Title: International, multicentre, observational, non-interventional prospective study of azilsartan medoxomil in patients with arterial hypertension who are overweight or obese in the Russian Federation and the Republic of Kazakhstan

NCT Number: NCT02756819

SAP Approve Date: February 20, 2019

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

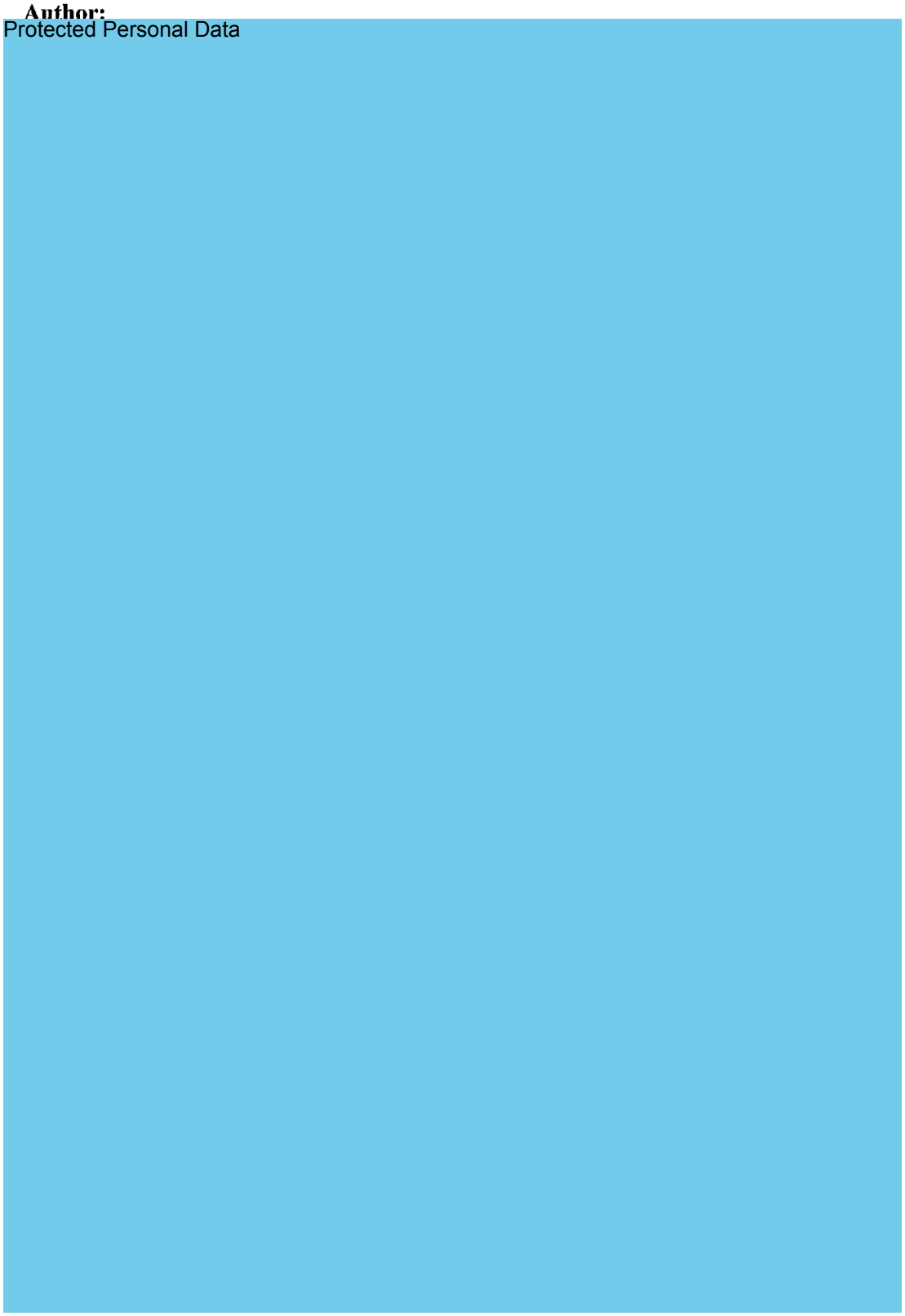
Protocol Number:	Azilsmedox-5008 (MACS-2014-10066)
Statandocs' project code:	0489
Protocol Title:	CONSTANT - International multicentre, observational, non-interventional prospective study of azilsartan medoxomil in patients with arterial hypertension who are overweight or obese in the Russian Federation and the Republic of Kazakhstan
Effective date:	20.02.2019
Version No.:	2.1

CHANGE HISTORY

Версия/ Version	Дата/Date	Описание/Description	Автор/Author
1.0	28.11.2016	Initial version	Protected Personal Data
1.1	15.02.2018	Amendment	
1.2	01.08.2018	Amendment	
2.0	25.12.2018	Efficacy analyses changes	
2.1.	20.02.2019	Statistical analysis on population of Republic of Kazakhstan	

SIGNATURES

Author:



CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
CSR	clinical study report
ECG	electrocardiogram
FAS	Full Analysis Set
HR	heart rate
Ln	logarithmic transformation (natural)
LOCF	last observation carried forward
MMRM	mixed effects model for repeated measures
NA	not applicable
PPS	Per Protocol Set
Q1	25th percentile
Q3	75th percentile
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SS	Safety Set
TEAE	treatment emergent adverse event
HTN	Hypertension

1. Contacts

1.1 Study sponsor

Name and address:	Takeda Pharmaceutical LLC (Takeda) 2, bld. 1, Usacheva str., Moscow 119048, Russian Federation Phone: + 7 495 933 5511 Fax: + 7 495 502 1625
Project Manager:	Protected Personal Data
Medical Responsible	

1.1 CRO – Ligand Research

Name and address:	Protected Personal Data
Project Manager:	

1.2 CRO responsible for interim and final statistical analysis

Name and address:	Protected Personal Data
Responsible for scientific oversight of statistical analysis and statistical report preparation	
Responsible for statistical processing and statistical analysis:	

1.3 CRO responsible for Statistical analysis of data of Republic of Kazakhstan

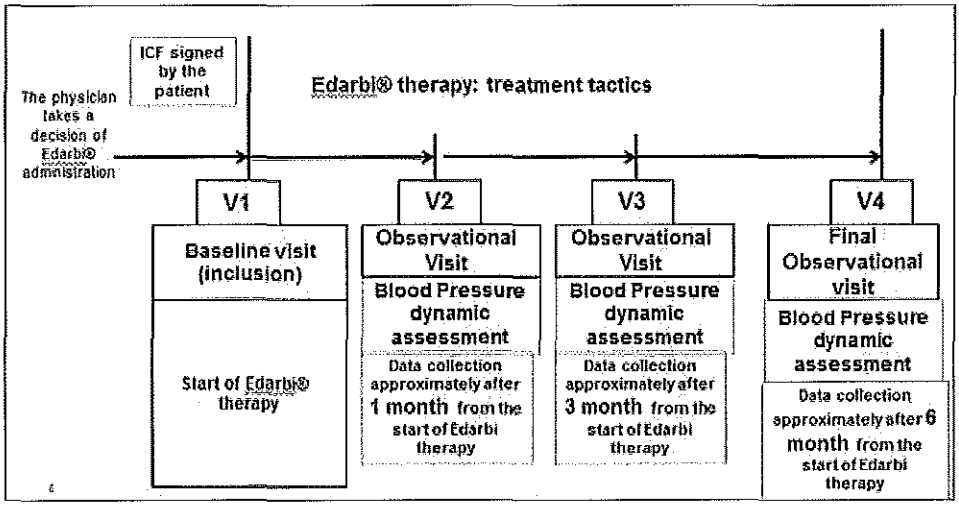
Name and address:	Protected Personal Data
Responsible for scientific oversight of statistical analysis and statistical report preparation	
Responsible for statistical processing and statistical analysis:	

2. PROTOCOL SUMMARY

2.1 Study design and conduct

This is an international, prospective, multicentre, non-interventional, observational study.

The observational study schematic:



For study details and study assessment's schedule see the Protocol of the Study.

Term	Baseline visit (V1)	Observational visit (Month 1)	Observational visit (Month 3)	Final Observational visit (Month 6)
Inclusion/exclusion criteria	X			
Signed Informed consent form	X			
Date of visit	X	X	X	X
Demographic information	X			
Medical history (incl. risk factors, prior diseases, prior HTN therapy etc)	X			
Body Mass Index (BMI)	X	X	X	X
Physical examination and vital signs*	X	X	X	X
HTN therapy (drugs, doses)	X	X	X	X
Laboratory tests and instrumental exams*	X	X	X	X
Concurrent medical conditions	X			

Concomitant medication		X	X	X
Adverse events		X	X	X

* All examinations (physical examination and vital signs, laboratory tests and instrumental exams) are done in accordance with clinical routine practice and physician's decision. Instrumental exams are measurement of blood pressure, hard rate, ECG, 24-hour ambulatory blood pressure monitoring. All examinations should be registered in the CRF only if they are done in routine practice.

2.2 Study objectives

2.2.1 Primary objective

1. To evaluate the effect of Edarbi® on clinic systolic blood pressure (SBP) among hypertensive (HTN) patients with overweight or obesity (Month 6).

2.2.2 Secondary objectives

1. To evaluate the effect of Edarbi® on clinic diastolic blood pressure (DBP) among HTN patients with overweight or obesity (Month 6);
2. To evaluate the proportion of overweight or obese patients who respond to Edarbi® therapy (defined as decrease of SBP≥ 20 mm Hg or decrease of DBP≥10 mm Hg) (Month 6);
3. To evaluate the proportion of overweight or obese patients who achieved target BP (defined as SBP<140 and DBP<90mm Hg) (Month 6);
4. To evaluate the effect of Edarbi® on clinic SBP among HTN patients with overweight or obesity in subgroups of patients: BMI (overweight, obese), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (Month 6);
5. To evaluate the effect of Edarbi® on clinic DBP among HTN patients with overweight or obesity in subgroups of patients: BMI (overweight, obese), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (Month 6);
6. To evaluate the proportion of overweight or obese patients who achieve target BP (SBP<140 mm Hg, DBP<90 mm Hg) in subgroups of patients: BMI (overweight, obese), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (Month 6).

2.2.3 Safety objectives

1. To describe AE characteristics.

2.2.4 Exploratory objectives

1. Company Confidential Information
2.
3.
4.
5.
6.
7.
8.

2.3 Study variables

2.3.1 Efficacy variables

Primary outcome variables:

1. Change from baseline in clinic SBP on Edarbi® therapy (Time Frame: Baseline and Month 6).

Secondary outcome variables:

1. Change from baseline in clinic DBP on Edarbi® therapy (Time Frame: Baseline and Month 6);
2. Proportion (%) of patients who respond to Edarbi® therapy (defined as decrease of SBP≥ 20 mm Hg or decrease of DBP≥10 mm Hg; Time Frame: Baseline and Month 6);
3. Proportion (%) of patients who achieve target BP <140 mm Hg (defined as SBP<140 and DBP<90mm Hg) (Time Frame: Baseline and Month 6);
4. Changes from baseline in clinic SBP in subgroups of patients: BMI (overweight, obese), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (Time Frame: Baseline and Month 6);
5. Changes from baseline in clinic DBP in subgroups of patients: overweight, obese (stages I-III), impaired glucose tolerance (yes, no), metabolic syndrome (yes, no), diabetes mellitus (yes, no) (Time Frame: Baseline and Month 6);
6. Proportion (%) of patients who achieve target BP (SBP<140 mm Hg, DBP<90 mm Hg) in subgroups of patients: overweight, obese (stages I-III), impaired glucose tolerance (yes, no), metabolic syndrome (yes, no), diabetes mellitus (yes, no) (Time Frame: Baseline and Month 6).

All variables listed above will be evaluated within final study analysis and within interim study analysis. It's planned that interim statistical analysis of study data will be performed as soon as470 first study patients have completed the study by achieving final study visit or discontinuing their participation

2.3.2 Safety variables

Safety Outcome variables:

1. Incidence and type of adverse events.

Safety outcomes will be evaluated within final study analysis and within interim study analysis. It's planned that interim statistical analysis of study data will be performed as soon as 470 first study patients have completed the study by achieving final study visit or discontinuing their participation

2.3.3 Other variables of interest

Exploratory outcome variables:

1. Company Confidential Information [redacted]

2.4 Sample size and power

This particular analysis is performed for the subgroup of study participants from Republic of Kazakhstan. There was no formal power or sample size calculation planned in the protocol for this subgroup, only the total sample size (taking Russian Federation and Republic of Kazakhstan as one sample for analysis). Therefore, certain results may be unavailable or not applicable due to the small sample size of subgroup from Republic of Kazakhstan.

3. DATA ANALYSIS CONSIDERATIONS

Overall analysis frame

This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data, i.e. all data listed in section 2.3 ("Study variables"), except for the data collected only for the purpose of data cleaning.

The primary and secondary outcomes of the study are presented in section 2.3.1 ("Efficacy variables").

Summary of study data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, 25 percentile, 75 percentile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. For variables marked "binary" exact (Clopper-Pearson) 95% confidence intervals will be calculated where appropriate. For categorical variables with more than 2 categories 95% confidence intervals will be calculated using Goodman`s method or other appropriate (e.g. Sison and Glatz) method.

In general, all data will be listed, sorted by site and patient, and when appropriate by visit number within patient. All summary tables will be structured with a column for each cohort in the increasing order and will be annotated with the total population size relevant to that table/dose cohort, including any missing observations.

Baseline data

The baseline visit is defined as the last observations collected prior to administration of the study drug.

Analysis of data from republic of Kazakhstan

All the study objectives listed in the section 2.2. of the current SAP will be evaluated within the final study analysis study analysis of data obtained in the Republic of Kazakhstan. As this analysis was not initially planned and accordingly was not formally powered, some of the endpoints and subgroup analysis can be not applicable given the actual amount of data collected. If the analysis is not possible, this will be noted in the corresponding section of the statistical analysis report, with the reasons listed.

Definitions of study-specific derived variables

In accordance with the Protocol of the Study, derived variables will be calculated using following conventions:

Target Blood Pressure (BP) – target BP for all categories of patients is <140/90 mm Hg, except of patients with diabetes in whom target BP is <140/85 mm Hg.

Target Diastolic Blood Pressure (DBP) –, target DBP for all categories of patients is <90 mm Hg, expect of patients with diabetes in whom target BP is <85 mm Hg

Target Systolic Blood Pressure (SBP) –, target SBP for all categories of patients is <140mm Hg

BP response – decrease of SBP≥ 20 mm Hg or decrease of DBP≥10 mm Hg

Overweight – elevation of body mass index (BMI) is from 25 to 30 (25 <= BMI < 30)

Obesity – elevation of BMI >= 30. Obesity is divided for 3 classes according to severity.

Class of obesity	BMI
Obesity class 1	30 ≥ BMI ≥ 34.9
Obesity class 2	35 ≥ BMI ≥39.9
Obesity class 3	BMI ≥ 40

Metabolic syndrome – according to the definition of the Russian Ministry of Health for the management of hypertension (HTN), metabolic syndrome is diagnosed in the presence of main criterion and 2 any additional criteria listed below:

Main Criterion	**Men**	**Women**
waist circumference	≥94 cm	≥80 cm
Additional Criteria	**Men**	**Women**
low-density lipoprotein cholesterol	>3.0 mmol/l	>3.0 mmol/l
high-density lipoprotein cholesterol	<1.0 mmol/L	<1.2 mmol/L
Triglycerides	>1.7 mmol/L	>1.7 mmol/L
impaired glucose tolerance (post-load plasma glucose)	post-load plasma glucose 7.8 - 11.0 mmol/L	post-load plasma glucose 7.8 - 11.0 mmol/L
fasting glucose	6.1 - 7.0 mmol/l	6.1 - 7.0 mmol/l

Body Mass Index (BMI) Calculation

BMI will be calculated using the formula provided below, rounded to 2 decimals:

BMI = weight [kg]**/height** [m]^2

4. CLINICAL DATABASE

Database for final analysis

A snapshot of the clinical database will be generated after all subjects have completed through the final visit of the study or discontinued participation in the study. Snapshot for final analysis will be performed after database lock according to relevant CRO`s Standard Operating Procedure (SOP) for database lock and data extraction. All tables, figures, and listings (TFLs) described in this SAP will be generated on this snapshot of the database.

Database for interim analysis

As soon as first 470 study patients have completed through final visit of the study or discontinue their participation a snapshot of the clinical database will be generated. The snapshot of the database will be performed in accordance with Standard operating procedures of CRO responsible for Data collection and data management. All tables, figures and listings described in this SAP will be generated on this interim snapshot of the database

Database for final analysis in the Republic of Kazakhstan

Analysis, according to this particular Statistical Analysis Plan, will be performed only for the data obtained in the Republic of Kazakhstan.

A snapshot of the clinical database will be generated after all patients have completed through the final visit of the study or discontinued participation in the study. Snapshot for final analysis will be performed after database lock according to relevant CRO`s Standard Operating Procedure (SOP) for database lock and data extraction. Statandocs will receive the data related to study participants from Republic of Kazakhstan only, via the agreed communication channels.

All tables, figures, and listings (TFLs) described in this SAP will be generated on this snapshot of the database (with data from Republic of Kazakhstan only).

5. STATISTICAL / ANALYTICAL ISSUES

Visit windows

In accordance with the protocol, due to the non-interventional study design it's not possible to appoint exact times for the study visits, although it is expected that the period of observation will be approximately 6 months. The frequency of the visits will be assigned by each physician according to their routine practice. It is anticipated that the patients will visit their physician every 3 months and more often at the beginning until the patient achieves target blood pressure.

So, for the analysis and summary of clinical laboratory, efficacy, and safety data in case of this analysis/summary performed on "by visit" base. In the event of multiple values for an assessment within an analysis window, the value closest to the scheduled visit date will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected as the analysis value.

Analysis Window	Start	End	Target	Assessment to be used if duplicates
Baseline visit	<1			NA
Month 1	2	45	30	Closest to target day, if equidistant use later result.
Month 3	46	135	90	
Month 6	136	NA	180	

The definition for the study days included in each study window is defined as below:

Treatment Day prior to first dose = Visit Date – Date of First Dose

Treatment Day on or after first dose = Visit Date – Date of First Dose + 1

Adjustments for Covariates

No specific adjustments for covariates will be made in all statistical analyses, unless specified otherwise per-analysis level.

Handling of Dropouts or Missing Data

Missing efficacy outcomes will be assumed to be missing at random (MAR) and thus will not be imputed in the primary analysis. However, if greater than 1% of all primary/secondary outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary MAR analysis.

This sensitivity analysis will include an evaluation of the results of models developed under the assumptions of:

1) last observation carried forward;

2) worst extreme case imputation and;

3) regression model imputation using all available information.

Outlier identification

During data Quality Control outlier identification will be performed using adjusted Z-score method (Iglewicz and Hoaglin, 1993).

$$M_i = \frac{0.6745(x_i - \tilde{x})}{\text{MAD}}$$

where MAD – median absolute deviation, x - median.

Values with Z-score > 3.5 will be considered outliers for study variables considered normally distributed. Preliminary normality test (Shapiro–Wilk criterion) will be performed for these variables. In case if normality distribution hypothesis will be rejected based on Shapiro–Wilk test results, median and IQR (interquartile range) will be used for outlier identification. Values > 1.5 IQR far from median value will be considered outliers. No data will be excluded / modified based on outlier identification, however, additional medical context assessment for these data will be performed and data quality control / source verification check will be considered.

Data Monitoring

Data quality monitoring, including safety data review and reconciliation, will be implemented periodically by the Data Manager from a Contract Research Organization (CRO). Details will be described in the Data Management Plan.

Multiple Comparisons/Multiplicity

When needed, corrections for multiplicity will be justified and performed according to Bonferroni. Overall alpha-level will be controlled and will not exceed 0.05

The interim analysis will not be taken into account within multiplicity adjustment procedure.

Examination of Subgroups

Primary and some secondary and exploratory endpoints will be analyzed in subgroups of patients: overweight, obese (stages I-III), impaired glucose tolerance (yes, no), metabolic syndrome (yes, no), diabetes mellitus (yes, no) etc (see "EFFICACY ANALYSES" chapter).

This analysis may be limited for the Republic of Kazakhstan sample as this sample has limited sample size. This will be noted in the statistical analysis report accordingly.

6. STUDY POPULATION CHARACTERISTICS

Patient Disposition

Data regarding how many patients reached the various stages of the trial, how many dropped out, discontinued the treatment and for what reasons (death, ADRs, treatment failure, withdrew consent, lost to follow-up) will be presented for each subgroup and for study in bulk. Standard diagram describing study patient flow will be provided.

7. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics

All demographic and other Baseline characteristics will be summarized for overall analysis population as well as for subgroups of patients listed in the section 9.3 of the document

Medical History, Concurrent Medical Conditions and comorbidities

Medical history is history of diseases indicated before signing of the Informed Consent Form.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent.

Comorbidities (concomitant disease) are diseases which occur after start of Edarbi® treatment and are not related to the Edarbi® treatment. Comorbidities may include not limited to cardiovascular disorders (coronary artery disease, peripheral artery disease, cerebrovascular disease), diabetes, chronic pulmonary artery disease, chronic kidney disease. The condition (ie, diagnosis) should be described.

Risk factors are conditions which increase probability of cardiovascular disease in patients with HTN at the moment of signing ICF. Risk factors are described in accordance with Russian guidelines "Diagnostics and treatment of hypertension" (2010).

Time of medical event/disease	How it should be documented
Birth to day before ICF signed	Medical history
At the moment of ICF signing	Risk factors
At the moment of ICF signing	Concurrent medical conditions
After ICF signing and start of Edarbi® treatment	Adverse Events

After coding, medical history, risk factors, concurrent medical conditions and adverse events will be summarized and reported in accordance with denoted conventions (see. "Summary of study data").

Treatments to be documented in the study

All medications recorded in accordance with study protocol, including:

- Prior HTN treatment
- HTN treatment received during follow-up
- Concomitant medication

- will be summarized using denoted descriptive statistics (see "Summary of study data"). Number of subjects with these treatments will be summarized.

Edarbi® treatments will be registered in the CRF The following information about Edarbi® treatment will be collected:

- start date of Edarbi®,
- end date of Edarbi® treatment or prolongation of Edarbi® treatment,
- single and total dose, dose regimen,
- reason(s) for discontinuation of Edarbi ® treatment (if applicable).

Edarbi® should be administered according to the official prescribing information (The Russian SmPC). The starting dosage will be 40 mg per day. In case of insufficient efficacy, the dosage could be increased up to 80 mg per day.

HTN treatment

In case of combination HTN-treatment all co-medications for HTN treatment should be registered in Case Report Form. For every type of co-medication following data should be documented:

- INN, trade name,
- dosage regimen (dose taken),
- duration of treatment.

Prior HTN treatment

Medication taken before start of the study is called prior medication. In case the patient already underwent HTN treatment during 12 weeks prior to start of Edarbi® treatment, details of the therapy should be recorded in the CRF.

Concomitant medication

Concomitant medication is any drug given in addition to the HTN treatment. These drugs may be prescribed by a physician or obtained by the patient over the counter. Concomitant medication is not provided by the sponsor.

The information about concomitant medication can be received both on base of medical records and on questions to patients (according to routine practice). During the visits the information about changes in the concomitant therapy is recorded. At each study visit, patients 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).

All drugs and drug combination for concomitant medication will be registered in CRF. For every type of drug there will be documented trade name, INN, dosage regimen (dose taken), duration of treatment, indications.

The area of interest is on antidyslipidemic and antidiabetic drugs.

Follow-up HTN treatment

If a patient withdraws from study due to change of Edarbi® treatment, the follow-up prescribed HTN treatment should be documented in the CRF.

8. MEASUREMENT OF EXPOSURE TO STUDY DRUG

The total duration of exposure is defined as the time interval between the first dose and the last dose, inclusive, of study drug based on the patient study drug dosing information. In case if significant (e.g. >5%) number of subjects will switch doses during the study, additional tabulation by dose will be performed. Total duration (weeks) of exposure to study drug in the FAS population will be summarized by descriptive statistics (ie, total number, mean, standard deviation, median, minimum, and maximum) - see "Summary of study data".

Data for study patients` compliance will be summarized and tabulated by visit.

Area under curve as product of compliance for distinct period (e.g. time between visits) and duration of this period) will be calculated and summarized.

9. EFFICACY ANALYSES

The primary, secondary, and exploratory efficacy analysis will be performed in two sets of data:

1) Full Analysis Set (defined as enrolled subjects who tookat least one dose of study drug)
2) Per protocol analysis set (defined as subjects who took at least one dose of study drug and having all inclusion and no exclusion criteria)

For performing interim analysis data of first 470 enrolled patients will be used for the efficacy analyses listed in this section. For the interim efficacy analyses applicable methodology listed in this section is planned to be used. The interim analysis will be performed on the base of full analysis set.

9.1. Statistical Analysis of the Primary Efficacy Variable(s)

Primary study outcome – change from baseline in clinic SBP value to Visit 4 will be estimated with 95% confidence interval construction and analyzed with paired t-test in pairwise comparison with baseline SBP

Changes in systolic BP (SBP) during the treatment with Edarbi® will be evaluated from baseline to Month 1,3 and 6. Additionally the changes of SBP from baseline to mentioned visits will be analyzed with paired T-test in pairwise comparisons with baseline level of the variable.

In addition, clinic SBP (DBP) change from baseline will be assessed and evaluated using Mixed model repeated measures (MMRM) methodology. The multiple visits for each patient will be incorporated as repeated measures within each patient. Visit will be treated as a categorical predictor and baseline SBP (DBP) will be included as a covariate. An appropriate covariance structure will be selected to provide estimates (Least Square Means) of change from Baseline and to perform statistical analysis at Visit 4 (Month 6). In addition, Least Squares Means, the associated standard errors and 95% confidence intervals will be displayed by each individual dose group (in case if exposition assessment will reveal distinct dose groups, then group factor and group * visit interaction will be added to the model).

Patients who reached target level of SBP (DBP) at visits 2, 3 and 4 will be presented using frequencies and percentages for the study population.

9.2 Statistical Analysis of the Secondary Efficacy Variables

Secondary and exploratory outcomes will be analyzed using descriptive statistics and frequencies and percentages as follows:

1. Changes in diastolic BP (DBP) during the treatment with Edarbi® (from baseline to Month 1, Month 3, Month 6) will be calculated and presented in summary tables using descriptive statistics for continuous variables for overall population of analysis and in subgroups of patients listed in the section 9.3. Additionally the changes of this variable in the population and mentioned subgroups will be analyzed with paired T-test in pairwise comparisons with baseline level of the variable.
2. Percentage of patients who achieve target SBP<140 mm Hg (at Month 1, Month 3, Month 6) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals,

3. Percentage of patients who achieve target DBP<90 mm Hg (at Month 1, Month 3, Month 6) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;

4. Percentage of patients who respond to Edarbi® therapy (defined as decrease of SBP≥ 20 mm Hg or decrease of DBP≥10 mm Hg; Month 1, Month 3, Month 6) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;

5. Percentage of patients who achieve target BP (defined as SBP<140 mm Hg, DBP<90 mm Hg; at Month 1, Month 3, Month 6) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;

6. Descriptive characteristics of patients before the start of Edarbi® therapy: age, gender, HTN stage and grade, Baseline SBP and DBP; BMI, previous therapy of HTN, risk factors, % of patients with diabetes mellitus, % of patients with metabolic syndrome; target organ damage by HTN, eGFR, comorbidities; type of antihypertensive therapy initiated at baseline (monotherapy; double therapy; triple therapy; other (>3)); distribution of classes of antihypertensive drugs used in combination therapy with a distribution of INNs used. The information will be presented in summary tables

7. Changes in serum creatinine, eGFR (CKD-EPI), urea, total cholesterol, triglycerides, low density lipoproteins, high density lipoproteins (from baseline to Month 1- Month 3- Month 6) will be assessed and presented in summary tables using descriptive statistics for continuous variables. Additionally the changes of this variable will be analyzed with paired T-test in pairwise comparisons with baseline level of the variable.

8. Changes of blood glucose level, glycated hemoglobin (HbA1c) from baseline to the visits 2, 3, and 4. For the analysis 95% Cis will be constructed. Additionally the changes of this variable will be analyzed with paired T-test in pairwise comparisons with baseline level of the variable.

   9.0 Analysis of BMI and waist circumference change from baseline to visit 4. 95% CIs will be constructed. Additionally the changes of this variable will be analyzed with paired T-test in pairwise comparisons with baseline level of the variable.

10. Reasons for discontinuation of Edarbi® therapy will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals.

9.3 Additional methods of analysis

9.3.1 Subgroup analyses. Primary efficacy variable as well as the variables listed at the items 1-10 in the section 9.2 will be analyzed both in general population and in the following subgroups (if applicable):

- patient sex (male/female);
- patient age (60 or more, <60 years old);
- BMI (normal (<25); overweight (25-30), obese (>30_) and according to grade of obesity (grade I - 30-34,9; Grade II - 35-39,9; Grade III ≥40)
- metabolic syndrome (yes, no),
- diabetes mellitus (yes, no),
- diabetes mellitus, impaired glucose tolerance or normal glucose metabolism
- subgroups with different eGFR according to CKD-EPI (eGFR <30; 30-59 and >=60);
- subgroups according to previous antihypertensive treatment (treated/not treated and treated patients according to class of antihypertensive treatment used before initiation of Edarbi); the group of patients who was treated with RAAS blocker monotherapy and the group of patients who was treated with combination of RAAS blocker and diuretic and the group of patients who was treated with RAAS blocker and Calcium channel blocker to be described separately.
- patients with newly diagnosed hypertension
- The subgroup of patients with isolated systolic hypertension (patients not treated with antihypertensive treatment before the study who has SBP ≥140 mm Hg and DBP <90 mmHg at visit 1).
- diabetes mellitus or metabolic syndrome or nothing;
- Subgroup of Patients with Chronic heart failure and patients without chronic heart failure in diagnosis
- Subgroups according to risk factors: smokers/non-smokers; family history of cardiovascular disease (yes/no)
- Subgroups according to target organ damage by HTN (yes/no; if yes – according to organs involved (heart, kidney, brain, eyes, vessels).

- Subgroups according to antihypertensive treatment initiated at baseline level: monotherapy with azilsartan and patients receiving combination therapy with azilsartan (both in general and according to type of used combination (double therapy; triple therapy, other) and per classes of used in combination))
- Subgroups of patients who was initiated with different doses of azilsartan at baseline. In addition to the variables listed above the following is to be evaluated in every baseline dose group: % of patients receiving different doses of Edarbi at visits 1, 2,3,4; % of patients receiving monotherapy; double, triple and more therapy at visits 1,2,3,4; distribution of classes used in combination therapy at visits 1,2,3,4: distribution of dosages used per region of site location
- Subgroup of patients who were maintaining initially prescribed dose of Edarbi throughout all the study duration namely: the group irrespective of the dose of Edarbi and type of therapy (combined or monotherapy); the groups according to Edarbi dose irrespective of the type of therapy (combined or monotherapy); the groups according to both Edarbi dose and the type of therapy (combined (double; triple or more or monotherapy);
- The group of patients who was prescribed the dose 20 mg at baseline; In addition to variables listed above the following information is required regarding this group: change of the dose at every visit; % of patients who were maintaining at the dose 20 mg until the end of the study; antihypertensive treatment before baseline: monotherapy or combination therapy (with description of the combinations according to the drugs used and types of combinations (double, triple etc); Additionally the following subgroups are to be analyzed: patients prescribed 20 mg who received no antihypertensive medication before; patients prescribed 20 mg who received any antihypertensive medication before baseline.
- The group of patients who achieved BP target of <140/90 mmHg at any of the timepoints of the month 1, 3, 6 vs patients who didn't achieve it
- The group of patients who achieved the target SBP of <130/80 at the month 1, 3, 6 vs patients who didn't achieve it.
- The group of patients who achieved SBP<140 or change>=20 at any of following timepoints: Month 1, Month 3, month 6).

- The group of patients who achieved DBP<90 or change>=10 (at any of the following timepoints: Month 1, Month 3, month 6
- The group of patients who achieved SBP<140 or change>=20 and DBP<90 or change>=10 at any of the following timepoints: Month 1, Month 3, month 6
- The group of patients with fasting hyperglycemia during the study
- The group of patients who reduced the weight during the study vs those who didn't reduce the weight
- The subgroups of patients: patients who wasn't receiving statins throughout the course of the study; patients who received statins throughout the study course without changes of drugs of doses; patients who received statins throughout the study and has had escalation of the dose or change in drug
- The subgroups according to level of urbanization: >1 000 000 citizens; 250 000–1 000 000; 100 000–250 000; 50 000–100 000; <50 000

9.3.2. Additional exploratory analyses. The following exploratory analyses are additionally planned:

- [redacted]

- [redacted]

10. SAFETY ANALYSES

Unless specifically stated otherwise, the Safety Set (patients who have taken at least one dose of Edarbi®) will be used for all safety summaries and analyses.

All safety data will be included in data listings.

For relevant safety variables, early Withdrawal Visits will be assigned to the closest scheduled visit for the particular assessment that is being summarized.

Adverse Events

Prior to analysis, adverse drug reactions will be coded using MedDRA.

Incidence and characteristic of adverse drug reactions will be described and presented in summary tables using absolute frequencies and percentages;

Evaluation of AEs will consist of the determination of total number of AEs, total number of patients with at least one AE and the number of AEs, the number of patients with AE leading to discontinuation of the study treatment. The incidence and severity of all AEs will be summarized by System Organ Class and Preferred Term within SOC. Treatment discontinuation due to AEs will be tabulated

AEs reported in the study as well as AEs reported directly to authorities and to Takeda International Drug Safety according to section 11.3 and not captured in the study database will be extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR). In addition AEs will be tabulated for Edarbi treatment doses (if any dosage groups, e.g. 40 mg and >40-80 mg will be determined).

Interim safety analysis will be based on the data of first 470 patients who either achieved final study visit or discontinued the study.

11. TABLES, FIGURES, LISTINGS (MOCK-VERSIONS)

Following tables and figures and listings (mock-versions) will be used for Statistical Analysis Report:

Table 1 Mock table for reporting descriptive statistics

		Subgroup A (N=xxx)	Subgroup B (if applicable) (N=xxx)	Total (N=xxx)
Sex				
	Female	x (xx.x%) [xx.x-xx.x]	x (xx.x%) [xx.x-xx.x]	x (xx.x%) [xx.x-xx.x]
	Male	x (xx.x%) [xx.x-xx.x]	x (xx.x%) [xx.x-xx.x]	x (xx.x%) [xx.x-xx.x]
Age				
	Mean	x	x	x
	Std.deviation	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
	Median	xx.xx	x.xx	x.xx
	25 percentile	xx	xx	xx
	75 percentile	xx	xx	xx

For repeated measures (e.g. subsequent SBP / DBP values for pre-treatment visit and visits after baseline) following tables will be used:

Table 2 Mock table for reporting descriptive statistics for repeated measures (e.g. SBP / DBP)

Systolic blood pressure (mgHg)	Subgroup A (N=xx)		Subgroup B (N=xx)		Total (N=xx)	
Visit						
Statistic	Value	Change	Value	Change	Value	Change
Systolic blood pressure (mgHg)						
Baseline						
n	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.xx		xxx.xx		xxx.xx	
Minimum	xxx		xxx		xxx	
Median	xxx.x		xxx.x		xxx.x	
Maximum	xxx		xxx		xxx	
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	
Month 1						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx

Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Maximum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	
Month 3						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Maximum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	
Month 6						
n	xxx	xxx	Xxx	xxx	xxx	xxx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Maximum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	

Following figures will be used for repeated measures representation:

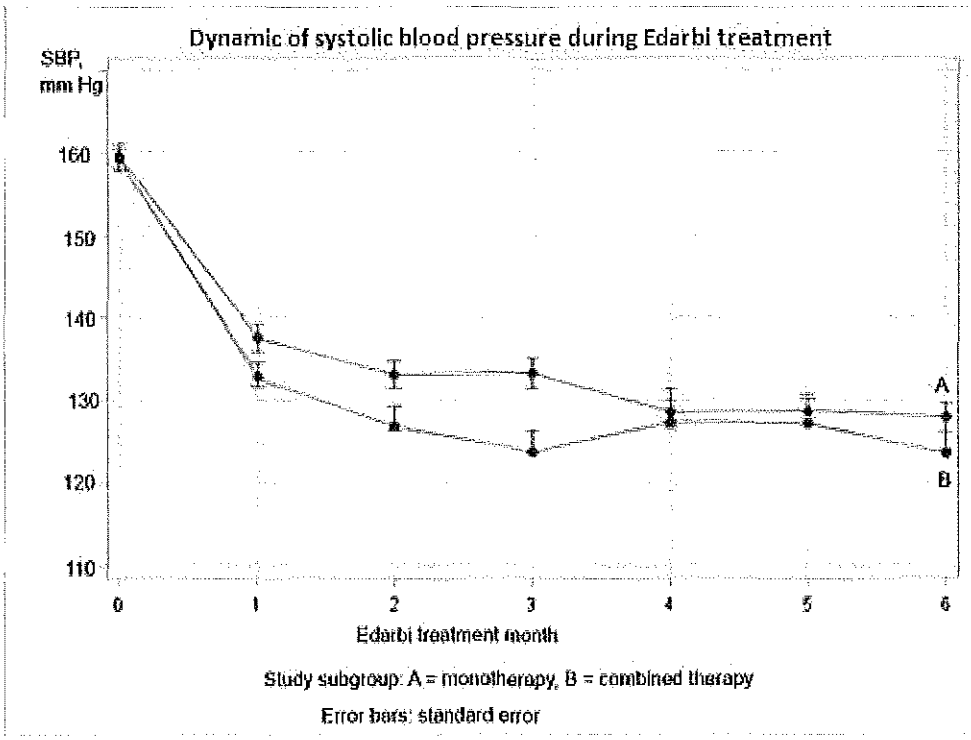


Figure 1 Mock version of graph for repeated measure (e.g. SBP) representation

Example of table for reporting Adverse Events in treatment subgroups (if applicable):

Table 3 Mock version of Adverse Event reporting table

	No of subjects (%) No of events	
	Subgroup A (N=xxx)	**Subgroup B (if applicable) (N=xxx)**
Psychiatric disorders		
Any SAE	x (x.xx%) x	x (x.xx%) x
Alcohol withdrawal syndrome	x (x.xx%) x	x (x.xx%) x
Alcoholism	x (x.xx%) x	x (x.xx%) x
Cardiac disorders		
Any SAE	x (x.xx%) x	x (x.xx%) x
Atrial fibrillation	x (x.xx%) x	x (x.xx%) x
Cardiovascular insufficiency	x (x.xx%) x	x (x.xx%) x
Coronary artery disease	x (x.xx%) x	x (x.xx%) x

Example of table for reporting Adverse Events and additional information (e.g. severity, causality) in treatment subgroups (if applicable):

Table 4 Mock version of Adverse Event with additional data reporting table

	Subgroup A (N=xxx)	**Subgroup B (if applicable) (N=xxx)**
Investigations		
Blood creatine phosphokinase increased		
Mild	xx (x.xx%) xx	xx (x.xx%) xx
Moderate	xx (x.xx%) xx	xx (x.xx%) xx
Severe	x (x.xx%) x	x (x.xx%) x
Gamma-glutamyltransferase increased		
Mild	x (x.xx%) x	x (x.xx%) x
Moderate	x (x.xx%) x	x (x.xx%) x
Severe	x (x.xx%) x	x (x.xx%) x

During statistical analysis report preparation all statistical procedures output (e.g. proc mixed, proc freq) will be included unmodified (original statistical package output) as they have necessary

diagnostics to assess validity of results. These diagnostic tables will not be included in Clinical Study Report.

When analyzing changes of variables from baseline: descriptive statistics (as appropriate according to the type of variable) and p-level for change from baseline is to be reported; for analyzing the changes from baseline in subgroups p-level for comparison between subgroups is to be reported additionally. For evaluation of baseline clinical characteristics in subgroups: p-level for comparisons of clinical characteristics between subgroups will be reported.

For MMRM: all regression coefficients, LSMs with Standard error, 95%CI and p-level for be reported.

Individual values listing will have subject id included, other data will be presented in listings unmodified.

Table 5 Mock version of individual value listings

Subject ID	Study subgroup (if applicable)	Treatment month	Systolic Blood Pressure, mm Hg
102-001	Monotherapy	0	xxx.xx
102-001	Monotherapy	1	xxx.xx
102-001	Monotherapy	2	xxx.xx
102-001	Monotherapy	3	xxx.xx
102-001	Monotherapy	4	xxx.xx
102-001	Monotherapy	5	xxx.xx
102-001	Monotherapy	6	xxx.xx
102-002	Combined therapy	0	xxx.xx
102-002	Combined therapy	1	xxx.xx
102-002	Combined therapy	2	xxx.xx
102-002	Combined therapy	3	xxx.xx
102-002	Combined therapy	4	xxx.xx
102-002	Combined therapy	5	xxx.xx
102-002	Combined therapy	6	xxx.xx

12. REFERENCES

1) ICH E9 Statistical Principles for Clinical Trials Adopted by CPMP, March 1998, issued as CPMP/ICH/363/96
2) GUIDELINES FOR STANDARD OPERATING PROCEDURES for Good Statistical Practice in Clinical Research: PSI Professional Standards Working Party
3) Wayne W. Daniel: Biostatistics: A Foundation for Analysis in the Health Sciences (Wiley Series in Probability and Statistics) Sixth (6th) Edition
4) David J.Sheskin Handbook of PARAMETRIC and NONPARAMETRIC STATISTICAL PROCEDURES SECOND EDITION 2000 by Chapman & Hall/CRC
5) Iglewicz B., Hoaglin D. (1993), "Volume 16: How to Detect and Handle Outliers", *The ASQC Basic References in Quality Control: Statistical Techniques*, Edward F. Mykytka, Ph.D., Editor.
6) Mallinckrodt CH, Clark WS, Carroll RJ, Molenberghs G. Assessing response profiles from incomplete longitudinal clinical trial data under regulatory considerations. J Biopharm Stat 2003; 13:179-90.
7) Siddiqui O, Hung HMJ, O'Neill R. MMRM vs LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 2009; 19:227-46.