



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: an 8-week study

NCT Number: NCT02480764

SAP Approve Date: 29 November 2017

Certain information within this Statistical Analysis Plan 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.



STATISTICAL ANALYSIS PLAN

Study Number: TAK-491_305

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

TAKEDA DEVELOPMENT CENTER ASIA, PTE. LTD.

Version: Final

Date: 29 November 2017

CONFIDENTIAL PROPERTY OF TAKEDA

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda.

APPROVAL SIGNATURES

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 Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Prepared at Quintiles by:

PPD

Date

TDC Approvals:

PPD

Date

PPD

Date

PPD

Date

PPD

Date

CONFIDENTIAL

1.0 TABLE OF CONTENTS

1.0	TITLE PAGE	1
1.1	APPROVAL SIGNATURES	2
2.0	TABLE OF CONTENTS.....	3
3.0	LIST OF ABBREVIATIONS	5
4.0	INTRODUCTION	6
5.0	OBJECTIVES	7
5.1	Primary Objective	7
5.2	Secondary Objective	7
5.3	Study Design	7
6.0	ANALYSIS ENDPOINTS.....	11
6.1	Primary Endpoint.....	11
6.2	Secondary Endpoints	11
6.3	Additional Endpoints	11
6.4	Safety Assessments.....	12
7.0	DETERMINATION OF SAMPLE SIZE	13
8.0	METHODS OF ANALYSIS AND PRESENTATION.....	14
8.1	General Considerations	14
8.1.1	Statistical Software	14
8.1.2	Summary Statistics and Precision.....	14
8.1.3	Definition of Study Day and Baseline	14
8.1.4	Definitions of Study Visit Windows.....	15
8.2	Significant Protocol Deviations.....	15
8.3	Analysis Sets	16
8.4	Disposition of Subjects	17
8.5	Demographic and Baseline Efficacy Characteristics.....	17
8.5.1	Demographic and Baseline Characteristics	17
8.5.2	Baseline Efficacy Parameters	18
8.6	Medical History and Concurrent Medical Conditions	18
8.7	Medication History and Concomitant Medications.....	19
8.8	Study Drug Exposure and Compliance.....	20
8.9	Efficacy Analysis.....	21
8.9.1	Primary Efficacy Endpoint.....	21
8.9.2	Secondary Efficacy Endpoints.....	22
8.9.3	Additional Efficacy Endpoints	23

8.9.4	Efficacy Analysis for ABPM Subgroup Subjects.....	23
8.10	Safety Analysis	25
8.10.1	Adverse Events	25
8.10.2	Clinical Laboratory Evaluations	27
8.10.3	Vital Signs and Weight	29
8.10.4	12-Lead ECGs	29
8.10.5	Physical Examinations	30
8.11	Interim Analysis	30
8.12	Changes in the Statistical Analysis Plan From the Protocol Analysis Plan.....	30
9.0	REFERENCES.....	31

LIST OF IN-TEXT TABLES

Table 5.a	Schedule of Study Procedures	9
Table 8.a	Visit Analysis Windows for Efficacy and Safety Variables	15
Table 8.b	Clinical Laboratory Tests	28

LIST OF IN-TEXT FIGURES

Figure 5.a	Schematic of Study Design	8
------------	---------------------------------	---

LIST OF APPENDIX

Appendix A.	Criteria for Identification of Markedly Abnormal Laboratory Values	32
-------------	--	----

2.0 LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
ICH	International Conference on Harmonization
LLN	lower limit of normal
LOCF	last observation carried forward
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
OC	observed case
PE	physical examination
PPS	per protocol set
PT	preferred term
QD	once daily
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SI	system International
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

3.0 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for TAK-391_305, a phase 3, double-blind, randomized, 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).

The purpose of this document is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of the double-blind data prior to database lock. This SAP was developed based on the International Conference on Harmonization (ICH) E3 and E9 Guidelines and in reference to the following document:

- Protocol TAK-491_305 Amendment No.4 dated 09 May 2016.

Any deviations during the analysis and reporting process from the current SAP will be described and justified in the final report. Analysis issues that suggest changes to the principal features stated in the protocol will be documented in a protocol amendment. Otherwise, the statistical analysis plan will be updated through an amendment with the changes in the analysis documented in the amendment.

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the antihypertensive effect of TAK-491 compared with valsartan in Chinese subjects with essential hypertension.

4.2 Secondary Objective

The secondary objective is to evaluate the safety and tolerability of TAK-491 compared with valsartan.

4.3 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 SBP ≥ 150 and ≤ 180 mm Hg on Day 1). A subgroup of approximately 60 subjects/arm from selected sites will undergo 24-hour ambulatory blood pressure monitoring (ABPM) 2 times during the study.

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.

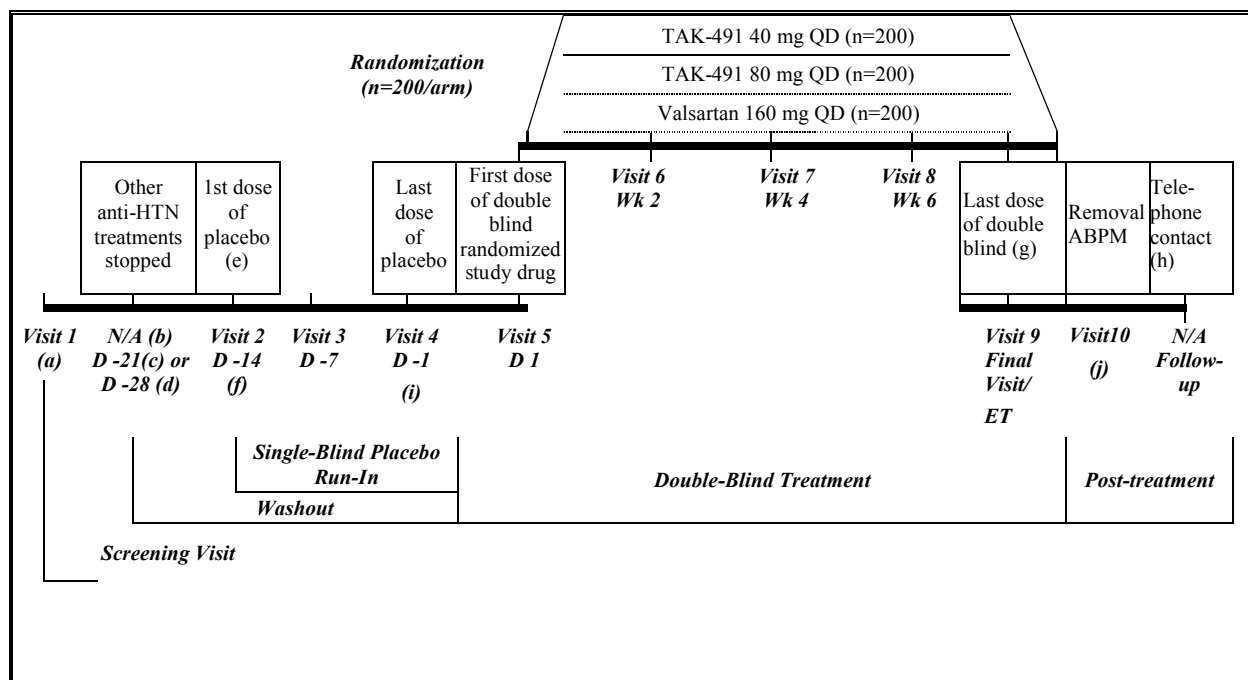
At Day 1 (Visit 5), eligible subjects will be randomly assigned to one of the following 3 groups with a 1:1:1 ratio:

- 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 4.a](#). A schedule of assessments is listed in [Table 4.a](#).

Figure 4.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.

Table 4.a Schedule of Study Procedures

Study Day:	Screen- ing Visit (a)	Washout				Double-Blind Treatment Period					Post-Treatment Period	
		D -21 (b) or D -28 (c)	Single-Blind Placebo Run-in									
			D -14 (d,e)	D -7	D -1 (v)	D1	W2	W4	W6	Final clinic/ET W8 (f)	ABPM Removal Visit (w)	Telephone 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		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	
Concurrent medical conditions (r)	X											
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X
Access IVRS/TWRS (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 Table 5.a are on the next page.

CONFIDENTIAL

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 protocol 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. 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 (\pm 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.

5.0 ANALYSIS ENDPOINTS

5.1 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 Secondary Endpoints

The secondary endpoints are as follows:

- 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.

5.3 Additional Endpoints

Additional endpoints for efficacy are as follows:

CCI

5.4 Safety Assessments

Safety will be assessed via adverse events (AEs), laboratory tests, 12-lead electrocardiogram (ECG) findings and vital signs (including orthostatic vital signs).

6.0 DETERMINATION OF SAMPLE SIZE

Assuming a standard deviation (SD) of 17 mm Hg and a 10% drop-out 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 non-inferiority with a margin of 1.5 mm Hg between TAK-491 and valsartan.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

7.1.1 Statistical Software

Statistical analysis will be performed using the SAS System[®], Version 9.2 or higher, on a Windows platform.

7.1.2 Summary Statistics and Precision

All tabulations of analysis results will include summaries for the following treatment groups: TAK-491 40 mg once daily (QD), TAK-491 80 mg QD and valsartan 160 mg QD.

Unless otherwise specified, confidence intervals (CIs), statistical tests, and resulting p-values will be reported as 2-sided and will be assessed at the 5% significance level. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, SD or standard error (SE) as appropriate, minimum, median, and maximum. In general, the number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the raw data received from data management.
- SD and SE: 2 more than the number of decimal places allotted in the raw data.
- Minimum and maximum: equal to the number of decimal places allotted in the raw data.
- CIs will be presented using the same number of decimal places as SD or SE.

Exceptions to the above may be made for derived data. The specific precisions for each derived variables will be included in the derived dataset specifications. For categorical data, frequency counts and percentages will be presented. Percentages will be reported to 1 decimal place.

When applicable, data listings will be accompanied by individual subject data listings sorted by treatment, study centre and subject identifier. The actual day relative to the start of treatment will be determined and included in the listings. All ABPM subjects will be marked in the listings.

Derived analysis datasets will be produced from raw data. This allows for convenient review of the data as well as any necessary supplemental analyses. All data from the raw datasets will be included in the derived datasets. Derived dataset specifications will be developed to include the names and definitions of derived variables in the derived SAS datasets. All analyses and data listings will be performed using the derived datasets.

7.1.3 Definition of Study Day and Baseline

Study Day 1 is defined as the date on which a subject took the first dose of double-blind study medication, as recorded on the electronic case report form (eCRF). Other study days are defined relative to Study Day 1 with Day -1 being the day prior to Study Day 1. If the date of an event is

on or after the date of first dose then Study Day = date of event – date of first dose + 1. If the date of an event is prior to the date of first dose then Study Day = date of event – date of first dose.

The baseline value for a variable is defined as the last non-missing observation collected before first dose on Day 1 (including a screening value or unscheduled assessment, if necessary). Time of first dose is collected, so baseline value will be determined based on both date and time when the time of the measurement is also available. In the case where the last non-missing measurement (except AE and concomitant medications) and the first dose on Day 1 coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value.

7.1.4 Definitions of Study Visit Windows

For each visit, a window will be defined; this window will establish a time interval around which data will be considered for the analysis of the scheduled visit pertaining to that window. The lower and upper bounds of each window are the approximate midpoints between the scheduled days for the current visit and its adjacent scheduled visits, with the exception of the Week 2 visit. The value used in analysis for by-visit summaries is the value within the specified window that is closest to the scheduled study day. If two observations are equidistant from the scheduled visit date, the observation with a later date will be used. The visit windows and applicable study day ranges are presented in [Table 7.a](#). Cut-off days for inclusion in the window (number of days following the date of the last dose of double-blind study drug) are provided.

Table 7.a Visit Analysis Windows for Efficacy and Safety Variables

Visit	Scheduled Visit Day	Visit Window (Days)					
		Variables Scheduled at Week 2, Week 4, Week 6, Week 8	Variables Scheduled at Week 2, Week 4, Week 6	Variables Scheduled at Week 2, Week 4, Week 8	Variables Scheduled at Week 8	Variables Scheduled at Week 4, Week 8	Safety Variables Summarized by Visit
Baseline	1	≤1	≤1	≤1	≤1	≤1	≤1
Week 2	14	2 - 21	2 - 21	2 - 21			2 - 21
Week 4	28	22 - 35	22 - 35	22 - 42		2 - 42	22 - 35
Week 6	42	36 - 49	36 - Last Dose + 7				36 - 49
Week 8	56	50 - Last Dose + 7		43 - Last Dose + 7	2 - Last Dose + 7	43 - Last Dose + 7	50 - Last Dose + Safety Cutoff

Note: Any value collected on Day 1 but after the administration of first dose will be grouped under Week 2.

7.2 Significant Protocol Deviations

Significant protocol deviations collected on the eCRF will be summarized by treatment group and overall. Significant protocol deviations will also be listed.

CONFIDENTIAL

7.3 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

The Randomized Set will consist of all subjects who were randomized. For subjects who were randomized more than once, only the first randomization is used.

The Safety Analysis Set will consist of all subjects who received at least one dose of double-blind study medication. Subjects will be analyzed according to the study medication they received. Subjects who were randomized more than once are excluded from the Safety Analysis Set.

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least one dose of double-blind study medication. A subject in FAS will be included in the analyses of a specific variable only when there is both a baseline value and at least one value during the double-blind treatment period. Subjects will be analyzed according to the treatment group to which they were randomized. Subjects who were randomized more than once are excluded from the Full Analysis Set.

The Per Protocol Set (PPS) will consist of all subjects in the FAS, excluding those who meet following criteria:

1. Subjects with SBP <150 mm Hg on Day 1.
2. Subjects who take study drug of a different treatment from the one randomized.
3. Subjects who are randomized more than once.
4. Subjects with a significant protocol deviation impacting baseline blood pressure.
5. Subjects with compliance outside of the range 70%-130%.
6. Subjects that took a prohibited medication potentially impacting baseline or Week 8 blood pressure.

Additional criteria may be identified prior to unblinding. If so, the additional criteria will be finalized and documented prior to database lock. Subjects who are included in the FAS but excluded from the PPS will be summarized for each criterion by treatment groups and overall. These subjects will also be presented in the listings.

The Ambulatory Blood Pressure Monitoring Set (ABPM Set) will consist of the subset of FAS subjects who received an ABPM recording at baseline. Subjects who have ABPM endpoints at both baseline and at least one post dose value will be included in all ABPM related summaries and analyses. Subjects who were randomized more than once are excluded from the ABPM Set.

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

7.4 Disposition of Subjects

Disposition of all screened subjects will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

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

Disposition of all randomized subjects will be tabulated by randomized treatment. For subjects who were randomized more than once, only the first randomization is used in the summary. The categories will include:

- Randomized subjects.
- Subjects who were randomized but not treated with double-blind study drug.
- Subjects who completed double-blind study drug.
- Subjects who prematurely (permanently) discontinued double-blind study drug.
- Subjects unblinded by the investigator (inadvertently or for safety reasons).

The primary reason for discontinuation of study drug and/or study visits (pretreatment event/adverse event, major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy, lack of efficacy and other), as entered on the eCRF, will be tabulated for all randomized subjects.

The above summaries will also be performed for ABPM subgroup subjects.

Double-blind treatment group, date of first double-blind dose, date of last double-blind dose, duration of treatment (study day of last dose) and the reason for premature discontinuation of study drug/study visit will be listed for each randomized subject in the listings. Subjects in ABPM subgroup will be flagged. A listing of inclusion/exclusion criteria responses by subject will also be provided.

7.5 Demographic and Baseline Efficacy Characteristics

7.5.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age (years) at the date of informed consent, gender, race, height (cm), weight (kg), body mass index (BMI) (kg/m^2), smoking classification, female reproductive status, estimated glomerular filtration rate (eGFR) ($\text{mL}/\text{min}/1.73\text{m}^2$) and baseline HbA1c (%) will be summarized for each treatment group and overall using the Safety Analysis Set. Demographic and baseline characteristics for the ABPM subgroup will also be summarized.

Age is computed as the difference in years between date of birth and informed consent date; one decimal will be kept for age in derived data. Age will be summarized as a continuous variable and will also be tabulated using the following categories: <45 years, 45 to 64 years, <65 years, ≥65 years and ≥75 years.

Race will be recorded on the eCRF as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander and White. Subjects who identify themselves as more than one race on the eCRF will be classified as Multiracial for tabulation, and will be included only in the Multiracial category.

Baseline BMI is derived as: $\text{BMI (kg/m}^2\text{)} = (\text{baseline weight in kg})/((\text{height in cm})/100)^2$; one decimal will be kept for baseline BMI in derived data. BMI will be summarized as a continuous variable and will also be tabulated using the following categories: <27 kg/m² and ≥27 kg/m².

Baseline eGFR will be summarized as a continuous variable and will also be tabulated using the following categories: <30 mL/min/1.73m², 30 to <60 mL/min/1.73m², 60 to <90 mL/min/1.73m² and ≥90 mL/min/1.73m².

There will be no inferential analysis of these demographic and baseline characteristics.

All individual demographic and baseline characteristics will be listed by treatment, study centre and subject number. The demographic data listing will include subject identifier, treatment, date of informed consent, date of birth, age at date of informed consent, gender, race, height, baseline weight and baseline BMI. Smoking classification, female reproductive status, baseline HbA1c level, baseline clinic measures of SBP and DBP and baseline eGFR will also be presented in a data listing.

7.5.2 Baseline Efficacy Parameters

Baseline values of continuous efficacy endpoints will be summarized and analyzed using an analysis of variance (ANOVA) with treatment as a fixed factor. These endpoints include calculated mean sitting SBP and DBP. For ABPM subgroup subjects, the endpoints include all ABPM parameters.

Baseline calculated mean sitting SBP and DBP will be summarized as continuous variables. Further, baseline calculated mean sitting SBP will be tabulated using the following categories: 140 to <160 mm Hg, 160 to <180 mm Hg and ≥180 mm Hg. A separate tabulation will be completed for the following categories: <median baseline calculated mean sitting SBP and ≥median baseline calculated mean sitting SBP. Baseline calculated mean sitting DBP will be tabulated using the following categories: <90 mm Hg and ≥90 mm Hg.

The baseline efficacy parameters will also be listed.

7.6 Medical History and Concurrent Medical Conditions

Summaries of medical history (significant conditions or diseases that stopped at or prior to the time of informed consent) and concurrent medical conditions (significant ongoing conditions or

diseases present at the time of informed consent) will be based on the Safety Analysis Set. No inferential statistics will be presented.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA), Version 20.0 MIXED coding system.

Medical history and concurrent medical conditions will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group. The tables will be sorted in alphabetic order by SOC and in decreasing frequency based on the total number of subjects in each PT. The number and percentage of subjects with any significant medical history and concurrent medical conditions will be summarized for each SOC and PT. The denominator used for calculating the percentages will be the total number of subjects included in each treatment group. For the tables, if a subject reports the same PT multiple times, then that PT will be counted only once for that subject. Similarly, if a subject reports multiple conditions within the same SOC, then that SOC will be counted only once for that subject.

A similar summary table will be provided for the ABPM subgroup.

All medical history and concurrent medical condition data will be listed.

7.7 Medication History and Concomitant Medications

Summaries of medication history and concomitant medications will be based on the Safety Analysis Set. No inferential statistics will be presented.

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.

Concomitant medications are recorded on the eCRF and include any medication other than study drug taken at any time between time of informed consent through the end of the study (including the follow-up visit).

Medication history and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version 01March2015 Enhanced coding system.

Medication history and concomitant medications will be summarized by treatment and preferred medication name. Preferred medication names will be sorted by decreasing frequency based on the total number of subjects.

Concomitant medications will be summarized separately according to the following subgroups:

- Concomitant medications that started and stopped prior to baseline. This includes any medication that was stopped after the time of informed consent and prior to the first dose of double-blind study medication.
- Concomitant medications that started prior to and were ongoing at baseline. This includes any medication that started before and was not stopped prior to the first dose of double-blind study medication.

- Concomitant medications that started after baseline. This includes any medication that started at or after the first dose of double-blind study medication.
- Concomitant medications that were ongoing at baseline and those that started after baseline. This includes any medication that started before and was not stopped prior to the first dose of double-blind study drug as well as any medication that started at or after the first dose of double-blind study medication.

Similar summaries will be provided for the ABPM subgroup.

Separate listings for medication history and concomitant medications will be presented by site and subject number.

7.8 Study Drug Exposure and Compliance

The duration of exposure to double-blind study medication is defined as date of last dose of double-blind study drug - date of first dose double-blind study drug + 1. The date of last double-blind dose will be obtained from the eCRF. In the event that the date of last dose is missing, the last dose date will be estimated as the later date between the last drug dispense date plus the number of days in the dosing interval (dispense date + next visit day – last visit day + 1) and the last study visit day for analysis and summary purposes.

The duration of exposure to double-blind treatment will be summarized by treatment group as a continuous variable and tabulated using following categories: 1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 28 days, 29 to 35 days, 36 to 42 days, 43 to 49 days, 50 to 56 days, 57 to 63 days and 64 days or more.

Subjects are to take 2 tablets for TAK-491 (40mg/80mg) and matching placebo or 2 capsules for valsartan and matching placebo each day. Overall percent study drug compliance for the double-blind treatment period will be calculated as: $100 \times [(\text{number of tablets dispensed} - \text{number of tablets returned}) / (\text{expected number of tablets to be taken})]$, where the expected number of tablets to be taken = $[4 \times (\text{date of last dose of medication} - \text{date of first dose of medication} + 1)]$. Compliance will be presented to 1 decimal place in the derived dataset.

Overall double-blind study drug compliance will be summarized using descriptive statistics and by the number of subjects in each of the following compliance categories: <70%, 70 to 130%, >130%. A missing category will also be included, if applicable.

The summary of study drug exposure and compliance will be based on the Safety Analysis Set. No inferential statistics will be presented.

The above tables will also be provided for the ABPM subgroup. A compliance for ABPM procedure will be provided. The number and percentage of subjects with qualified ABPM recordings will be summarized by treatment group and overall at baseline and Week 8.

All study drug administration (single-blind placebo and double-blind study drug) and accountability data will be listed by site and subject number.

7.9 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. Efficacy analyses based on the PPS will also be performed, if appropriate.

The trough sitting clinic SBP/DBP will consist of an average (arithmetic mean) of the non-missing SBP/DBP measurements performed at each visit that satisfy the trough requirements. Post-baseline clinic BP measurements qualify as trough if they are obtained 20-28 hours (inclusive) after the previous study drug dose. Baseline clinic BP measurements are considered trough by default as no double-blind study drug has yet to be taken by subjects.

For the clinic sitting SBP and DBP, missing values will be handled using last observation carried forward (LOCF) methodology. In the LOCF analysis data set, the last observed post-baseline double-blind value will be carried forward and used for all subsequent scheduled time points where data are missing (e.g., the subject has missing data or has dropped out of the study). The efficacy analysis for the response criteria will also be based on the LOCF data set.

7.9.1 Primary Efficacy Endpoint

The primary efficacy endpoint, change from Baseline to Week 8 in trough sitting clinic SBP, will be analyzed using an analysis of covariance (ANCOVA) model, with treatment group as a fixed effect and baseline sitting clinic SBP as a continuous covariate. Estimates of treatment LS mean, differences in LS means between TAK-491 treatment groups and valsartan, p-value and 2-sided 95% CIs for the treatment difference will be determined from the framework of the ANCOVA model. 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 non-inferiority of TAK-491 80 mg to valsartan 160 mg will be performed using a non-inferiority 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 non-inferiority of TAK-491 40 mg to valsartan 160 mg will be performed using a non-inferiority 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 [4]. Therefore, the non-inferiority 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 non-inferior 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 following sensitivity analyses will be performed for the primary endpoint (change from Baseline in trough sitting clinic SBP at Week 8):

- Conduct the described primary analysis in the PPS to explore the robustness of the primary efficacy result.
- A multiple imputation (MI) procedure to assess the impact of missing data and drop-outs for the FAS and PPS. The analysis based on MI assumes the data to be missing at random stratified within each treatment group while retaining consistency for each subject across various visits.
- ANCOVA method which is identical to the primary efficacy analysis, using only the observed case (OC) data for the FAS and PPS.

In addition, the following subgroup analyses will be performed for the primary endpoint where appropriate. Only LOCF data for the FAS will be used:

- gender (males and females).
- age (<45 years, 45 to 64 years, ≥ 65 years and ≥ 75 years).
- baseline BMI(<27 kg/m² and ≥ 27 kg/m²).
- baseline sitting SBP(140 to <160mm Hg, 160 to <180mm Hg and ≥ 180 mm Hg).
- baseline sitting SBP (<baseline median and \geq baseline median).
- baseline sitting DBP (<90 mm Hg and ≥ 90 mm Hg).

7.9.2 Secondary Efficacy Endpoints

Change from Baseline in trough clinic sitting DBP at Week 8 will be analyzed using the ANCOVA model described for the primary endpoint in Section 7.9.1, excluding the sequential testing. Baseline sitting clinic DBP will be the continuous covariate in the ANCOVA model. Subgroup analyses and OC sensitivity analyses described for the primary endpoint will also be performed for trough clinic sitting DBP secondary endpoints.

The percentage of subjects responding to treatment and percentage of subjects reaching the target blood pressure 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 (e.g., 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.

Response criteria for clinic sitting SBP at Week 8 will be analyzed using a logistic model with treatment group as fixed effect and baseline clinic sitting SBP as a covariate. The odds ratio and its 95% CI will be estimated from the framework of the logistic model. Similarly, a logistic model with treatment as a fixed effect and baseline clinic sitting DBP as a covariate will be used to analyze the response criteria for sitting clinic DBP. The joint response criteria for both clinic sitting SBP and DBP will be analyzed using a logistic model with treatment as a fixed effect and baseline clinic sitting 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 efficacy analysis for the response criteria will be based on the LOCF data set.

7.9.3 Additional Efficacy Endpoints

CCI

7.9.4 Efficacy Analysis for ABPM Subgroup Subjects

All ABPM related summaries and analyses will be based on OC data for the ABPM Set.

The average and change from baseline ABPM values will be calculated by hour and 2-hour over the entire duration of the ABPM measurements. The following comparisons will be presented in figures:

- Average baseline ABPM values by hour for the 0- to 24-hour interval, final ABPM values by hour for the 0- to 24-hour interval, and change from baseline in ABPM values by hour for the 0- to 24-hour interval.

- Average baseline ABPM values by hour for the 0- to 12-hour interval, final ABPM values by hour for the 0- to 12-hour interval, and change from baseline in ABPM values by hour for the 0- to 12-hour interval.

The analysis of ABPM will be based on the following variables that are obtained by summarizing the individual ABPM measurements, namely, 0- to 24-hour mean ABPM, 0- to 12-hour mean ABPM, daytime mean ABPM, nighttime mean ABPM, peak effect, 22- to 24-hour trough ABPM and trough-to-peak ratios.

The baseline 0- to 24-hour mean ABPM will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the first ABPM observation and including all observations recorded over the subsequent 24 hours (any observations that are recorded ≥ 24 hours after the first observation will be excluded).

The final 0- to 24-hour mean ABPM will consist of the average of ABPM measurements over the time period beginning with the final study medication dose and including all observations recorded over the 24-hour period following that dose.

The baseline 0- to 12-hour mean ABPM will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the first ABPM observation and including all observations recorded over the subsequent 12 hours (any observations that are recorded ≥ 12 hours after the first observation will be excluded). The final 0- to 12-hour mean ABPM will consist of the average of ABPM measurements over the time period beginning with the final study medication dose and including all observations recorded over the 12-hour period following that dose.

The daytime mean ABPM will consist of the average of those ABPM measurements that were included in the respective 24-hour mean ABPM calculations and were also recorded between the hours of 6 AM (inclusive) and 10 PM (exclusive).

The nighttime mean ABPM will consist of the average of those ABPM measurements that were included in the respective 24-hour mean ABPM calculations and were also recorded between the hours of 12 AM (inclusive) and 6 AM (exclusive).

The baseline 22- to 24-hour trough ABPM will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning 22 hours (inclusive) after the first ABPM observation and ending 24 hours (exclusive) after the first ABPM observation.

The final 22- to 24-hour trough ABPM will consist of the average of ABPM measurements over the time period beginning 22 hours (inclusive) after the final study medication dose and ending 24 hours (exclusive) after the final study medication dose.

The peak effect interval was determined for each subject as the 2-hour interval during the 24 hours after dosing in which the maximum decrease from baseline was observed for SBP. Peak effect is defined as the change from baseline to Week 8 in BP values by ABPM during the peak effect interval.

Trough-to-Peak Ratio was calculated as mean trough response divided by peak effect, where trough response is defined as the change from baseline in the mean trough (22- to 24 hour) ABPM to Week 8.

The variables based on ABPM will be presented in summary tables by descriptive statistics (including mean, SD, median, minimum, and maximum). Change from Baseline for the ABPM variables will also be summarized in this fashion.

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 for ABPM Set. This analysis will be performed separately for DBP. Similar analyses will be performed for other ABPM parameters:

- 24-hour mean SBP and DBP.
- Trough (22-24h) SBP and DBP.
- Mean daytime (6 AM to 10 PM) SBP and DBP.
- Mean nighttime (12 AM to 6 AM) SBP and DBP.
- Mean SBP and DBP at 0 to 12 hours after dosing.
- Peak SBP and DBP effect

Only observed data will be used for the summary and analyses of ABPM parameters. No imputation will be performed for missing data.

ABPM parameters and ABPM related data collected on the eCRF will be included in the data listings. Raw 24-hour ABPM recordings will not be presented in a listing.

7.10 Safety Analysis

All safety summaries will be based on the Safety Analysis Set. The safety analysis will use OC data and be restricted to descriptive statistics unless otherwise specified.

7.10.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject that has been administered a pharmaceutical product, including placebo. It does not necessarily have to have a causal relationship with this treatment. AEs will be coded using MedDRA Version 20.0 MIXED.

A pretreatment event is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study that occurs prior to administration of any study medication. It does not necessarily have to have a causal relationship with study participation. Pretreatment events will be summarized by SOC and PT.

Run-in AEs are defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, which occurred on or after the first

dose of run-in placebo and prior to administration of double-blind study drug. Run-in AEs will be summarized by SOC and PT.

A treatment-emergent adverse event (TEAE) will be defined as any AE, regardless of relationship to study drug, that occurs after the first dose of double-blind study drug and 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 serious AEs. TEAEs will be summarized by SOC and PT.

AEs are recorded in the eCRF as being related or not related to study drug and study procedure. TEAEs that are recorded as related to study drug and/or study procedure will be summarized separately. TEAEs will also be summarized by intensity/severity (mild, moderate, severe). Serious TEAEs, TEAEs leading to study drug discontinuation and TEAEs leading to death will also be summarized.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. Thus, if a subject has two distinct AEs, each of which corresponds to a distinct PT but both of which correspond to the same SOC, then that subject will be counted once at that SOC subject-count summary level and once at each of the two PT subject-count summary levels. For the intensity summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, then the TEAE with maximum intensity will be included in the summary. For the relationship summaries, if a subject reports multiple TEAEs coded to the same SOC or PT then the TEAE related to study drug will be included in the summary. If a TEAE is missing causality and/or intensity, then it will be assumed that the TEAE is related and/or severe in summary tables.

TEAEs will be summarized by treatment group, which will include the number and percentage of subjects as follows:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Events by SOC and PT (Overall and by Age groups: <45 years-old; 45-64 years old, inclusive; <65 years old; ≥65 years old; ≥75 years old).
- Treatment-Emergent Adverse Events by SOC.
- Treatment-Emergent Adverse Events by PT.
- Most Frequent (≥5% in any treatment arm) Treatment Emergent Adverse Events by SOC and PT (Overall and by Age groups: <45 years-old; 45-64 years old, inclusive; <65 years old; ≥65 years old; ≥75 years old).
- Most Frequent (≥5% in any treatment arm) Non-Serious Treatment Emergent Adverse Events by SOC and PT.
- Drug-Related Treatment-Emergent Adverse Events by SOC and PT (Overall and by Age groups: <45 years-old; 45-64 years old, inclusive; <65 years old; ≥65 years old; ≥75 years old).
- Intensity of Treatment-Emergent Adverse Events by SOC and PT

- Intensity of Drug-Related Treatment-Emergent Adverse Events by SOC and PT.
- Procedure-Related Treatment-Emergent Adverse Events by SOC and PT
- Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by SOC and PT.
- Serious Treatment-Emergent Adverse Events by SOC and PT.
- Pretreatment Adverse Events by SOC and PT.
- Run-in Adverse Events by SOC and PT.

Subject mappings will be presented by SOC and PT for the summary of TEAEs, serious TEAEs and TEAEs leading to the discontinuation of study drug.

All AEs will be listed by site and subject number.

7.10.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the Safety Analysis Set and will be presented using System International (SI) units unless otherwise stated. Refer to [Table 4.a](#) for the schedule of measurements for clinical laboratory tests and to [Table 7.b](#) for a list of all clinical laboratory tests. Clinical laboratory data will be presented by subject and no inferential statistics will be presented.

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, lipid panel, other screening/safety parameters and other tests listed in [Table 7.b](#). Only data obtained within 7 days of the last dose of study drug will be included in the summaries. All data will be presented in the listings.

Table 7.b Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Hemoglobin	Albumin	Specific gravity
Hematocrit	Alanine aminotransferase	pH
Platelet count	Alkaline phosphatase	
Red blood cell count	Aspartate aminotransferase	<u>Qualitative</u>
White blood cell count with differential	Bicarbonate	Protein
	Bilirubin, total	Blood
	Bilirubin, direct (only if total is above ULN)	Ketones
	Blood urea nitrogen	Bilirubin
	Calcium	Glucose
	Chloride	
	Creatinine	<u>Microscopy</u>
	Creatine kinase	Red Blood Cells
	γ -Glutamyl transferase	White Blood Cells
	Glucose (serum)	
	Magnesium	
	Potassium	
	Protein, total	
	Sodium	
	Uric Acid	
	High-density lipoprotein cholesterol	
	Low-density lipoprotein cholesterol	
	Total cholesterol	
	Triglycerides	
Other		
HbA1c	Urine albumin	
Female subjects of childbearing potential only:	Urine creatinine	
Serum human chorionic gonadotropin for pregnancy	Albumin: creatinine ratio	
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 following summaries of hematology, serum chemistry, urinalysis lab tests, lipid panel, and other will be presented for each scheduled time point (each visit and final visit):

Descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment group for the observed and change from baseline laboratory test values will be based on a single data value selected according to the window convention described in [Table 7.a](#). Note that qualitative urinalysis parameters will only be listed.

Shifts in laboratory test values will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with low, normal and high values relative to the normal range used at the central laboratory. Marginal totals will be provided for the baseline visit (e.g. total number of subjects with low, normal and high values at baseline) for each treatment group. Shifts from normal at baseline to high at visit (as well as normal to low) will be supplemented with the percentage (n in shift category/total normal at baseline). This classification will be based on the low, normal and high alert flags reported by the central laboratory. If a subject has

multiple values within a particular visit window, the most abnormal result will be used for summary. All clinical laboratory tests with reference ranges will be included in the shift summary.

Subjects with markedly abnormal values (MAV), identified by the criteria in Appendix A, for laboratory tests will be tabulated. If a subject has multiple values within a particular visit window, the most abnormal result will be used for summary. MAV tables will include all laboratory parameters with available MAV criteria.

The number and percentage of subjects with one or more post-baseline serum creatinine level $\geq 1.3 \times$ baseline AND $>$ upper limit of normal (ULN) (e.g., 30% creatinine elevation) and $\geq 1.5 \times$ baseline AND $>$ ULN (e.g., 50% creatinine elevation) will be summarized by visit. Subjects meeting these criteria at any post dose visits and remain elevated at the final visit will also be summarized and listed. The number and percentage of subjects with consecutive elevations will also be determined. The relationship between the change of creatinine and change of clinic BP may be assessed.

Listings of all clinical safety laboratory data will be provided by site and subject number. Listings will be produced for hematology, serum chemistry and urinalysis categories separately. Laboratory data outside of the normal reference ranges will be indicated in the listings. A listing of subjects with MAVs will be provided.

7.10.3 Vital Signs and Weight

Refer to [Table 4.a](#) for scheduled measurements of Vital Signs and weight. Trough sitting clinic SBP/DBP are efficacy endpoints in Section 7.9 and therefore will not be included in this section.

Vital signs (including sitting and standing pulse rate, weight and standing BP) at each scheduled visit and changes from baseline will be summarized using descriptive statistics for the Safety Analysis Set.

Orthostatic vital signs will be calculated as the decrease in BP from sitting (the one that is two minutes after standing and the closest to standing BP in terms of the time of the measurement) to standing (e.g., standing BP – sitting BP). The number and percentage of subjects with one or more decreases in BP meeting the criteria of orthostatic hypotension (SBP decreases ≥ 20 mm Hg or DBP decreases ≥ 10 mm Hg after standing for 2 minutes) will be summarized by treatment and visit. A listing of the orthostatic vital signs for such subjects will also be provided. Only the values meeting the criteria will be included in the listing. No inferential statistics will be presented.

Only data obtained within 7 days of the last dose of study drug will be included in vital signs summaries. All data will be presented in the listings.

7.10.4 12-Lead ECGs

ECG data will be summarized using the Safety Analysis Set. The ECG endpoints include Heart Rate (beats/minute), RR interval (msec), PR interval (msec), QT interval (msec) and QRS interval (msec). Missing values of RR will be imputed as $RR(msec) = 1000 * (60/HR)$. The

corrected QT interval will be computed using both Bazett's ($QTcB = QT/RR^{1/2}$) and Fridericia's ($QTcF = QT/RR^{1/3}$) formulas, where RR is presented in seconds. The QTc intervals computed by both methods will be summarized along with other vital signs parameters. No decimal place will be presented in the derived dataset and TLF outputs.

Descriptive statistics (n, mean, SD, median, minimum and maximum values) will be used to summarize 12-lead ECG values at Baseline, Week 8 or final visit and change from Baseline to Week 8 or final visit by treatment group.

The number and percentage of subjects with an increase ≥ 30 and ≥ 60 msec from Baseline in QTc interval will be tabulated as well as a tabulation of subjects with a post-baseline value > 500 msec and an increase ≥ 60 msec from baseline.

Overall ECG interpretation category (normal, not clinically significant abnormal, clinically significant abnormal) will be collected on the eCRF according to the scheduled measurements. Shifts in ECG interpretation will be presented as cross-tabulations of numbers of subjects with normal, not clinically significant abnormal, and clinically significant abnormal ECG interpretation results (and will include categories for missing and totals). Marginal totals will be provided for the baseline visit (e.g. total number of subjects in each category at baseline) for each treatment group. Percentage will also be provided.

Shifts in QTc intervals between Baseline and Week 8 will also be tabulated based on the value categories listed below:

- Females: ≤ 450 , > 450 to 470 , > 470 to 500 and > 500 msec.
- Males: ≤ 430 , > 430 to 450 , > 450 to 500 and > 500 msec.

Only data obtained within 7 days of the last dose of study drug will be included in the summaries. No inferential statistics will be presented. All ECG data will be presented in the data listings.

7.10.5 Physical Examinations

All physical examination findings will be listed by treatment, study centre and subject number.

7.11 Interim Analysis

Not applicable.

7.12 Changes in the Statistical Analysis Plan From the Protocol Analysis Plan

Not applicable.

8.0 REFERENCES

1. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
2. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.
3. 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, Takeda Development Center Asia, Pte. Ltd., Protocol No. TAK-491_305, Amendment Number 4, 09 May 2016.
4. 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. Clinical Therapeutics 1998; 20:1106-14.

Appendix A. Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology

Parameter	Low Abnormal	High Abnormal
Hemoglobin	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
Hematocrit	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
RBC count	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
WBC count	$<0.5 \times \text{LLN}$	$>1.5 \times \text{ULN}$
Platelet count	$<75 \times 10^9/\text{L}$	$>600 \times 10^9/\text{L}$

LLN=lower limit of normal, ULN=upper limit of normal, RBC=red blood cell, WBC=white blood cell.

Chemistry

Parameter	Low Abnormal	High Abnormal
ALT	--	$>3 \times \text{ULN}$
ALT	--	$>5 \times \text{ULN}$
ALT	--	$>10 \times \text{ULN}$
AST	--	$>3 \times \text{ULN}$
AST	--	$>5 \times \text{ULN}$
AST	--	$>10 \times \text{ULN}$
GGT	--	$>3 \times \text{ULN}$
Alkaline phosphatase	--	$>3 \times \text{ULN}$
Total bilirubin	--	$>34.2 \mu\text{mol/L}$
ALT and Total Bilirubin	--	ALT $>3 \times \text{ULN}$ and TB $>2 \times \text{ULN}$
AST and Total Bilirubin	--	AST $>3 \times \text{ULN}$ and TB $>2 \times \text{ULN}$
Albumin	$<25 \text{ g/L}$	--
Total protein	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
Creatinine	--	$>177 \mu\text{mol/L}$
Sodium	$<130 \text{ mmol/L}$	$>150 \text{ mmol/L}$
Potassium	$<3.0 \text{ mmol/L}$	$>6.0 \text{ mmol/L}$
Blood Urea Nitrogen	--	$>10.7 \text{ mmol/L}$
Calcium	$<1.75 \text{ mmol/L}$	$>2.88 \text{ mmol/L}$
Creatine kinase	--	$>5 \times \text{ULN}$
Uric Acid	--	$>773 \mu\text{mol/L}$

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT= γ -glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal, TB=total bilirubin.


Urinalysis

Parameter	Low Abnormal	High Abnormal
Blood	--	≥1+
Glucose	--	≥1+
Ketones	--	≥2+
Casts	--	Any
Microscopic RBCs*	--	≥5/hpf
Microscopic WBC	--	≥20/hpf
pH	≤4	≥8
Protein	--	≥1+
Specific Gravity	--	--

Hpf=high power field, RBC=red blood cell, WBC=white blood cell.

* Markedly abnormal if repeated values both meet the criteria; e.g., if two values are greater than or equal to 5/hpf within 30 days of one another.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD 	Biostatistics Approval	30-Nov-2017 20:59 UTC
	Biostatistics Approval	30-Nov-2017 21:12 UTC
	Clinical Science Approval	30-Nov-2017 21:29 UTC
	Pharmacovigilance Approval	30-Nov-2017 21:57 UTC