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

Protocol Approve Date: January 9, 2019

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

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

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

Non-Interventional Study Protocol

Short 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

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

Study ID: Azilsmedox-5008 (MACS-2014-100663)

Sponsor: Takeda Pharmaceutical LLC
2, bld. 1, Usacheva str., Moscow 119048, Russian Federation
Phone: + 7 495 933 5511
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Study phase: Non-interventional (Observational) Company Sponsored Study

Date: 09 January 2019 **Amendment Number:** 5

Amendment History:

Date	Amendment Number	Amendment Type	Region
02 December 2014	Initial Protocol	Not applicable	the Russian Federation
18 December 2015	1	Substantial	the Russian Federation and the Republic of Kazakhstan
28 June 2016	2	Non-Substantial	the Russian Federation and the Republic of Kazakhstan
16 March 2017	3	Non-Substantial	the Russian Federation and the Republic of Kazakhstan
14 August 2017	4	Non-Substantial	the Russian Federation and the Republic of Kazakhstan
09 January 2019	5	Non-Substantial	the Russian Federation and the Republic of Kazakhstan

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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 except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

1 Administrative information

1.1 Contacts

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

Issue	The Russian Federation, Contact information
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol, compound, and medical management of patients) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Protected Personal Data

Issue	The Republic of Kazakhstan, Contact information
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol, compound, and medical management of patients) Responsible Medical Officer	Protected Personal Data

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

The ethical principles that have their origin in the Declaration of Helsinki [1]; International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline [2]; Guidelines for Good Pharmacoepidemiology practices (GPP) [3]; Guidelines on Good Pharmacovigilance Practices (GVP) [4]; All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

SIGNATURES

Protected Personal Data

2 Study summary

Short Title of the Study

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

Study sites

The study sites will be selected according to following criteria:

- out-patient clinics,
- availability of cardiologist specialists in out-patient clinics,
- significant patient flow with essential hypertension (the sites should treat at least 350 patients with hypertension per year).

Number of sites: about 80 investigational sites from the Russian Federation and about 10 investigational sites in the Republic of Kazakhstan.

Objectives

Primary objective:

- To evaluate the effect of Edarbi® on clinic systolic blood pressure (SBP) among HTN patients with overweight or obesity (V4).

Secondary objectives:

- To evaluate the effect of Edarbi® on clinic diastolic blood pressure (DBP) among HTN patients with overweight or obesity (V4);
- 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) (V4);
- To evaluate the proportion of overweight or obese patients who achieved target BP (defined as SBP<140 and DBP<90mm Hg) (V4);
- 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 (V4);
- 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 (V4);
- 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: overweight, obese (stages I-III), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (V4).

Safety Objective:

- To describe AEs characteristics.

Methodology

Study Design: international, multicentre, observational, non-interventional prospective study.

Study plan: The definition of a Non-Interventional study is provided in EU Directive 2001/20/EC (of April 4, 2001) [5]. During participation in the study patients are observed according to the local routine practice. The assignment of a particular therapeutic strategy to the patient including all diagnostic procedures is decided in accordance with Russian guidelines "Diagnostics and treatment of hypertension" (2010) [6] and Kazakh protocol on clinical diagnosis and treatment of hypertension (2013) [7] and local routine practice. The patients would take Edarbi® according to the local SmPC.

Number of patients

Approximately 1916 patients.

Diagnosis/Disease/Condition and main criteria for inclusion

Inclusion criteria:

1. Male and female patients ≥ 18 years of age with HTN 1-2 grade
2. Patients with:
   - Newly diagnosed arterial HTN or
   - inadequately controlled previously prescribed monotherapy with RAAS blocker or
   - inadequately controlled previously prescribed combination therapy with RAAS blocker + diuretic or RAAS blocker + calcium antagonist[i].
3. The physician decides to prescribe Edarbi®:
   - as monotherapy or
   - as a part of combination therapy including diuretics or calcium antagonists;
4. Overweight or obesity of any degree (body mass index> 25 kg/m2);
5. Is capable of understanding the written informed consent, provides signed and written informed consent, and agrees to comply with protocol requirements. In case the patient is blind or unable to read, informed consent will also be witnessed.

Exclusion criteria:

Any patient who meets any of the following criteria will not be qualified for entry into the study:

1. Confirmed secondary HTN ;
2. Contraindications for Edarbi® of respective approved local SmPC of Edarbi®;

3. Any reasons of medical and non-medical character, which in the opinion of the physician can prevent patient participation in the study.

4. Is an employee or family member of the investigator or study site personnel.

5. Is currently participating in a clinical trial. Participation in non-interventional registries is permitted.

6. Vulnerable patients who are unable to understand information about study or those who depend on investigator.

Duration of data collection per patient

Data collection per patient will be carried out within the framework of the routine practice. 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. Information for the study will be collected from 4 patients' visits to the physician.

Criteria for evaluation

Population descriptors

The main variables, which will be collected in the study, are presented in the table.

Variables collected	Baseline visit (V1)	Observational visit 1 (V2)	Observational visit 2 (V3)	Final visit (V4)
Demographic information	X			
Medical history (incl. risk factors, prior diseases, prior HTN therapy etc)	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
Concomitant medication	X	X	X	X
Adverse events	X	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, heart rate, ECG, 24-hour ambulatory blood pressure monitoring. All examinations should be registered in the CRF only if they are done in routine practice.

Primary outcomes:

- Change from baseline in clinic SBP on Edarbi® therapy (Time Frame: Baseline and V4)

Secondary outcomes:

- Change from baseline in clinic DBP on Edarbi® therapy (Time Frame: Baseline and V4);
- 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 V4);
- Proportion (%) of patients who achieve target SBP <140 mm Hg (Time Frame: Baseline and V4);
- Changes from baseline in clinic SBP in subgroups of patients: BMI (overweight, obese), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (Time Frame: Baseline and V4);
- 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 V4);
- 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 V4).

Safety Outcome:

- Incidence and type of adverse events.

Statistical methods

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 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 [8].

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

3 Table of Contents

4 List of Abbreviations and Definition of Terms

4.1 List of Abbreviations

ACE:	Angiotensin-Converting-Enzyme
ADR:	Adverse Drug Reaction
AE:	Adverse Event
ARB:	Angiotensin Receptor Blocker
AT1:	Angiotensin II receptor Type 1
BMI:	Body Mass Index
BP:	Blood Pressure
CA:	Competent Authority
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Curriculum Vitae
DBP:	Distolic Blood Pressure
DMP:	Data Management Plan
DSO:	Drug Safety Officer
EC:	Ethics Committee
eCRF:	electronic Case Report Form
FPLV:	First Patient Last Visit (end of enrollment)
GCP:	Good Clinical Practice
GEP:	Good Epidemiologycal Practice
GPP:	Good Pharmacoepidemiology Practices
GVP:	Good Pharmacovigilance Practices
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
INN:	International Nonproprietary Name
IRB:	Institutional Review Board

HTN:	Hypertension
LEC:	Local Ethics Committee
LPLV:	Last Patient Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
NIS:	Non-interventional study
pCRF:	paper Case Report Form
PPAR:	Peroxisome Proliferator-Activated Receptors
PSUR:	Periodic Safety Update Report
QA:	Qality Asurance
RK:	the Republic of Kazakhstan
RAAS:	Renin-Angiotensin-Aldosteron System
RF:	the Russian Federation
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SAE:	Serious Adverse Event
SBP:	Sistolic Blood Pressure
SD:	Standrad Deviation
SDV:	Source Data Verification
SPC:	Summary of Product Characteristics
WHO:	World Health Organization

4.2 Definition of Terms

According to guidelines of the Russian Ministry of Health for the management of HTN, [6] protocols of the Republic of Kazakhstan on clinical diagnosis and treatment of hypertension and protocol on the management of patients with type II diabetes [7,9]:

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 Distolic 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 Sistolic 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

Obesity – elevation of BMI > 30 [8, 9]. Obesity is divided for 3 classes according to severity.

Class of obesity	BMI
Obesity class 1	30-34,9
Obesity class 2	35-39,9
Obesity class 3	BMI≥40

Metabolic syndrome – according to the definition of the Russian Ministry of Health for the management of HTN [6], 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 7.8	post-load plasma glucose 7.8

(post-load plasma glucose)	- 11.0 mmol/L	- 11.0 mmol/L
fasting glucose	6.1 - 7.0 mmol/l	6.1 - 7.0 mmol/l

5 Introduction

5.1 Disease background

Hypertension (HTN) is the established main risk factor of cardiovascular diseases, leading to the progressive impairment of its target organs: heart, kidneys, brain and vessels [6, 12]. High blood pressure (BP) is the leading global risk factor for mortality in the world. According to the epidemiological data, about 44% of Russian population is hypertonic [13]. Among them only 23% of patients achieve BP goals on antihypertensive treatment [13].

According to official statistics the prevalence of arterial hypertension in Kazakhstan in 2008 was 35% [14.]. Moreover, surveys showed that just 1 in 4 respondents diagnosed with high blood pressure were taking medication daily in 2010 [15]. Thus, the problem of diagnostic and treatment of HTN in Russia and Kazakhstan is the matter of high significance.

The special concern is necessary of treatment of HTN patients with overweight and obesity. The frequency of such combination is very high. According to World Health Organization data, in 2008 35% of people ≥20 years old were overweight and 11% were obese (overweight was define as body mass index (BMI) >25kg/m2; obesity – as BMI>30 kg/m2) [16]. Among patients with HTN prevalence of overweight is about 39%, of obesity is as high as about 52% [17].

Situation with BP control among patients with metabolic syndrome and diabetes mellitus is even worse. Epidemiological data suggest that target BP is achieved only in 64% with HTN and metabolic syndrome and in 61% of patients with diabetes [14]. Local observational studies in Russia reveal that 13% of patients with uncontrolled HTN have diabetes [15]. Trial REGATAa-PRIMA revealed, that as many as 61% of patients with uncontrolled BP have metabolic syndrome [20].

5.2 Drug background

5.2.1 Drug description

Edarbi® (Azilsartan medoxomil) is the new angiotensin II receptor type 1 (AT1) blocker (ARB). Azilsartan has a number of specific characteristics. It is structurally similar to candesartan except that it bears a 5-oxo-1,2,4-oxadiazolemoiety in place of the tetrazole ring. Further it has a carboxyl group at the 7-position of the benzimidazole ring, which is believed to result in insurmountable receptor antagonism.

Trade name: Edarbi®

International Non-proprietary Name (INN): azilsartan medoxomil

Pharmacotherapeutic group: Angiotensin II antagonists.

Pharmaceutical form: tablets 40 and 80 mg.

Composition:

1 tablet 40 mg contains:

Active substance: azilsartan medoxomil potassium 42.68 mg corresponding to azilsartan medoxomil 40 mg. Excipients: mannitol 95,63 mg, fumaric acid 2 mg, sodium hydroxide 0,69 mg, hydroxypropylcellulose 5,4 mg, croscarmellose sodium 13,8 mg, cellulose microcrystalline 18 mg, magnesium stearate 1,8 mg.

1 tablet 80 mg contains:

Active substance: azilsartan medoxomil potassium 85.36 mg corresponding to azilsartan medoxomil 80 mg. Excipients: mannitol 191,26 mg, fumaric acid 4 mg, sodium hydroxide 1,38 mg, hydroxypropylcellulose 10,8 mg, croscarmellose sodium 27,6 mg, cellulose microcrystalline 36 mg, magnesium stearate 3,6 mg.ATC code: C09CA09

Description

Tablets 40 mg: from white to nearly white round biconvex tablets, debossed "ASL" on one side and "40" on the other.

Tablets 80 mg: from white to nearly white round biconvex tablets, debossed "ASL" on one side and "80" on the other.

5.2.2 Summary of trials and studies

Azilsartan medoxomil has shown more potent blockage of AT1 receptors in vitro than several other comparable ARBs and the ability to remain tightly bound to AT1 receptors for very long periods of time after drug washout [21]. These pharmacological characteristics result in significant advantages of Azilsartan medoxomil in BP control. In direct comparative studies with over antihypertensive drugs Azilsartan medoxomil was more effective in decreasing BP than ARBs olmesartan [22] and valsartan [23].

The subanalysis of data pooled from Azilsartan medoxomil studies revealed, that Azilsartan medoxomil lowers systolic BP more effectively than olmesartan and valsartan at their maximally approved doses in patients with diabetes and prediabetes [24].

Besides its significant effect on the BP Azilsartan has demonstrated several positive pleiotropic effects. On the preclinical studies on animal models Azilsartan increased the insulin sensitivity and the glucose tolerance [25], decrease the concentration of glucose and free fatty acids in the blood , decrease the adipose tissue weight and the size of adipocites increase the expression of adiponectin and PPAR-- receptors [26].

These data indicates that Azilsartan medoxomil could be effective in long-term treatment of patients with HTN and improving the prognosis not only due to decrease of BP, but also due to its beneficial metabolic effects

5.3 The study rationale

Reaching the target BP in HTN patients with overweight and obesity is highly complicated [6] It is partially related with the fact that some pathological processes involved in obesity lead to BP elevation [11]. According to the epidemiological studies, the percentage of HTN patients with overweight who reach BP goals is as low as 22% and of HTN patients with obesity – as low as 15% [17]. Clinical studies conducted in Russia revealed that among patients with uncontrolled BP the incidence of overweight is 56% [18], of obesity – 63% [27]. In addition, epidemiological studies highlighted, that patients with overweight and obesity have significantly higher risk of cardiovascular complications, that individuals with normal weight [28].

Thus, although there are many effective antihypertensive drugs available, treatment of patients with HTN and overweight or obesity still is the unsolved problem [6]. Reaching the BP goals and improvement of prognosis in such patients require the new, highly effective antiHTN medications.

The new angiotensin receptor blocker (ARB), azilsartan medoxomil, opens new opportunities in the treatment of HTN [20-22]. Particularly, it may be effective in patients with HTN and overweight or obesity, which have difficulties in BP control and high risk of cardiovascular complications. So, the assessment of efficacy of azilsartan medoxomil in treatment of HTN patients with overweight or obesity in routine clinical practice is a matter of significant interest.

6 Study Objective(s) and outcomes

6.1 Study objectives

Primary objective:

- To evaluate the effect of Edarbi® on clinic systolic blood pressure (SBP) among HTN patients with overweight or obesity (V4).

Secondary objectives:

- To evaluate the effect of Edarbi® on clinic diastolic blood pressure (DBP) among HTN patients with overweight or obesity (V4);
- 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) (V4);

- To evaluate the proportion of overweight or obese patients who achieved target BP (defined as SBP<140 and DBP<90mm Hg) (V4);
- 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 (V4);
- 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 (V4);
- 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 (V4).

Safety Objective:

- To describe AE characteristics.

Exploratory objectives:

- Company Confidential Information [redacted]

6.2 Study outcomes

Primary outcome:

- Change from baseline in clinic SBP on Edarbi® therapy (Time Frame: Baseline and V4).

Secondary outcomes:

- Change from baseline in clinic DBP on Edarbi® therapy (Time Frame: Baseline and V4);
- 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 V4);
- Proportion (%) of patients who achieve target BP <140 mm Hg (defined as SBP<140 and DBP<90mm Hg) (Time Frame: Baseline and V4);
- Changes from baseline in clinic SBP in subgroups of patients: BMI (overweight, obese), impaired glucose tolerance, metabolic syndrome, diabetes mellitus (Time Frame: Baseline and V4);
- 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 V4);
- 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 V4).

Safety Outcome:

- Incidence and type of adverse events.

Exploratory outcomes:

Company Confidential Information

7 Study Administrative Structure

Contact and responsibilities of all parties contributing to the study, including all investigators, are detailed below.

The sponsor is responsible for all study-related activities including study set-up activities and study documentation development. The responsible CRO for specific study-related activities will perform these activities in full or in partnership with the sponsor.

7.1 Steering Committee

The Steering Committee serves to provide overall supervision of the study activities across the study. The Steering Committee is responsible for composing and evaluating the research/scientific/medical questions and issues; guiding and coordinating; maintaining open and active communication about the goals, process, and findings of the Study; compiling and editing the final Study Report and study publication.

The members of the Steering Committee are the following.

Protected Personal Data

7.2 Study Sites

The study is planned to be conducted in approximately 80 investigational sites from the Russian Federation and about 10 investigational sites in the Republic of Kazakhstan.

The study sites will be selected according to following criteria:

- out-patient clinics,
- availability of cardiologist specialists in out-patient clinics,
- significant patient flow with essential hypertension (the sites should treat at least 350 patients with hypertension per year).

The Sponsor/responsible CRO will keep a record of the individuals responsible for each participating Study Site, the Investigators. The chosen Investigators must have qualifications and expertise directly related to the Study.

7.3 Sponsor Personnel

Takeda will keep a record of all relevant sponsor personnel.

Name and address of the Sponsor:	Takeda Pharmaceutical LLC 2, bld. 1, Usacheva str., Moscow 119048, Russian Federation Phone: + 7 495 933 5511 Fax: + 7 495 502 1625
Name, position, address and telephone of specialist who is responsible for preparation of the protocol	Protected Personal Data
Name and position of person who responsible for coordinating management of the non-interventional study	Protected Personal Data

	Protected Personal Data
Name, position, address and telephone of healthcare professional who is responsible for the study, signs the protocol and protocol amendments on behalf of the Sponsor	Protected Personal Data
Name and position of specialist who is responsible for drug safety on behalf of the Sponsor	Protected Personal Data
Name and position of specialist who is responsible for drug safety on behalf of the Sponsor in the Republic of Kazakhstan	Protected Personal Data
Name and position of specialist who is medical responsible on behalf of the Sponsor in the Repablic of Kazakhstan	Protected Personal Data

	Protected Personal Data

7.4. Contract Research Organisation (CRO)

Summary of tasks delegated to the CRO:

- The study documentation development (project management plan, data management plan etc),
- Study implementation and initiation, study conducting and study close-out,
- Data management,
- Project management,
- Statistical analysis, including the statistical analysis plan,
- Study report development

Every task has more detailed description in the Takeda-CRO contract.

The CRO will keep a record of all involved CRO personnel (e.g. CVs of monitors and data manager involved in the study as well as CV and other confirming documentation of the persons who are responsible for database constructing and all the medical operations).

Name, address and telephone of the Contract Research Organization:	
Name and position of person who responsible for coordinating management of the study and for drug safety on behalf of the CRO	

Name and position of person who responsible for data management on behalf of the CRO:	
Name and position of specialist who is responsible for statistical strategy and analysis of the study on behalf of the CRO:	
Name and position of specialist who is responsible for quality assurance and quality control on behalf of the CRO:	

7.5 Essential Documents

The following essential documents must be received by the Sponsor before the study is initiated at a site:

- Written agreement between Takeda and CRO;
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the investigator;
- Patient Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required);
- Written IEC / IRB approval / vote according to local regulations;
- Authority notification according to local regulations.

8 Ethics

This study is an observational study where the existence of the study has no impact on the patient except for collection of informed consent to use of the patient's data.

8.1 Ethical conduct of the Study

This study is a non-interventional study where there is no assignment of a patient to a particular therapeutic strategy, and no additional diagnostic or monitoring process is required for participation or during the study [5]. Epidemiological methods shall be used for the analysis of the collected data [5]. All the activities during the study to be performed according to the ethical rules and considerations, described in the Declaration of Helsinki (2013, Fortraleza) [1].

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline,

Good Epidemiological Practice requirements and any local regulations [1 -5]. Special attention will be paid to data protection.

Takeda/the responsible CRO will ensure that the protocol, any amendments and the Patient Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

Takeda as the Sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

8.2 Independent Ethics Committee / Institutional Review Board and Authorities (IEC/ IRB)

According to applicable regulations, the responsible CRO or the Investigators will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Patient Information Sheet / Informed Consent Form

The responsible CRO or the Investigator will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study,
- notification of the end-of-study,
- a summary of the study results.

The Sponsor or the responsible CRO will supply relevant documents for submission to the Independent Ethic Committee for the protocol's review and approval. This protocol, amendments to the protocol, the informed consent form, and other documents required by all applicable laws and regulations, must be submitted to a central IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or the responsible Contract Research Organisation before start of the study. Documented approval from central IECs will be obtained for all participating investigational sites (principle investigators) prior to the study start.

If necessary, the Sponsor will get prolongation, change or resumption of approval by IEC. IEC should submit to the Sponsor, at its request, the list of the members of IEC taking part in voting and the confirmation that IEC is organized and is conducting its activities in conformity with the principles of ICH GCP, the principles stated in the Helsinki declaration, the applicable legislation and normative documents.

The Sponsor/responsible CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Investigators with a copy of this list prior to the study start.

8.3 Local Ethics Committee (LEC)

This non-interventional study will be submitted to Local Ethics Committees (LECs) upon the regulations of the participated countries LEC should also approve all amendments to the protocol.

If necessary, investigator should get prolongation, change or resumption of approval by LEC. LEC should submit to the Sponsor, at its request, the list of the members of EC/LEC taking part in voting and the confirmation that EC/LEC is organized and is conducting its activities in conformity with the principles of ICH GCP, the principles stated in the Helsinki declaration, the applicable legislation and normative documents. When necessary, an extension, amendment or renewal of the LEC approval must be obtained and also forwarded to the Sponsor.

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8.4 Authorities approval

Non-interventional (observational) studies are not covered by the definition of the «clinical trials» stated in the Directive 2001/20/EC [5]. In this connection for conduction of the present study, a written approval of IEC and (if necessary) of LECs of the sites of NIS to be with the ethical principles of NISs and protection of rights of the patients taking part in it.

Authorities approval in the Russian Federation

There is no need in permission of other competent authorities (CA) of the Russian Federation for conduction of the present NIS.

The Sponsor will send required documents to the CA and/or other national or regional authorities for their notification. The Sponsor will keep an updated list of submission and notification dates and a copy of all documents submitted.

Authorities approval in the Republic Kazakhstan

The Sponsor or responsible CRO on behalf on Sponsor will send all the required documents to the CA. In case of a positive conclusion, experts appointed by CA notify the customer of the possibility provide the documents to the Commission on Ethics for the ethical evaluation of material. After getting an approval from the Commission on Ethics experts notify the CA, then CA makes the decision on whether to approve the conduct of the study or not. The Sponsor will keep an updated list of submission and notification dates and a copy of all documents submitted [33].

8.5 Patient Information Sheet and Informed Consent Form

The investigator must have the IEC/IRB written approval/favourable opinion of the written Informed Consent Form and any other written information to be provided to patients/legal representatives prior to the beginning of the observation.

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and will be in accordance with all applicable laws and regulations. The informed consent form and patient information sheet describe disclosures of the patient's personal and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given.

In the event the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The informed consent form will detail the requirements of the patient and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care. The patient information sheet and informed consent form must be written in a language fully comprehensible to the prospective patient.

The patient must agree that Sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the patient's data / personal records which were collected, processed and stored in an anonymous form. The patient must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, which may be located in other countries with potentially different regulations for data.

The patient/legal representative has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept (for details, please see the section 9.4.).

For details, see the Patient Information Sheet and Informed Consent Form.

8.6 Signing of Informed Consent Form

The investigator must give the patient/legal representative oral and written information about the study in a form that the patient/legal representative can understand, and obtain the patient's/legal representative's written consent before collection of identifiable patient information (hereinafter referred to as personal data).

Before consenting, the patient/legal representative must be left with ample time to: (1) inquire about details of the study, (2) decide whether or not to participate in the study and (3) consider and to pose questions. Since the study is observational the consent only concerns the data collection per see and is not consent to any interventional procedure or treatment.

If the patient/legal representative determines he or she will participate in the study, then the informed consent form must be signed and dated by the appropriate person, at the time of consent and prior to the patient entering into the study. The patients/legal representatives should be

instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to patient entering into the study.

The original, signed Informed Consent Forms must be kept on the Site. Copies of the signed informed consent form and patient information sheet shall be given to the patient.

8.7 Patient identification

The Patient Information Sheet and Informed Consent Form will explain that study data will be stored in an paper or electronic CRF (pCRF/eCRF) and computer database, maintaining confidentiality. Patients in this database will be identified by unique central patient identification code (patient number).

This code is only used for study purposes. After informed consent is signed every patient is given an identification code. The patient code consists of:

– study ID number (MACS-2014-100633),

– patient number; patient will be given as a four-digit figure attributed to the patient (0001, 0002, 0003 … etc).

Sites which will choose the paper type of CRF will get an amount of paper CRF with patient identification code preprinted. The Investigator will sign a form where numbers of CRFs will be denoted for his/her particular site. Sites which will choose the electronic type of CRF will amount of identification codes via database.

For the duration of the study and afterwards, only Investigator is able to identify the patient based on the identification code. The Investigator must keep a Patient Identification List of all patients that have signed the informed consent, including patient number, full patient' name, date of birth and date of Informed Consent signing (see section 8.9).

Authorized representative of a regulatory authority may require direct access to parts of the trial site records relevant to the study, including patients' medical records for data verification purposes.

8.8 Patient insurance

In this study, data on routine treatment of patients in daily practice are analyzed with the help of epidemiological methods, and treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the physicians and, respectively, the institutions involved provide sufficient protection for both patient and physician.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

8.9 Confidential and non-disclosure of personal data

The sponsor and responsible CRO affirm and uphold the principle of the patient's right to protection against invasion of privacy. The personal data of the NIS participants will be kept and processed with observance of the provisions of the RF federal law No. 152 "On personal data" and law of the Republic of Kazakhstan "On personal data and their protection" [25, 34]. Throughout this study, a patient's source data will only be linked to the study database or documentation via a unique identification number (see Section 8.7).

The necessary personal data of the patients (for example, demographic parameters) will be gathered solely for achieving the objectives of the NIS, envisaged by its design and the minimal volume. Names, addresses, numbers of medical records/ambulatory record will not be entered into CRF. No documentation identifying the patients will be disclosed.

The patients' names will not be disclosed to the sponsor. If the patient's name is mentioned in a document, such name should be deleted before submission of the copy/original of the document to the sponsor/responsible CRO. The results of the NIS kept in the electron form, should be stored in accordance with the laws of information protection.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any competent authority, the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation. Before inclusion in the NIS, the patient will be acquainted with the terms and conditions of confidentiality of using his/her personal data, including the necessity of access to them of the monitor and other authorized persons of the Sponsor. These terms and conditions will be presented in the information for patient. The patient will be included into the NIS only after getting acquainted with the above-mentioned information and signing of the Informed Consent Form.

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e. patient name, address, and other identifier fields not collected on the CRF).

The investigator will keep the list of the patients' names (Patient Identification List) so that to use it if the patients' primary documentation is needed. If SADR is reported, the representative of the regulatory authorities can ask for additional explanations. In this case the Sponsor is prohibited to contact the patient directly. All additional information will be presented by the investigator.

9 Study Design and Plan

9.1 Overall study design

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

This study is a 'non-interventional study' as defined in Directive 2001/20/EC [5] and will follow the guidelines for GPP and GVP [3,4]. This means that:

- the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice;
- the prescription of the medicine is clearly separated from the decision to include the patient in the study;
- no additional diagnostic or monitoring procedures shall be applied to the patients;
- epidemiological methods shall be used for the analysis of collected data.

9.2 Study Schedule

Milestone	Planned Date
Planned Start of the study	May, 2016
Planned End of the enrolment (LPFV)	October, 2017
Planned End of the patient observation (LPLV)	April, 2018
Planned End of the study (end of data collection)	May, 2018
Final study report	August, 2018

Due to the observational design, patient visits to the referring physician are not pre-specified by the study protocol, but will follow usual clinical practice. All patient-care decisions, including diagnostic and therapeutic interventions, will be made by and conducted at the discretion of the participating study physicians according to their clinical judgment and the local standard of medical care.

Start of the study is defined as the date of the start of data collection (first patient signed ICF for data collection).

End of the enrolment (Last Patient First Visit) is defined as the date when the last patient signs ICF and enrolled in the study.

End of the patient observation (Last Patient Last Visit) is defined as the last date when the patients are observed in the scope of the study.

End of study (end of data collection) is defined as the date when the last data point is collected. Up to this date all the CRFs should be completed and all the data clarifications (queries) should be done.

The Sponsor will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB. The Sponsor will ensure that results are posted on "clinicaltrials.gov" and as required by local authorities.

The study is considered to be completed after the database is closed, the final statistical analysis is performed and the study report is written. The study report will be signed within 12 months after the collection of the last data point.

9.3 Discussion of Study Design

The primary study objective is to estimate antihypertensive effect of Edarbi® therapy on blood pressure in patients with overweight or obesity in routine clinical practice of HTN treatment in the Russian Federation. So the non-interventional study design was chosen as it helps to obtain data in routine clinical practice.

Non-interventional principles defined in Directive 2001/20/EC [5] permits to estimate "real life" conditions. Besides non-interventional studies help to analyze big sample sizes without special selection and screening within routine clinical practice. Thus, non-interventional design allows attaining the objective of the study.

Non-interventional study design has number of limitations. It doesn't suppose randomization or blinding, so no control group will be used. Other limitations of this study are the absence of control arm and comparator, less well defined population, compared with controlled clinical trials. But this limitation is not critical as there are direct comparisons of Edarbi® with commonly used angiotensin-converting-enzyme (ACE) inhibitors (ramipril) and ARB (valsartan, candesartan and olmesartan). Besides comparators are not used in the study due to the defined in the protocol study objectives and outcomes.

The population that is planned to include in the study supposed to be heterogeneous in terms of clinical characteristics. It is planned to avoid this bias by subgroup analysis, including patients with overweight obesity, metabolic syndrome and diabetes mellitus.

9.4 The Study Population

The patients will be treated in accordance with local routine clinical practice. Patient eligibility is determined according to the following inclusion and exclusion criteria. Patients should be included in the study only once.

Investigator should consult with appropriate approved local SmPC of Edarbi® before including patients into the study and get acquainted with the information about dosage and method of administration of the drug, duration of treatment, special warnings and precautions regarding the use. The approved local SmPC Edarbi® will be included into the documentation on the study.

Approximately 1916 patients should be included into the study in accordance with the inclusion/exclusion criteria below.

9.4.1 Criteria inclusion

Every eligible patient at participating investigational sites must meet the following criteria:

1. Male and female patients ≥ 18 years of age with HTN 1-2 grade*
2. Patients with:
    - Newly diagnosed arterial HTN or
    - inadequately controlled previously prescribed monotherapy with RAAS blocker or
    - inadequately controlled previously prescribed combination therapy with RAAS blocker + diuretic or RAAS blocker + calcium antagonist.
3. The physician decides to prescribe Edarbi®
    - as monotherapy or
    - as a part of combination therapy including diuretics or calcium antagonists;
4. Overweight or obesity of any degree (body mass index> 25 kg/m^2);
5. Is capable of understanding the written informed consent, provides signed and written informed consent, and agrees to comply with protocol requirements. In case the patient is blind or unable to read, informed consent will also be witnessed.

* in accordance with guidelines of the Russian Ministry of Health for the management of HTN [6] and Kazakh protocol on clinical diagnosis and treatment of hypertension (2013) [7].

9.4.2 Criteria exclusion

Any patient who meets any of the following criteria will not be qualified for entry into the study:

1. Confirmed secondary HTN;
2. Contraindications for Edarbi® of respective approved local SmPC of Edarbi®;
3. Any reasons of medical and non-medical character, which in the opinion of the physician can prevent patient participation in the study.
4. Is an employee or family member of the investigator or study site personnel.

5. Is currently participating in a clinical trial. Participation in non-interventional registries is permitted.
6. Vulnerable patients who are unable to understand information about study or those who depend on investigator.

9.4.3 Justification for criteria inclusion and exclusion

The criteria are set to ensure a patient population that will enable the investigation of the set objectives.

Results of azilsartan clinical trials suggest that this drug provides potent and fast antihypertensive effect, so it could be effective in newly diagnosed HTN patients in achieving BP goals. Comparative studies of azilsartan with ACE (Ramipril) and ARBs (valsartan, candesartan, olmesartan) have shown the superior efficacy of Edarbi® over comparators. Thus, azilsartan could be effective in patients with insufficient BP control on other RAAS blockers in monotherapy or combination therapy. So, inclusion criteria are designed to provide the inclusion of patients with either newly diagnosed HTN or with poorly controlled BP on mono- or combination therapy, including RAAS blockers.

Current approach of administration of combination therapy with RAAS in routine clinical practice in the Russian Federation suggest the addition of calcium channel blockers or diuretics. These types of combinations also are specified as reasonable in current Russian guidelines on HTN treatment and Kazakh protocol on clinical diagnosis and treatment of hypertension [6, 7]. So these types of combination therapy are defined in inclusion criteria.

As this is non-interventional observational study, we don't restrict exclusion criteria artificially. According to ethical rules, all patients must write informed consent before enrolling. Data erroneously collected from patient for which written consent is not available, will not be included in or will be deleted from the database.

Exclusion criteria are just based on contraindication approved local SmPC of Edarbi® and routine practice. Exclusion criteria were designed to prevent inclusion of patients who cannot receive Edarbi® therapy for medical reasons (due to contraindications or secondary HTN).

9.4.4 Patient selection and procedure for avoiding of selection bias

In order to reduce selection bias, each patient who are planned to treat of arterial HTN by Edarbi® has to be documented in an anonymous patient log file (independent of prescribed treatment and signing of the Informed Consent Form) in a consecutive manner at each site.

Eligible patients who receive Edarbi® must be enrolled consecutively into the study and documented in the case report form. No eligible Edarbi® patient must be skipped. In case a patient

is not eligible (e.g. no informed consent signed), the reason for non-eligibility must be documented in the patient log file.

9.4.5 Discontinuation/withdrawal of patients from the study

9.4.5.1. Criteria for Discontinuation or Withdrawal of a patient

Patients may be discontinued from study or study drug at any time, at the discretion of the investigator. Specific reasons for discontinuing a patient from the study are:

1. Voluntary withdrawal of informed consent in patient's request or at the request of patient's legally acceptable representative.

The patient (or patient's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

2. Development of exclusion criteria or other safety reasons (not a AE or SAE) during the study.
3. Adverse Events (AE)/ Serious Adverse Events (SAE), including Patient's death

The patient has experienced an AE or SAE that requires early termination because patient is unwilling to continue because of the AE or SAE or continuation of patients' visit to the clinic is impossible or any other occurrence which can be happened.

4. Protocol deviations, incorrect enrolment of the patient. The investigator and the sponsor will decide whether there is a deviation from the protocol.
5. Lost for observation within the framework of the study. The patient did not return to the clinic and attempts to contact the patient were unsuccessful.
6. Study termination. Sponsor decision or regulatory authorities' requirement about cessation of the study.
7. Pregnancy. The patient is found to be pregnant.

   Note: If the patient is found to be pregnant, the patient must be withdrawn immediately.
8. Other (specify)

If the patient is lost for observation within the framework of the study that is, it is impossible to conduct the final visit; the investigator must do its best to get in touch with the patients for getting full information and clarifying the reasons of the loss of contact. Premature end of HTN treatment by Edarbi® automatically means end of data collection.

Details for the premature termination of the study/sites as a whole are provided in section 9.6 (Premature termination or Suspension of Study or Investigational Site).

9.4.5.2. Procedures for Discontinuation or Withdrawal of a patient

There are no special procedures of discontinuation of patients. The investigator may terminate a patient's study participation at any time during the study when the patient meets the study termination criteria described above in Section 9.4.4.1. In addition, patient/legal representative may discontinue participation in the study without giving a reason at any time during the study.

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records. The patients who prematurely withdrew from the study are not replaced with new ones, and their data will be included into the final analysis. In case if investigator loses contact with the patient during the study observation, the investigator may contact with the patient directly or through the other health care professionals who observe this patient in routine practice. In that case part of CRF "End of observation" can be filled in basing on data received via e-mails/calls.

9.5 The study plan (plan of observation)

A physician makes the decision to prescribe Edarbi® to a patient. Afterwards the physician evaluates inclusion/exclusion criteria and offers the patient participation in the observational study.

The investigator gives the patient necessary information about the study and asks the patient to read the Patient Information Sheet and Informed Consent Form. If the patient agrees to participate in the study then the patient and the investigator sign the Inform Consent Form and the investigator includes the patient in the study.

During participation in the study patients are observed according to the local routine practice. The assignment of a particular therapeutic strategy to the patient including all diagnostic procedures is decided in accordance with Russian guidelines "Diagnostics and treatment of hypertension" (2010) and Kazakh protocol on clinical diagnosis and treatment of hypertension (2013) [6, 7] and local routine practice. The patients would take Edarbi® according to local SmPC.

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. Information for the study will be collected from 4 patients' visits to the physician:

- Visit 1 (Baseline visit): is carried out after the physician made the decision to prescribe medication and the patient signed the Informed Consent Form. Baseline visit is the visit when the patient was prescribed appropriate medication.

- Visit 2 (Observational visit): assessment of blood pressure dynamics, data collection is performed approximately one month after therapy beginning

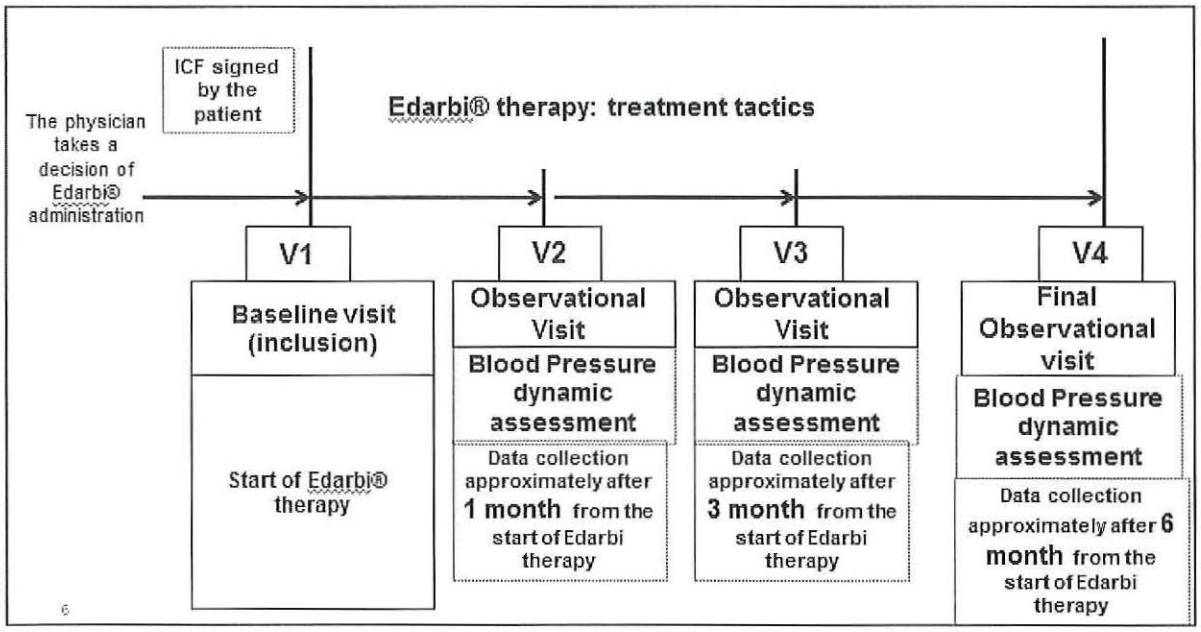
- Visit 3 (Observational visit): assessment of blood pressure dynamics, data collection is performed approximately 3 months after therapy beginning

- Visit 4 (Final observational visit): assessment of therapy effectiveness. Data collection is performed approximately 6 months after therapy beginning

Last visit can occur later than 6 months after baseline but not more than 7 months total.

Conditions when the special form "End of observation" should be filled in earlier than patient passes 6 months are described in the Section 10.5.

Scheme 1. The observational study schematic



9.6. Premature Termination or Suspension of Study or Investigational Site

The study will be completed as planned unless appearing of situation which will require temporary suspension or early termination of the study.

The sponsor has the right to close the study with serving a preliminary written notice to investigators and hospitals. The sponsor has the right to unilaterally stop at any time enrollment of patients and / or gathering of data in the study with serving a preliminary written notice thereof on

the Investigator indicating the date of stop of enrollment. The sponsor should ensure that notification about premature termination or suspension of the study is submitted to the concerned authorities and IEC.

The investigator has the right to stop recruitment at any time with serving a preliminary written notice to the Sponsor/responsible CRO.

In case of premature closure of the site/termination of the study, all completed and also unused (including the unused pages of partially completed CRFs) CRFs and all documentation forms (except documentation that has to remain stored at site) must be returned to the Sponsor, even unused ones. Study material may be destroyed only with permission of the Sponsor.

10 Conduct

10.1. Data source

Data collection should be started only after Informed Consent Form is signed by the investigator and patient. A unique patient identification number (patient number) will be assigned to each patient at the time that informed consent is obtained; this patient number will be used throughout the study. Source data will include medical records or other sources of information (e.g. laboratory tests forms, validated copies of medical summaries given by other specialists etc.).

10.2. Data collection overview

The documentation of study data will be reported by the attending physician via paper or electronic case report form (CRF).

Term	Baseline visit (V1)	Observational visit (V2)	Observational visit (V3)	Final Observational visit (V4)
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.

10.3. Data collected on the Baseline visit

Baseline visit is a visit after physician makes a decision to prescribe Edarbi® for HTN treatment. It means that investigator inform patient about the study only after taking decision about strategy of HTN treatment.

Data to be collected:

- Date of visit (day, month, year)
- Date of Informed consent form signing (day, month, year)
- Compliance with Inclusion/exclusion criteria
- Demographic information: sex, date of birth, ethnicity, region of residence (city, town etc)
- Medical history:
  - History of HTN
    - Duration of HTN/first diagnosed
    - Presence of HTN target organ damage
  - Risk factors of cardiovascular disease (smoking, dyslipidaemia, glucose intolerance, obesity, abdominal obesity, family history of cardiovascular disease,)
  - Cardiovascular diseases history:
    - established cardiovascular diseases (coronary artery disease, chronic heart failure, arrhythmias, peripheral artery diseases, ischemic heart disease etc.)
    - history of cardiovascular events (myocardial infarction, stroke, etc.)
  - Alcohol use
- Diagnose of HTN: grade, stage, risk.
- Physical examination and vital signs: height (cm), weight (kg), waist circumference (cm), body mass index, systolic and diastolic blood pressure (position, time, values), heart rate, physical inactivity

- HTN treatment:
  - previous HNT-treatment (if applicable),
  - reason(s) for discontinuation of previous HNT-treatment (if applicable),
  - monotherapy/combination treatment,
  - Edarbi® dosage regimen,
  - other HTN co-medications: INN, trade name, dosage regimen (if applicable).
- Laboratory data (last available measurements, if done within routine practice):
  - total cholesterol,
  - triglycerides,
  - low-density lipoproteins,
  - high-density lipoproteins,
  - blood glucose,
  - serum creatinine,
  - urea,
  - glycated haemoglobin
- Concurrent medical conditions (diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, etc.)
- Concomitant medication: INN, trade name, dosage regimen (single and total daily dose), duration of treatment, indication for administration
- Adverse events: seriousness, severity, causality, start and stop dates, action, outcomes

10.4. Data collected on the Observational visits 2, 3 and 4

Data to be collected:

- Date of visit (day, month, year)
- Diagnose of HTN: grade, stage, risk.
- Physical examination and vital signs: height (cm), weight (kg), waist circumference (cm), body mass index, systolic and diastolic blood pressure (position, time, values), heart rate
- HTN treatment:
  - monotherapy/combination treatment,
  - Edarbi® dosage regimen,
  - other HTN co-medications: INN, trade name, dosage regimen.
- Laboratory data (last available measurements, if done within routine practice):
  - total cholesterol
  - triglycerides,

- low-density lipoproteins,
- high-density lipoproteins,
- blood glucose,
- serum creatinine,
- urea,
- glycated haemoglobin.

- Concomitant diseases
- Concomitant medication: INN, trade name, dosage regimen (single and total daily dose), duration of treatment, indication for administration
- Adverse events: seriousness, severity, causality, start and stop dates, action, outcomes

10.5. Data collected on the End of observation

The end of observation in this study should be documented when:

- Voluntary withdrawal of informed consent in patient's request or at the request of patient's legally acceptable representative;
- Development of exclusion criteria or other safety reasons (not a AE or SAE) during the study;
- Adverse Events (AE)/ Serious Adverse Events (SAE) that requires early termination because patient is unwilling to continue because of the AE or SAE or continuation of patients' visit to the clinic is impossible or any other occurrence which can be happened;
- Lost for observation within the framework of the study. The patient did not return to the clinic and attempts to contact the patient were unsuccessful;
- Patient's death;
- Study termination. Sponsor decision or regulatory authorities' requirement about cessation of the study;
- Pregnancy;
- Premature end of HTN treatment by Edarbi®,
- End of HTN treatment by Edarbi®,

In case if one of described above events become, investigator should fill in the last appropriate Observational visit Form and the "End of observation" Form.

The following data on the CRF titled "End of Observation" should be documented:

- Diagnose of HTN and cardiovascular diseases (changes in comparison with Baseline visit):
  - HTN target organ damage,
  - risk factors of cardiovascular diseases,
  - cardiovascular diseases.
- HNT treatment:
  - Date of the last Edarbi® intake or prolongation of Edarbi® treatment,
  - Reason(s) for discontinuation of Edarbi ® treatment,
  - planned HTN treatment (if applicable) (INN, trade name, dosage regimen (single and total daily dose),
  - assessment of Edarbi® treatment by investigator (very satisfied, satisfied, neutral, unsatisfied, very unsatisfied),
  - assessment of HTN treatment by investigator (very satisfied, satisfied, neutral, unsatisfied, very unsatisfied).
- Reason(s) for discontinuation of observation

For patients who will discontinue observation in this study for any reason but continue treatment with Edarbi®, the investigator needs to report that therapy with Edarbi® will be continued on the appropriate CRF entitled "End of Observation".

10.6. Treatments to be documented in the study

All medications should be administered according to approved local SmPCs.

10.6.1. Documentation of the study medication

Due to non-interventional design of the study, the decision about particular HTN treatment strategy to the patient is taken by attending physician. Treatment of interest is Edarbi®. The study medication is not provided by the sponsor.

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.

10.6.2. 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.

10.6.3. 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.

10.6.4. 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.

10.6.5. 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.

10.6.6. Pregnancy

If any patient is found to be pregnant during the study she should be withdrawn. The pregnancy should be reported immediately, using an AE report form.

All pregnancies in patient on active study drug will be followed up to final outcome. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation of child wellness after the birth must be reported to the Sponsor.

10.7. Laboratory, instrumental exams, physical examination and vital signs to be documented in the study

All examinations (physical examination and vital signs, laboratory tests and other exams) will be performed in accordance with common clinical routine practice, routine practice of a particular medical institution. All examinations are solely based on the physician's decision about strategy of diagnostics and treatment.

All examinations should be registered in the CRF only the protocol required lab tests will be recorded in the CRFs if they are done in routine practice. The documentation of laboratory and instrumental tests will strictly follow clinical practice. The reference ranges for each protocol required lab test performed according to routine practice will be collected as well.

10.8. Body Mass Index (BMI) Calculation

The BMI is calculated using metric units with the formula provided below: The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: BMI = weight (kg)/height (m)2[optional]

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then BMI=79.2/1.762=25.56818 kg/m2The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m2. As the BMI is used as entry criteria based on >25kg/m2 cut-off point, then this determination must be made after rounding.

10.9. Documentation of 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) [21].

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

11 Safety Reporting

11.1 Definitions

11.1.1. Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient administered a drug; it does not necessarily have to have a causal relationship with this treatment.

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

11.1.2. Additional Points to Consider for AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

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

Worsening of AEs:

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

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the patient's medical condition should not be recorded as AEs. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

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

11.1.3. Serious AEs

A serious AE (SAE) is any AE which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

A serious AE are defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.

2. Is LIFE THREATENING.

   The term "life threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an OTHER IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the patient to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List.

Blood and lymphatic System	**Immune system**
Bone marrow failure	Anaphylaxis
Disseminated Intravascular Coagulation	Progressive multifocal
Haemolytic anaemia	leukoencephalopathy (PML)
Thrombotic Thrombocytopenic Purpura	Transplant rejection
Cardiovascular System	**Nervous System**
Cardiac arrest	Cerebrovascular accident
Cardiac failure	Coma
Cardiomyopathy acute	Convulsive seizures
Malignant hypertension	Hyperthermia malignant
Myocardial infarction	Macular oedema
Ventricular arrhythmias	Meningoencephalitis
	Neuroleptic malignant syndrome
	Suicidal behaviour
Endocrine System	**Musculoskeletal System**
Adrenal crisis	Rhabdomyolysis
Gastrointestinal System	**Respiratory System**

Acute pancreatitis GI haemorrhage GI perforation GI obstruction Necrotising colitis Peritonitis	Acute respiratory failure Pulmonary hypertension Pulmonary thromboembolism
Hepatobiliary System Acute hepatic failure Fulminant hepatitis	**Reproductive System** Abortion Uterine perforation
Urinary System Acute renal failure	**Skin and subcutaneous tissue** Toxic epidermal necrolysis Stevens-Johnson syndrome

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction.

11.1.4. Severity AEs

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

Mild: The event is transient and easily tolerated by the patient.

Moderate: The event causes the subject discomfort and interrupts the patient's usual activities.

Severe: The event causes considerable interference with the patient's usual activities.

11.1.5. Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

11.1.6. Start and Stop Dates

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

The stop date of the AE is the date at which the patient recovered, the event resolved but with sequela or the patient died. If AE is ongoing at the moment of end of observation, it should be indicated in the CRF.

11.1.7. Frequency

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

11.1.8. Action Concerning Study Medication

- *Drug withdrawn* – a study medication is stopped due to the particular AE.
- *Dose reduced* - the dose was reduced due to the particular AE.
- *Dose Increased* – the dose was increased due to the particular AE
- *Dose not changed* – the particular AE did not require stopping a study medication.
- *Dose Interrupted* – the dose was interrupted due to the particular AE
- *Unknown* – only to be used if it has not been possible to determine what action has been taken.

11.1.9. Outcomes of AEs

- *Fatal*: The patient died due to the AE. If the patient died due to other circumstances than the AE the outcome should be stated as 'Not recovered' or 'Recovering'. The date of death will be recorded.

- *Recovered/Resolved*: The patient has fully recovered from the event or the condition has returned to the level observed at baseline

- *Recovering/Resolving*: The event is improving but the patient is still not fully recovered

- *Not Recovered/Not Resolved*: The event is ongoing at the time of reporting and the patient has still not recovered

- *Recovered with Sequelae/Resolved with Sequelae*: As a result of the event, the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed).

- *Unknown*: If Outcome is not known or not reported.

11.2. Reporting of Adverse Events

11.2.1. Legislation for Pharmacovigilance

Applicable legal base Pharmacovigilance for the Russian Federation is following:

- Federal law of 12 April 2010 "On the Circulation of Pharmaceuticals"

- **Good Pharmacovigilance Practice of Eurasian Economic Union" (came into force May, 06, 2017).**

- **Roszdravnadzor order #1071 "On Approval of the Pharmacovigilance Procedure" (came into force April, 01, 2017).**

- Order of the Ministry of health care and social development of 26 August 2010 N757n "On approval of the procedure for drug safety monitoring, reporting of side effects, serious adverse drug reactions, unexpected adverse drug reactions"

- RF Government statement of 30.06.2004 #323 «On approval of the Federal Service on Surveillance in Healthcare»

- RF Government statement of 15.10.2012 №1043 «On approval of the Federal State Supervision in medicine circulation»

Applicable legal base Pharmacovigilance for the Republic Kazakhstan is following:

- The Code of Republic of Kazakhstan on people's health and the health system (with amendments and additions from 19.05.2015)

- Order of the Minister of Health of the Republic of Kazakhstan dated November 19, 2009 № 744 On approval of rules of clinical trials and (or) pharmacological tests of medicines, medical devices and medical equipment (with amendments from September 28, 2012)

- Order No. 421 of the Health and Social Development Minister of the Republic of Kazakhstan as of 29 May 2015 On Approval of the Rules for Medicines Pharmacovigilance and Monitoring of Adverse Reactions of the Medicines, Medical devices and Medical Equipment

- Order #9 on amendments to the Order #735 of the Minister of Health of the Republic of Kazakhstan from 18 November, 2009 On approval of the rules for state registration, renewal and amendments into the registration dossier of the Medicines, Medical devices and Medical Equipment

11.2.2. AE Reporting Form

All AEs will be documented in the special AE page of the CRF – "AE reporting form". The following information will be documented for each event:

- event term,
- start and stop date/ ongoing {and time},
- severity,
- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related),
- action concerning study medication,
- outcome of AE,
- seriousness.

The "AE reporting form" contents all information which is required to the form "Report about side effect, adverse drug reaction or lack of expected therapeutic endpoint of drug".

11.2.3. Collection and reporting of AE

Any AEs observed during the study and follow-up information on these should be reported by the investigator as soon as possible after having knowledge to the Sponsor and/or responsible CRO. Start of AEs collection: AEs must be collected from start of Edarbi® treatment.

Collection of AEs will commence from the time of the first Edarbi® intake (Baseline visit). Routine collection of AEs will continue until Observational visit 4 (Final visit).

A physician must report all reportable AEs on the special "AE reporting form" provided by the Sponsor. The physician should record only one AE per 1 "AE reporting form". The physician

has to record the diagnosis if available. If no diagnosis is available, the physician should record each sign and symptom as separate reports.

11.2.4. Collection and reporting of SAE and pregnancies

The physician should report all reportable SAEs and pregnancies to Takeda Pharmacovigilance Drug Safety Officer **immediately (within 24 hours)** after obtaining knowledge of the event by one of the following way:

- by email to Protected Personal Data using the separate "AE reporting form",
- by fax number: + 7 (495) 502 16 25 using the separate "AE reporting form".

If information is not available at the time of the first report becomes available at a later date or upon on the sponsor's request, the investigator should complete an additional SAE form and provide it by one of mentioned above way **immediately within 24 hours** of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

11.2.5. Safety reporting to Investigators, IRBs or IECs, and Regulatory Authorities

All safety-related data on study patient collected in the study database or reported to Takeda according to the normal procedure for marketed drugs, e.g. serious and non-serious AEs, will be summarised in the Non-Interventional Study Report.

In case of changes in benefit-risk assessment of Edarbi® the Sponsor will also prepare an expedited report for safety issues. The investigational site also will forward a copy of all expedited reports to their IRB or IEC.

Specialized safety reporting in the Russian Federation

The Sponsor is responsible for reporting all ADRs, SADR and pregnancies to the Federal Service on Surveillance in Healthcare not later than 15 calendar days from the day when relevant information becomes known to the sponsor.

Periodic Safety Update Report (PSUR) contains drug safety information obtained from spontaneous reports, literature and in clinical trials for a certain reporting period. According to the Russian legislation PSUR submission periodicity is determined by International Birth Date of a drug. PSUR submission time: Every 6 months during first 2 years from International Birth Date;

- Annually during the following 2 years;
- Once in three years – thereafter.

Specialized safety reporting in the Republic Kazakhstan:

The Investigator informs the Authorized organization, Ethics Committee and the Sponsor/responsible CRO about all ADRs not later than 15 calendar days from the day when relevant information becomes known.

Periodic Safety Update Report (PSUR) contains drug safety information obtained from spontaneous reports, literature and in clinical trials for a certain reporting period.

The marketing authorization holder, within the marketing authorization validity period, shall provide the authorized organization with the Periodic Safety Report from the date of registration in the Republic of Kazakhstan in accordance with the following standard periodicity:

- once every six months within two years after registration;
- annually - within the next three years;
- then - every three years or after receiving a report from the central office (if applicable);
- in future - upon subsequent medicine re-registration - once in five years;
- immediately at the authorized organization's request.

12 Data Quality Control and Assurance

12.1 Quality Control

12.1.1. Training of investigators

Before start of data collection all investigators will be trained on:

- the background and objectives of the study,
- study procedures,
- safety reporting,
- ethical regulations,
- data entering and database
- etc.

12.1.2. Quality reviews during the study conducting

The data quality will be assured by using the following methods of quality review:

- telephone interview,

- monitoring in the study sites (the monitoring will consist of two parts: on-site interview and verification of the compliance of the data presented in the CRF with the data of the primary documentation - source data verification (SDV)).

Due to non-interventional study design source documents will be partly reviewed for verification of data recorded on the CRF. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation can be patient to review by the sponsor or responsible CRO, including but not limited to the Investigator's Binder, patient medical records, informed consent documentation and review of CRF and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process. The investigator and institution guarantee access to source documents by the sponsor or responsible CRO and by the IRB or IEC.

Due to the non-interventional study design it can be able to conduct quality review only on subset of investigational sites and case report forms. Exact extent of quality reviews will be defined in the Monitoring Plan. The detailed description of the quality review will be presented in the Monitoring Plan, the Data Management Plan (DMP) and Statistical Analysis Plan.

The investigational sites where telephone interview or monitoring visit will take place will be determined randomly. Due to long overall duration of the study several waves of quality reviews will be performed.

12.1.3. Data checks and data queries

The data from paper CRFs will be doubly entered into the common database by the authorized officers of CRO in accordance with the internal standard operational procedures. After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the sponsor and responsible CRO and will be answered by investigators.

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

12.1.4. Quality Assurance Audits

The Quality Assurance (QA) unit or out-sourced by the Sponsor agency may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

12.2. Inspection by IRB/IEC or Competent Authority

Representatives from IRB/IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the investigator must immediately contact to the Sponsor and must make the records available as requested. The Inspector must be reminded up front that consent to access to personal data has not been obtained from the participants in this study.

12.3. Data Management

12.3.1. Data Management Plan

Data Management will be carried out according to a Data Management Plan, which must be written and approved before the design of the study database is finalised. Responsible CRO will provide all the data management service including data transferring, data clarification and quality control of the process. The data management provider should approve all data formats before the data collection tools are made available to the sites.

The data from paper CRFs will be doubly entered into the common database by the authorized officers of CRO in accordance with the internal standard operational procedures. After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the Sponsor and responsible CRO and will be answered by investigators.

12.3.2. Data privacy

The sponsor and responsible CRO affirm and uphold the principle of the patient's right to protection against invasion of privacy. The personal data of the NIS participants will be kept and processed with observance of the provisions of the RF federal law No. 152 "On personal data". Throughout this study, a patient's source data will only be linked to the study database or documentation via a unique identification number (for details, please, see Sections 8.5, 8.6., 8.7., 8.9).

If the written informed consent of a patient is known not to be available in spite of it being required, data for this patient is not entered into or is deleted from the database.

If a patient is included in the study in spite of being treated off-label (not according to the local SmPC), data is kept in the database and analysed separately and as part of the overall analyses as described in the Statistical Analysis Plan.

The patients will be identified in the database only by patient identification code (for details, please, see the section 8.7)

12.3.3. Case Report Form (CRF)

Both types of CRF – electronic and paper will be used in the study. The decision about type of CRF should be taken by investigator before start of ICF signing.

The sponsor or responsible CRO will supply investigators with paper CRFs if investigator chooses the paper type of CRF. The CRF must be completed in Russian. All data are entered directly into CRF. The investigator must sign off the complete data set for each patient, confirming the collected data. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRF. ADR data reported according to section 11 and data on serious ADRs collected according to section 11.3 should be signed off by investigator separately.

The completed CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

The study database will be set up and maintained by responsible CRO.

Paper Case report Form (pCRF)

Part of the study data will be collected using paper Case Report Form (pCRF). In the beginning of the study every site should select type of CRF. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

All paper CRFs must be filled out legibly in black or blue ballpoint ink (use of black ink is preferred)/ Data are transcribed directly onto eCRFs.

Corrections to paper CRFs are to be made by making a single-line strikeout of the incorrect information and writing in the revisions. All corrections must be initiated and dated. Reasons for significant corrections should additionally be included. All new additions are to be made with the date and signature or seal affixed.

After the CRFs are transmitted to the sponsor/responsible CRO, any change of, modification of or addition to the data on the pCRF should be made by the investigator with use of change and modification records of pCRF (Data Clarification Form) provided by the sponsor/responsible CRO. Any changes to the data must be signed by the investigator.

Electronic Case Report Form (eCRF)

The sponsor or responsible CRO will supply investigators with access to eCRF. Patient data will be entered directly into the database by authorized investigators. The sponsor will make arrangements to train investigators in the use of the eCRF.

12.3.4. Coding of AEs and concomitant medications

Adverse events, medical history and concurrent medical conditions are coded with MedDRA dictionary (Medical Dictionary for Regulatory Activities). Concomitant Medication is coded with WHO Drug Dictionary.

12.3.5. Record retention

The investigator agrees to keep the records stipulated in Section 12.3.3 and those documents that include (but are not limited to) the study-specific documents, the Patient Identification list, medical records, all original signed and dated informed consent forms to enable evaluations or audits from regulatory authorities, the sponsor or responsible CRO. The study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Study agreement. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13 Statistical Methods and Determination of Sample Size

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This section describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

13.1 Patient Population

Due to observational nature of this study patients will not be excluded from analysis based on their performance and/or data availability. All obtained data will be summarised after procedures of data cleaning and verification. All planned analyses (including descriptive analyses and study listings) will be performed for Full Analysis Set of data.

The following patient's populations will be included into statistical analysis:

- *Safety population*: Patients who have taken at least one dose of Edarbi® after enrolling in the study (Baseline visit)
- *All Patients Enrolled population.*

13.2 The study data and Statistical Analysis methods

This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning, i.e. all data listed in section 9.

The primary and secondary outcomes of the study are presented in section 6.2.

13.2.1. Summary of study data

All continuous variables will be summarised 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 [8].

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.

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

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 CONSORT diagram describing study patient flow will be provided

13.2.2. Statistical analysis methods

Primary study outcome – change from baseline in clinic SBP value tot Visit 4 will be estimated with 95% confidence interval construction.

In addition, clinic SBP (DBP) change from baseline will be assessed and evaluated using Mixed model repeated measures (MMRM) methodology [30, 31]. 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. The dose-response trend hypothesis test will be conducted using the appropriate contrast statement for a linear (ordinal dose) trend. In addition, Least Squares Means, the associated standard errors and 95% confidence intervals will be displayed by each individual dose group.

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. Patients who respond to therapy at visits 2, 3 and 4 will also be presented using frequencies and percentages. Secondary and exploratory outcomes will be analysed using descriptive statistics and frequencies and percentages as follows:

- Changes in systolic BP (SBP) during the treatment with Edarbi® (V2-V3) will be calculated and presented in summary tables using descriptive statistics for continuous variables;
- Changes in diastolic BP (DBP) during the treatment with Edarbi® (V2, V3) will be calculated and presented in summary tables using descriptive statistics for continuous variables;
- Percentage of patients who achieve target SBP<140 mm Hg (V2, V3, V4) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals,
- Percentage of patients who achieve target DBP<90 mm Hg (V2, V3, V4) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Percentage of patients who respond to Edarbi® therapy (defined as decrease of SBP≥ 20 mm Hg or decrease of DBP≥10 mm Hg; V2, V3, V4) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Percentage of patients who achieve target BP (defined as SBP<140 mm Hg, DBP<90 mm Hg; V2, V3, V4) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Company Confidential Information
- [redacted]
- [redacted]
- [redacted]

Company Confidential Information [redacted]

13.2.3. Analysis of Safety Data

All safety data will be analysed on the safety population. 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 as well as 95% confidence intervals;

Evaluation of AEs, including the AEs, will consist of the determination of total number of AEs, total number of patients with AEs and the number of AEs requiring discontinuation of the study treatment. The incidence and severity of all AEs will be summarized by body system. 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).

13.2.4. Potential study biases

The study limitations are those inherent to uncontrolled observational studies. Taking into account observational and uncontrolled nature of the study, fully evaluating of azilsartan medoxomil efficacy will not be available. However data regarding blood pressure (SBP and DBP) dynamic during and after azilsartan medoxomil titration in real-life practice will be gathered and analyzed. The inclusion criteria are those that used when administering azilsartan medoxomil in practice and therefore, the same criteria as those that would have been used if we had performed a similar prospective study. This type of experimental design should prevent selection bias that could occur when patient enrollment is related to the development of the outcome. In prospective observational study like this attrition bias is possible, however, in case of early leaving study last BP data will be gathered and efficacy will be estimated, these cases will not be excluded from efficacy analysis.

Details of the statistical analyses will be presented in the Statistical Analysis Plan.

13.2.5. Data handling

13.2.5.1. Missing data and invalid data

Missing data will not be restored. No procedures for missing data pattern assessment and/or imputation are planned. Outlier detection will be performed during blind data review, using modified Z-score([32] calculation

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

with MAD denoting the median absolute deviation and $\tilde{x}$ denoting the median.

Values of modified Z-score >3.5 will be considered outliers for univariate data sets that are assumed to follow an approximately normal distribution. If the normality assumption for the data being tested is not valid, then a determination of outlier using interquartile range and median (values more than 1.5 times the interquartile range will be considered outliers). Outliers will not be excluded from primary analysis *en bloc*, however, the medical context for each outlier will be defined and appropriate action taken. List of outliers flagged and actions taken will be included into Statistical Analysis Report. An additional sensitivity analysis will be performed excluding outliers.

13.2.5.2. Multiplicity

It is planned to use statistical analysis methods, which incorporates corrections for 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

13.3 Interim Analyses

No interim Analysis is planned in the study

13.4 Determination of Sample Size

Sample size was calculated for the primary objective of the study: to estimate the effect of Edarbi® treatment on blood pressure for patients with increased weight or obesity. This estimation will be conducted with 95% confidence interval construction. Sample size was calculated using SAS 9.3 proc power procedure (Confidence Interval for Paired Mean Difference) for following parameters (fixed scenario elements):

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Alpha	0.05
CI Half-Width	1
Standard Deviation	17.79
Correlation	0.4375
Nominal Prob(Width)	0.9
Number of Sides	2

Prob Type	Conditional

Where the distribution is assumed to be normal, alpha specifies the level of significance, Nominal Prob (Width) specifies the desired probability of obtaining a confidence interval half-width less than or equal to the value specified as CI Half-Width. Half-width of the desired confidence interval was set to 1 mm Hg. Standard deviation and correlation coefficient were estimated by pooling recent studies data [12, 13, 14, 19, 20] for clinic Systolic Blood Pressure after at least 6 weeks of antihypertensive treatment with azilsartan medoxomil. Pooled effect estimation (clinic SBP difference at the end of the treatment from baseline SBP value) is -17.311 with pooled SD of 17.7887, which corresponds to the standardized difference of -0.9731 and correlation coefficient of 0.4375. For the denoted scenario, it is required to receive data from at least 1437 patients before-after the treatment.

Computed N Pairs	
Actual Prob(Width)	N Pairs
0.903	**1437**

Taking into account a possible dropout of 25%, it is recommended to enrol at least 1916 patients into the study.

According to the reference studies [24-29], the SD for effect for DBP is less than the SD for SBP, so the denoted number of patients will be sufficient for the corresponding secondary outcomes.

14 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to the Sponsor for distribution. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised. Composed the study report should be provided to the IEC.

15 Publications

15.1 Publication and Disclosure

During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as

otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study contracts. In the event of any discrepancy between the protocol and the study contracts, the study contracts will prevail.

The sponsor aims to have the results of this study published and acknowledges the right of the participating sites to publish results from this study. The sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners

15.2 Study Registration

The sponsor aims to have the results of this study published.

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

16 Archiving of Study Documentation

During the course of the study the investigator must as a minimum file the essential documents (Section 7.4), the protocol, any amendments, the list of participating patients, the written informed consents, the CRFs and the progress reports in the Study Site File. After final database lock the investigator must as a minimum store the list of participating patients and the signed Informed Consent Forms on site for 5 years. The investigator should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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