the central laboratory.
- Serum pregnancy test (female subjects of childbearing potential only).
- Guidance on avoidance of pregnancy, **ova donation**, and acceptable methods of contraception **(female subjects of childbearing potential only)**.

Rationale for Amendment

To clarify that renin concentration and activity, and plasma and urine aldosterone will be measured. To clarify study procedures as follows: "lipid panel" is now part of the list of serum chemistry tests so is no longer stated separately; guidance regarding "ova donation" was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure), and "if applicable" was replaced with "female subjects of childbearing potential" for consistency with Section 9.1.9.

Page 54, Section 9.3.8: ABPM Removal (Visit 10) (bullet points)

Existing Text

This visit only applies to the ABPM subgroup. Assessments scheduled for ABPM Removal Visit (Visit 10) should be completed (safety permitting) for subjects. The following procedures will be performed:

- Remove ABPM and ensure ABPM reading is successful.

  Reminder: If the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within **3** days
- Vital signs (including standing measurements) and weight.
- AE assessment.
- Concomitant medications.

Revised Text

This visit only applies to the ABPM subgroup. Assessments scheduled for ABPM Removal Visit (Visit 10) should be completed (safety permitting) for subjects. The following procedures will be performed:

- Remove ABPM and ensure ABPM reading is successful.

  Reminder: If the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within **3** days
- Vital signs (including standing measurements) and weight.
- AE assessment.
- Concomitant medications.
- **Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception (female subjects of childbearing potential only).**

Rationale for Amendment

To add guidance for avoidance of pregnancy, ova donation, and acceptable methods of contraception at this Visit to be consistent with the current Takeda standard.

Page 54, Section 9.3.9: Follow-up (bullet 1)

Existing Text

- Subjects should receive a follow-up telephone call to assess any new or ongoing AEs and changes to concomitant medications 14 days after the last dose of study medication (single-blind placebo or double-blind). Female subjects of childbearing potential should be counseled on avoidance of pregnancy and use of acceptable methods of contraception through 30 days after the last dose of study medication.

Revised Text

- Subjects should receive a follow-up telephone call to assess any new or ongoing AEs and changes to concomitant medications 14 days after the last dose of study medication (single-blind placebo or double-blind). Female subjects of childbearing potential should be counseled on avoidance of pregnancy, **ova donation**, and use of acceptable methods of contraception through 30 days after the last dose of study medication.

Rationale for Amendment

The guidance regarding “ova donation” was added to the avoidance of pregnancy and acceptable methods of contraception procedure for consistency with Appendix A and Section 9.1.9 (Contraception and Pregnancy Avoidance Procedure).

Page 58, Section 10.1.4: SAEs

Existing Text

Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

Revised Text

Is a CONGENITAL ANOMALY/BIRTH DEFECT.

Rationale for Amendment

To be consistent with ICH and USFDA definitions.

Page 67, Section 13.1.1: Analysis Sets (paragraphs 4 and 6)

Existing Text

Per-Protocol Set (PPS): All subjects in the FAS, excluding any subjects who had major protocol violations. Major *deviations* from the protocol leading to exclusion from the Per Protocol Set will be identified prior to unblinding of subject's treatment assignment.

The FAS will be the primary data set used for efficacy analyses. Efficacy analysis based on the Per Protocol Set will also be performed where appropriate. All routine safety analysis will be based on the Safety Analysis Set.

Revised Text

Per-Protocol Set (PPS): All subjects in the FAS, excluding any subjects who had major protocol violations. Major **violations** from the protocol leading to exclusion from the Per Protocol Set will be identified prior to unblinding of subject's treatment assignment.

The FAS will be the primary data set used for efficacy analyses. Efficacy analysis based on the Per Protocol Set will also be performed where appropriate. All routine safety analysis will be based on the Safety Analysis Set.

All subjects who were randomized more than once will be excluded from the safety analysis set, the FAS, and the PPS.

Rationale for Amendment

For clarity.

Pages 79-81, Appendix A: Schedule of Study Procedures

Existing Text

		Washout				Double-Blind Treatment Period					Post-Treatment Period	
			Single-Blind Placebo Run-in									
Study Day:	**Screen-ing Visit (a)**	**D -21 (b) or D -28 (c)**	**D -14 (d,e)**	**D -7**	**D -1 (v)**	**D1**	**W2**	**W4**	**W6**	**Final clinic/ ET W8 (f)**	**ABPM removal visit (w)**	**Tele-phone Follow-up (g)**
Visit Windows	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**N/A**	**N/A**
Visit Number:	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N/A**
Informed consent	X											
Inclusion/exclusion criteria	X		X	X	X	X						
Demographics and medical history	X											
Medication history	X											
Physical examination	X					X				X		
PTE assessment (h)	X		X									
AE assessment (i,j,r)			X	X	X	X	X	X	X	X	X	X
Vital signs (k)	X		X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (l)	X					X	X	X	X	X	X	
12-lead ECG	X					X				X		
Clinical laboratory tests (m)	X					X		X		X		
Urine albumin and creatinine and UACR (n)						X				X		
Lipid panel	*X*					*X*				*X*		
HbA1c	X					X				X		
Estimated GFR (n)	X					X		X		X		
Serum hCG (o)	X					X		X		X		
Urine pregnancy test (o,p)				*X*		X		*X*				
Guidance on avoidance of pregnancy and ova donation	X		X	X	X	X	X	X	X	X		X
Notify subject to begin washout period (q)		X										
Plasma renin concentration and activity, Plasma and urine Aldosterone						X		X		X		
ABPM start (subgroup only)					X					X		
ABPM removal (subgroup only)						X					X	
Concurrent medical conditions (r)	X											
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X
Access IVRS/IWRS (s)	X		X			X	X	X	X	X		
Dispense single-blind study placebo for run-in and dose in-clinic (t)			X									
Redispense single-blind placebo for run-in				X								
Last dose of single-blind placebo (u)					X							

		Washout				Double-Blind Treatment Period					Post-Treatment Period	
			Single-Blind Placebo Run-in									
Study Day:	**Screen-ing Visit (a)**	**D -21 (b) or D -28 (c)**	**D -14 (d,e)**	**D -7**	**D -1 (v)**	**D1**	**W2**	**W4**	**W6**	**Final clinic/ ET W8 (f)**	**ABPM removal visit (w)**	**Tele-phone Follow-up (g)**
Visit Windows	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**N/A**	**N/A**
Visit Number:	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N/A**
Dispense double blind study drug						X	X	X	X			
Last dose of double blind study drug										X		
Clinic dosing (u)			X	X	X	X	X	X	X	X		
Compliance assessment				X	X	X	X	X	X	X	-	

Footnotes are on the last table page.

(a) The Screening Visit should be scheduled before the washout/run-in period begins so that laboratory tests results can be reviewed and subject eligibility can be confirmed before other treatments are stopped or placebo is initiated.
(b) Subjects taking previous antihypertensive agents are required to participate in a 3-week washout period (Days -21 to -1).
(c) If the subject's previous antihypertensive treatment includes amlodipine or chlorthalidone, then the washout must be extended to 4 weeks (Days -28 to -1).
(d) Subjects who have not received antihypertensive treatment within 28 days before screening can be entered into the run-in period as soon as all inclusion and exclusion criteria, including laboratory results, have been verified.
(e) At minimum, the run-in should be 10 days but can extend to as long as the subject has an adequate supply of single-blind placebo run-in study medication.
(f) Conduct Final Visit procedures for subjects who are randomized and discontinued early per Section 7.6.
(g) Telephone contact for the follow-up AE and concomitant medication assessments should be made approximately 14 days after the last dose (single-blind placebo or double-blind).
(h) Reports of pretreatment events should be solicited at each visit from the time that informed consent is acquired until the first dose of placebo run-in study medication.
(i)AEs should be solicited at each visit from the time that single-blind placebo run-in study medication is started through 14 days after the last dose (via the telephone follow-up AE assessment).
(j) Spontaneous reports of AEs and SAEs should be collected from the time of the first dose of single-blind placebo run-in medication through 14 or 30 days, respectively, after the last dose.
(k) Includes sitting and standing BP and pulse rate. Pulse rate will be taken manually while sitting and standing.
(l) Collect height at the Screening (Visit 1) only; BMI will be calculated during data analysis at Screening (Visit 1).
(m) Hematology, serum chemistry, and urinalysis tests (as listed in Table 9.a). *Subjects should be fasted for at least 8 hrs prior to Visits 5, 7 and 9.*
(n) UACR and estimated GFR will be calculated by the central laboratory.
(o) Women of childbearing potential only.
(p) Urine pregnancy test is performed at the site *at Day -7 (Visit 3) and* prior to randomization on Day 1 (Visit 5).
(q) Subject can be notified by telephone to begin the washout period.
(r) *Continuous Positive Airway Pressure (CPAP) data will be collected during the study. If CPAP is ongoing at the time of informed consent, this data will be captured on the concurrent medical conditions (e)CRF. If CPAP is administered after first dose of study drug administration, then this will be captured as an AE.*
(s) If a subject withdraws early, contact IVRS/IWRS to document the ET.
(t) Subjects to take the first dose of single-blind placebo run-in study medication in-clinic.
(u) Instruct subjects to withhold their dose of study drug, if applicable so they can be dosed in-clinic. For ABPM subgroup subjects, clinic dosing at 8:00AM((±2 hours) for visit 4 and 9.
(v) Visit 4 is only applied to ABPM subgroup subjects; if the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within 3 days.
(w)Visit 10 is only applied to ABPM subgroup subjects; if the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within 3 days.

Revised Text

		Washout			Double-Blind Treatment Period					Post-Treatment Period	
			Single-Blind Placebo Run-in								
Study Day or Week:	**Screening Visit (a)**	**D -21 (b) or D -28 (c)**	**D -14 (d,e)**	**D -7**	**D -1 (v)**	**D1**	**W2**	**W4**	**W6**	**Final clinic/ ET W8 (f)**	**ABPM Removal Visit (w)**	**Tele-phone Follow-up (g)**
Visit Window	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**N/A**	**N/A**
Visit Number:	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N/A**
Informed consent	X											
Inclusion/exclusion criteria	X		X	X	X	X						
Demographics and medical history	X											
Medication history	X											
Physical examination	X					X				X		
PTE assessment (h)	X		X									
AE assessment (i,j,r)			X	X	X	X	X	X	X	X	X	X
Vital signs (k)	X		X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (l)	X					X	X	X	X	X	X	
12-lead ECG	X					X				X		
Clinical laboratory tests (m)	X					X	**X**	X		X		
Urine albumin and creatinine and UACR (n)						X				X		
HbA1c	X					X				X		
Estimated GFR (n)	X					X	**X**	X		X		
Serum hCG (o)	X		**X**			X		X		X		
Urine pregnancy test (o,p)						X						
Guidance on avoidance of pregnancy, ova donation, and acceptable methods of contraception	X		X	X	X	X	X	X	X	X	**X**	X
Notify subject to begin washout period (q)		X										
Plasma renin concentration and activity, plasma and urine aldosterone						X		X		X		
ABPM start (subgroup only)					X					X		
ABPM removal (subgroup only)						X					X	

		Washout			Double-Blind Treatment Period					Post-Treatment Period	
			Single-Blind Placebo Run-in								
Study Day or Week:	**Screening Visit (a)**	**D -21 (b) or D -28 (c)**	**D -14 (d,e)**	**D -7**	**D -1 (v)**	**D1**	**W2**	**W4**	**W6**	**Final clinic/ ET W8 (f)**	**ABPM Removal Visit (w)**	**Tele-phone Follow-up (g)**
Visit Window	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**N/A**	**N/A**
Visit Number:	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N/A**
Concurrent medical conditions (r)	X											
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X
Access IVRS/IWRS (s)	X		X			X	X	X	X	X		
Dispense single-blind study placebo for run-in and dose in-clinic (t)			X									
Redispense single-blind placebo for run-in				X								
Last dose of single-blind placebo (u)					X							
Dispense double blind study drug						X	X	X	X			
Last dose of double blind study drug										X		
Clinic dosing (u)			X	X	X	X	X	X	X	X		
Compliance assessment				X	X	X	X	X	X	X		

Footnotes for Appendix A are on the next page.

Footnotes for Appendix A

D=Day, W=Week.

(a) The Screening Visit should be scheduled before the washout/run-in period begins so that laboratory tests results can be reviewed and subject eligibility can be confirmed before other treatments are stopped or placebo is initiated.
(b) Subjects taking previous antihypertensive agents are required to participate in a 3-week washout period (Days -21 to -1).
(c) If the subject's previous antihypertensive treatment includes amlodipine or chlorthalidone, then the washout must be extended to 4 weeks (Days -28 to -1).
(d) Subjects who have not received antihypertensive treatment within 28 days before screening can be entered into the run-in period as soon as all inclusion and exclusion criteria, including laboratory results, have been verified.
(e) At minimum, the run-in should be 10 days but can extend to as long as the subject has an adequate supply of single-blind placebo run-in study medication.
(f) Conduct Final Visit procedures for subjects who are randomized and discontinued early per Section 7.6.
(g) Telephone contact for the follow-up AE and concomitant medication assessments should be made approximately 14 days after the last dose (single-blind placebo or double-blind).
(h) Reports of pretreatment events should be solicited at each visit from the time that informed consent is acquired until the first dose of placebo run-in study medication.
(i)AEs should be solicited at each visit from the time that single-blind placebo run-in study medication is started through 14 days after the last dose (via the telephone follow-up AE assessment).
(j) Spontaneous reports of AEs and SAEs should be collected from the time of the first dose of single-blind placebo run-in medication through 14 or 30 days, respectively, after the last dose.
(k) Includes sitting and standing BP and pulse rate. Pulse rate will be taken manually while sitting and standing.
(l) Collect height at the Screening (Visit 1) only; BMI will be calculated during data analysis at Screening (Visit 1).
(m) Hematology, serum chemistry, and urinalysis tests (as listed in Table 9.a). **After informed consent is provided, subjects will be asked to fast prior to blood draws within the Screening Period, and will be instructed to fast for at least 8 hours prior to blood draws on Day 1 (Visit 5), Week 2 (Visit 6), Week 4 (Visit 7), and Week 8/ET (Visit 9).**
(n) UACR and estimated GFR will be calculated by the central laboratory.
(o) Women of childbearing potential only.
(p) Urine pregnancy test is performed at the site **and must be negative for subject** prior to randomization on Day 1 (Visit 5).
(q) Subject can be notified by telephone to begin the washout period.
(r) **Data on medical conditions that require Continuous Positive Airway Pressure (CPAP) will be collected during the study. If CPAP is ongoing at the time of informed consent, the medical condition that required CPAP will be captured on the concurrent medical conditions (e)CRF. If CPAP is administered after first dose of study drug, then the medical condition will be captured as an AE.**
(s) If a subject withdraws early, contact IVRS/IWRS to document the ET.
(t) Subjects to take the first dose of single-blind placebo run-in study medication in-clinic.
(u) Instruct subjects to withhold their dose of study drug, if applicable so they can be dosed in-clinic. For ABPM subgroup subjects, clinic dosing at 8:00 AM (±2 hours) for Visits 4 and 9.
(v) Visit 4 is only applied to ABPM subgroup subjects; if the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within 3 days.
(w)Visit 10 is only applied to ABPM subgroup subjects; if the ABPM measurement does not pass the predefined criteria (fails), the subject must continue the current treatment and ABPM should be repeated within 3 days.

Rationale for Amendment

To add clinical laboratory tests (clinical chemistry, hematology, and urinalysis) and eGFR at Week 2 (Visit 6) to be consistent with the current Takeda standard. Week 2 blood draw will allow full characterization of possible early postdose laboratory parameter changes that are considered relevant for monitoring with use of an ARB class of drug, including serum creatinine, electrolytes, liver enzyme tests, CPK, and hemoglobin. Mild ALT and AST elevations above ULN (but not exceeding 3×ULN) were observed in 7 of 16 subjects on Day 11 of a phase 1 study of TAK-491 in healthy Chinese subjects.

To add a serum pregnancy test at Day -14 (Visit 2), remove urine pregnancy tests from Day -7 (Visit 3) and Week 4 (Visit 7), and add guidance on avoidance of pregnancy and ova donation to Visit 10 to be consistent with the current Takeda standard. Footnote (r) modified for clarity.

The row for "lipid panel" was removed as it is now included in the list of serum chemistry tests in Table 9.a. To state that after informed consent is provided, that subjects will be asked to fast prior to blood draws within the Screening Period as certain serum chemistry test results are not accurate unless the subject has fasted. "Acceptable methods of contraception" was added to the procedure regarding guidance on avoidance of pregnancy and ova donation for consistency with Section 9.3 of the protocol.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Operations Approval	17-May-2016 03:43 UTC
	Clinical Science Approval	17-May-2016 10:46 UTC
	Pharmacovigilance Approval	17-May-2016 18:25 UTC
	Statistical Approval	17-May-2016 19:18 UTC