Title: Local, multicentre, observational, non-interventional prospective study of Alogliptin benzoate in patients with Diabetes mellitus type 2

NCT Number: NCT02756832

Protocol Approve Date: 19-Dec-2018

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: **ENTIRE** - Local, multicentre, observational, non-interventional prospective study of Alogliptin benzoate in patients with Diabetes mellitus type 2

Title: **ENTIRE** - Local, multicentre, observational, non-interventional prospective study of Alogliptin benzoate in patients with Diabetes mellitus type 2

Study ID: Alogliptin-4018 (MACS-2015-101024)

Sponsor: Takeda Pharmaceutical LLC

2, bld. 1, Usacheva str., Moscow 119048, Russian Federation

Personal Protected Data

Study phase: Non-interventional (Observational) Company Sponsored Study

Date of version of protocol: version 1.4, 19-Dec--2018

Amendment History:

Date	Amendment Number	Amendment Type	Region
19 January 2016	Initial Protocol	Not applicable	Russian Federation
31 March 2016	1	Administrative	Russian Federation
12 May 2016	2	Administrative	Russian Federation
16 March 2017	3	Administrative	Russian Federation
18 July 2017	4	Administrative	Russian Federation
19 December 2018	5	Administrative	Russian Federation

1 Administrative information

1.1 Contacts

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

Issue	<Country or region>Contact
Serious adverse event and pregnancy reporting	Personal Protected Data
Medical Monitor (medical advice on protocol, compound, and medical management of patients)	CRO
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Personal Protected 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];
- Guidelines for Good Pharmacoepidemiology practices (GPP) [2];
- Guidelines on Good Pharmacovigilance Practices (GVP) [3];
- All applicable laws and regulations, including, without limitation, data privacy laws, and regulations.

SIGNATURES

Personal Protected Data

2 Study summary

This is an observational study and no medication will be provided. Patients enrolled into the study will be patients that are currently being treated by their physician. No intervention or change in the patients' management will be required as a result of this study

Name of Sponsor(s): Takeda Pharmaceutical LLC, Russian Federation	**Compound:** alogliptin benzoate (Vipidia®)	
Title of Protocol: Local, multicenter, observational, non-interventional prospective study of alogliptin benzoate in patients with Diabetes mellitus type 2 (DMT2).	**IND No.:** not applicable	**EudraCT No.:** not applicable
Study Number: Alogliptin-4018 (MACS-2015-101024)	**Phase:** non-interventional study	
Study Design: Study Design: Local, 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) [4]. 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 "Algorithms of specialized medical care to patients with diabetes mellitus" (2015) [5] and local routine practice. The patients would take Vipidia® according to the Russian SmPC. 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. Information for the study will be collected from 3 patients' visits to the physician.		
Primary Objectives: – to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3).		
Secondary Objectives: – to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in		

patients with diabetes mellitus type 2 (V3) in dependence on clinical characteristics.

– to describe the real-world clinical response to treatment with Vipidia® as assessed by glycosylated hemoglobin (HbA1c) level reduction to the goal <7.0%;

– to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);

– to evaluate the proportion of patients with diabetes mellitus type 2 and marked hyperglycemia (V2);

– to evaluate the effect of Vipidia® on fasting plasma glucose dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);

– to evaluate changes in weight during Vipidia® treatment period (V1-V2-V3);

– to evaluate changes in metabolic parameters (pre- and postprandial glycemia, total cholesterol triglycerides, low density lipoproteins, high density lipoproteins) during Vipidia® treatment period (V1-V2-V3);

– to estimate proportion of patients with diabetes mellitus type 2 who decrease in HbA1c ≥ 0.3% over time (V1-V2-V3);

– to estimate proportion of patients who used healthcare resources (rate of hospitalization, reason, emergency, emergency room visits, and physician office visits; in case of hospitalization, length of stay, reason, and urgency [urgent/not urgent]).

Safety Objective:

– to describe patient incidence and type of adverse events as assessed by adverse drug reactions (ADRs), serious AEs (SAEs), and AEs of special interest (AESIs) to treatment with Vipidia®;

– to describe incidence of newly diagnosed co-morbidities and complications.

Subject Population: Male and female patients with diagnosis of T2DM (newly diagnosed DM type 2 (drug naive) or inadequate glycemic control on previously prescribed any oral antidiabetic drug).

Number of patients: Approximately 1403 patients	**Number of Sites:** about 70 investigational sites from the Russian Federation
Dose Level(s): Alogliptin benzoate must be prescribed in accordance with the Russian SmPC: tablets 12.5 and 25 mg.	**Route of Administration:** Alogliptin benzoate: oral
Duration of Observation: 6 months	**Period of Evaluation:** 12 months

Main Criteria for Inclusion:

1. Patient is male or female $\geq$ 18 years of age;
2. Has a diagnosis of T2DM;
3. Patients with:
   - newly diagnosed DM type 2 (drug naive) or
   - inadequate glycemic control on previously prescribed any oral antidiabetic drug.
4. Vipidia® is prescribed according to the approved label for the Russian Federation
5. The patient's physician decides to prescribe Vipidia®:
   - as monotherapy or
   - as a part of combination therapy.
6. The patient (or, when applicable, the patient's legally acceptable representative) signs and dates a written, informed consent form prior to the start of data collection. Patient 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.

Main Criteria for Exclusion:

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

- Contraindications of respective approved Russian SmPC;
- In the opinion of the physician, the patient has any reasons of medical and non-medical in character, which should prevent patient participation in the study;
- Patient has used Dipeptidyl peptidase-4 inhibitors (DPP-IV inhibitors) or Glucagon like peptide-1 agonists (aGLP-1) within the 3 months prior to the start of Vipidia® treatment.
- The patients is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress

Primary endpoint:

- Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3) .

Secondary endpoints:

- Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3) in subgroups with different clinical characteristics
- Proportion (%) of patients with diabetes mellitus type 2 who assessed by glycosylated hemoglobin (HbA1c) level reduction to the goal <7.0% by V3;
- Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy over time (V1-V2-V3);
- Proportion (%) of patients with marked hyperglycemia (V2) (Marked Hyperglycemia is

defined as fasting plasma glucose higher than or equal to 11 mmol/L);

– Change from baseline in fasting plasma glucose level on Vipidia® therapy over time (V1-V2-V3);

– Change from baseline in weight during Vipidia® treatment period (V1-V2-V3);

– Change from baseline in metabolic parameters (pre- and postprandial glycemia, total cholesterol triglycerides, low density lipoproteins, high density lipoproteins) during Vipidia® treatment period(V1-V2-V3);

– Proportion (%) of patients with diabetes mellitus type 2 who decrease in HbA1c $\geq$ 0.3% over time (V1-V2-V3);

– Proportion (%) of patients who used healthcare resources - rate of hospitalization, reasons, emergency, emergency room visits, and physician office visits; in case of hospitalization, length of stay, reason, and urgency [urgent/not urgent].

Safety endpoints:

– Patient incidence and type of adverse events as assessed by adverse drug reactions (ADRs), serious AEs (SAEs), and AEs of special interest (AESIs) to treatment with Vipidia®;

– Incidence of newly diagnosed co-morbidities and complications.

Statistical Considerations:

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 (*L.A. Goodman, On simultaneous confidence intervals for multinomial proportions, Technometrics 7 (1965) 247–254*).

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.

Sample Size Justification: Sample size was calculated for the primary objective of the study: to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3) in dependence of baseline clinical characteristics. Sample size was calculated using SAS 9.3 proc power procedure (power for Multiple Linear Regression). Where the computational method set to exact, assumed distribution of the tested predictors set to joint multivariate normal distribution for the response and tested predictors, number of predictors in the full model, not counting the intercept assumed to be 7 (prior therapy of DM, sex, age, cardiovascular risk group, therapy type (monotherapy or combined therapy), baseline BMI, initial glycemic control), number of predictors in the reduced model, not counting the intercept assumed to be at least 1, level of significance of the statistical test set to 0.05, desired power of the test set to 0.9, partial correlation between the tested predictors and the response, adjusting for any other predictors in the model assumed to be at least 0.1 (small effect size).

For the denoted scenario, it is required to receive data from at least 1052 patients after the treatment of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics. Taking into account a possible dropout of 25%, it is recommended to enrol at least 1403 patients into the study.

Table of Contents

3. Study Reference Information

3.1. Study-Related Responsibilities

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.

3.1.1. Study Sites

The study is planned to be conducted in approximately 70 investigational sites from the Russian Federation.

The study sites will be selected according to the following criteria:

- out-patient,
- any types of health care institutions and high level health care educational institutions in the Russian Federation with outpatient units,
- availability of qualified endocrinologists,
- significant patient flow with DM2 (the sites should treat at least 350 patients with DM2 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

3.1.2. Sponsor Personnel

Takeda LOC 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 Personal Protected Data
Name, position, address and telephone of specialist who is responsible for preparation of the protocol	Personal Protected Data

	Personal Protected Data
Name and position of person who responsible for coordinating management of the non-interventional study	Personal Protected 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	Personal Protected Data
Name and position of specialist who is responsible for drug safety on behalf of the Sponsor	Personal Protected Data

	Personal Protected Data

3.1.3. Contract Research Organisation (CRO)

Summary of tasks transferred 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:	

3.2. 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.

The Chair of the Steering Committee:

Personal Protected Data

The members of the Steering Committee:

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3.3. 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 (approved by Independent Ethics Committees (IECs));

- Written IEC / IRB approval / vote according to local regulations;
- Authority notification according to local regulations.

3.4. List of Abbreviations

ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
aGLP-1	Agonist of Glucagon-like peptide-1
BMI:	Body Mass Index
BP:	Blood Pressure
CA:	Competent Authority
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Curriculum Vitae
DM2T:	Diabetes mellitus type 2
DMP:	Data Management Plan
DPP-IV:	dipeptidyl peptidase IV
DSO:	Drug Safety Officer
EC:	Ethics Committee
eCRF:	electronic Case Report Form
FPLV:	First Patient Last Visit (end of enrollment)
FPG:	Fasting Plasma Glucose
GCP:	Good Clinical Practice
GEP:	Good Epidemiologycal Practice
GLP-1:	Glucagon-like peptide-1
GPP:	Good Pharmacoepidemiology Practices
GVP:	Good Pharmacovigilance Practices
HbA1c:	glycosylated hemoglobin
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
LEC:	Local Ethics Committee
LPLV:	Last patient Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
NIS:	Non-interventional study
PPG:	Postprandial Blood Glucose
pCRF:	paper Case Report Form
PSUR:	Periodic Safety Update Report
QA:	Quality Asurance
RF:	Russian Federation
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SAE:	Serious Adverse Event
SD:	Standrad Deviation
SDV:	Source Data Verification
SmPC:	Summary of Product Characteristics
WHO:	World Health Organization

3.5. Definition of Terms

The main definitions are provided below according to 7th edition of "Algorithms of specialized medical care for diabetic patients" [5].

Diabetes Mellitus (DM) – is group of metabolic disorders characterized by chronic hyperglycemia, which results from a dysfunction in insulin secretion, action of insulin, or both.

Glycosylated hemoglobin (HbA1c) as a diagnostic criteria of DM is ≥ 6.5 % (48 mmol/mol).

Individual targets of glycemic control by HbA1c level in DM type2 are 6.5 – 8.0 % and it depends on age, presents/absence of micro-, macro-complications, or/and risk of severe hypoglycaemia, life expectancy.

Target Fasting Plasma Glucose (FPG) depends on defined individual targets of glycemic control by HbA1c level and is ≤6.5-8.0 mmol/l.

Target Postprandial Blood Glucose (PPG) depends on defined individual targets of glycemic control by HbA1c level and is ≤8.0-11.0 mmol/l.

4 Introduction

4.1 Disease background

According to recent data, prevalence of diabetes mellitus in the world has more than doubled over the past 10 years. In 2013 the number of patients with DM was 371 million. In Russia as in other countries has been matched a rapid increase in the DM incidence. According to the State Register in January 2013 there were registered 3,779 millions of patients with DM. However, according to the epidemiological studies, the true prevalence of DM in Russia is approximately 3-4 times higher and reaches 9-10 millions of people [6].

The most serious consequences of DM are the complications: nephropathy, retinopathy, macroangiopathy with involvement of arteries of the heart, brain and lower extremities. These complications lead to the higher morbidity and mortality of patients with DM.

4.2 Drug background

4.2.1. Drug description

Vipidia® (alogliptin benzoate) is a DPP-4 inhibitor and it is indicated in adults aged 18 years and older with Type 2 diabetes mellitus to improve glycaemic control in monotherapy or in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Trade name: Vipidia®

International Non-proprietary Name (INN): alogliptin benzoate

Pharmacotherapeutic group: Hypoglycaemic drug - dipeptidyl peptidase 4 (DPP-4) inhibitor

Pharmaceutical form: tablets 12.5 and 25 mg.

Composition:

1 film coated tablet 12,5 mg contains:

Active ingredients: alogliptin benzoate 17 mg (equivalent to 12,5 mg alogliptin)

Excipients:

Tablet core: Mannitol 96,7 mg, Microcrystalline cellulose 22,5 mg, Hydroxypropylcellulose 4,5 mg, Croscarmellose sodium 7,5 mg, Magnesium stearate 1,8 mg.

Film coating: Hypromellose 2910 5,34 mg, Titanium dioxide 0,6 mg, Ferric oxide yellow 0,06 mg, Macrogol 8000 trace amount, Printing ink Gray F1* trace amount.

Printing ink Gray F1 contains: shellac 26 %, Iron oxide black 10 %, ethanol 26 %, butyl alcohol 38 %.

1 film coated tablet 25 mg contains:

Active ingredients: alogliptin benzoate 34 mg (equivalent to 25 mg alogliptin)

Excipients:

Tablet core: Mannitol 79,7 mg, Microcrystalline cellulose 22,5 mg, Hydroxypropylcellulose 4,5 mg, Croscarmellose sodium 7,5 mg, Magnesium stearate 1.8 mg.

Film coating: Hypromellose 2910 5,34 mg, Titanium dioxide 0,6 mg, Iron oxide red 0,06 mg, Macrogol 8000 trace amount, Printing ink Gray F1* trace amount.

Printing ink Gray F1 contains: shellac 26 %, Iron oxide black 10 %, ethanol 26 %, butyl alcohol 38 %.

Description

Vipidia® 12.5 mg film-coated tablets:

Yellow, oval, biconvex, film-coated tablets with "TAK" and "ALG-12.5" printed in grey ink on one side.

Vipidia® 25 mg film-coated tablets:

Light red, oval, biconvex, film-coated tablets with "TAK" and "ALG-25" printed in grey ink on one side.

4.2.2. Summary of trials

In-vitro studies have shown alogliptin benzoate to have greater selectivity for DPP-4 than other currently available agents within the class, demonstrating more than 10,000-fold greater selectivity for DPP-4 than the related enzymes DPP-8 and DPP-9. In a randomised study evaluating the pharmacokinetic and pharmacodynamic profiles of alogliptin, DPP-4 inhibition of between 81.8% and 96.7% was observed with all doses of alogliptin benzoate 24-hours after dosing on Day 14. Furthermore, DPP-4 inhibition was observed up to 168

hours after dosing on Day 14. These data support the use of a once-daily dosing regimen for alogliptin [7].

The DPP-4 inhibitory effects of alogliptin benzoate were further demonstrated in a 16-week randomised, parallel group study in patients with Type 2 diabetes. At week 16, a statistically significant increase in postprandial active GLP-1 and statistically significant decrease in glucagon levels were obtained following treatment with alogliptin benzoate compared with placebo [8]. No drug–drug interactions have been observed in clinical studies when alogliptin benzoate was administered concomitantly with a range of other medications and drug classes including: other oral antidiabetic agents, cimetidine, and substrates or inhibitors of P-glycoprotein and the liver enzyme CYP. Therefore, alogliptin benzoate is considered to have only a low potential for drug-drug interactions.

Alogliptin benzoate produced significant reductions in HbA1c over 26 weeks in all Phase 3 studies (-0.5 to -0.8%). HbA1c reductions were rapid and sustained. In long-term treatment over 2 years, alogliptin benzoate showed significant and sustained glycaemic advantages over SU in patients with Type 2 diabetes [9]. The Examination of Cardiovascular Outcomes with Alogliptin benzoate versus Standard of Care in Patients with Type 2 Diabetes and Acute Coronary Syndrome (or EXAMINE) study is a pivotal study that evaluated the cardiovascular safety of alogliptin benzoate in 5380 patients with Type 2 diabetes and acute coronary syndrome, ie patients at very high cardiovascular risk. The primary objective of EXAMINE was to evaluate non-inferiority of cardiovascular risk based on a primary composite endpoint of CV death, nonfatal myocardial infarction and nonfatal stroke. The study showed that alogliptin benzoate is not associated with an increase in cardiovascular events compared to placebo [10].

4.3 Rationale for the Proposed Study

An important goal of treatment is to achieve and maintain blood glucose, as measured by glycated haemoglobin levels as close to normal as possible, without producing hypoglycaemia. A key component of recent guidelines is the recommendation that glycaemic targets and blood-glucose lowering therapies should be individualized and it depends on age of patient, life expectancy, severity of complications [5, 11].

Depending on the initial level of blood glucose and the target level of glycated haemoglobin doctor can prescribe one hypoglycemic drug or the combination of the drugs. In accordance with recommendations of Russian association of endocrinologists, patients with newly diagnosed DM type 2 and the level of glycated haemoglobin 6,5-7,5% can be prescribed monotherapy with metformin, DDP-4 inhibitor or a GLP-1 [5].

For the patients with glycated hemoglobin levels of 7,6 - 9% at the time of diagnosis is recommended to start treatment with combination of 2 antidiabetic drugs acting on different mechanisms of disease development. There are several most rational combinations:

metformin (first-line drug decreasing insulin resistance) and drugs increasing insulin secretion - sulfonylureas, glinides, DDP-4 inhibitors or a GLP-1 [5].

The efficacy of hypoglycemic therapy should be performed every 3 months. Intensification of hypoglycemic therapy in case of its insufficiency (i.e. in the absence of achieving target level of HbA1c) should be performed not later than in 6 months [5].

Thus, the new DPP-4 inhibitor, alogliptin benzoate (Vipidia®) opens new opportunities in the treatment of patients with DM type 2. Particularly it may be effective in patients with newly diagnosed DM as monotherapy or in combination with other oral antidiabetic drugs. Therefore the assessment of effects of alogliptin benzoate in treatment of patients with DM type 2 in Russian routine clinical practice is a matter of significant interest.

5 Study Objectives and endpoints

5.1 Study objectives

5.1.1. Primary objective

– to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3).

5.1.2. Secondary objectives

– to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3) in dependence on clinical characteristics

– to describe the real-world clinical response to treatment with Vipidia® as assessed by glycosylated hemoglobin (HbA1c) level reduction to the goal <7.0%;

– to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);

– to evaluate the proportion of patients with diabetes mellitus type 2 and marked hyperglycemia (V2);

– to evaluate the effect of Vipidia® on fasting plasma glucose dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);

– to evaluate changes in weight during Vipidia® treatment period (V1-V2-V3);

– to evaluate changes in metabolic parameters (pre- and postprandial glycemia, total cholesterol triglycerides, low density lipoproteins, high density lipoproteins) during Vipidia® treatment period (V1-V2-V3);

– to estimate proportion of patients with diabetes mellitus type 2 who decrease in HbA1c $\geq$ 0.3% over time (V1-V2-V3);

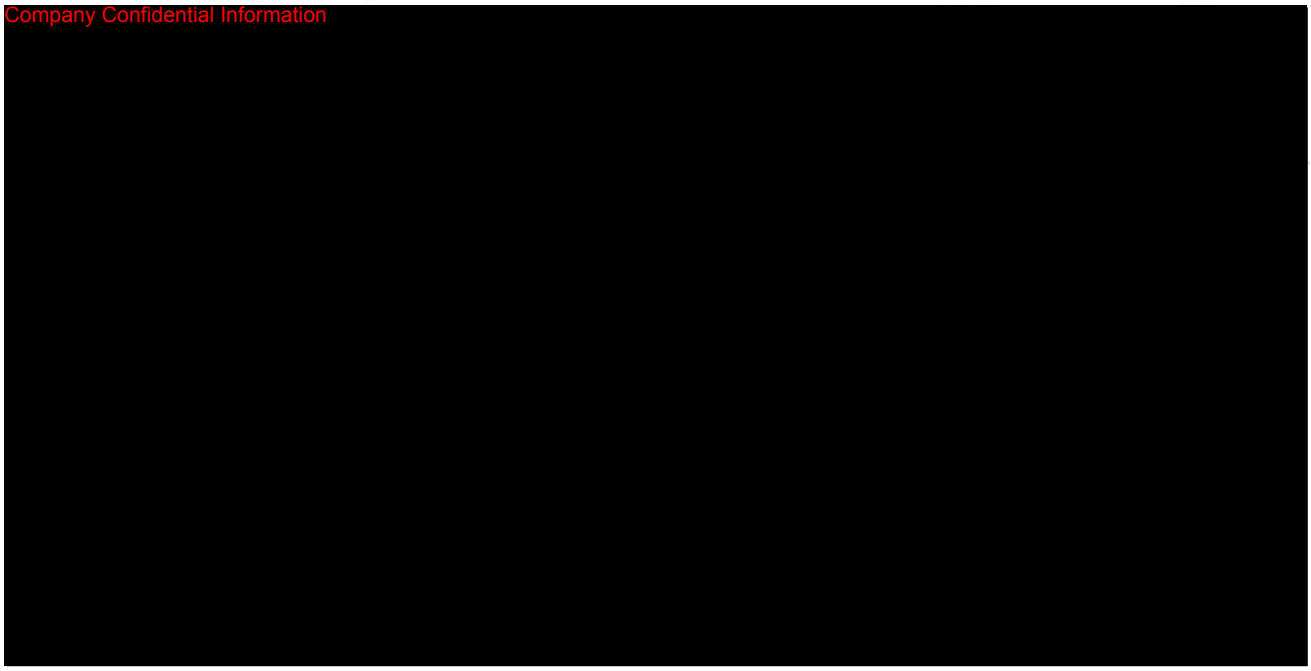
– to estimate proportion of patients who used healthcare resources (rate of hospitalization, reason, emergency, emergency room visits, and physician office visits; in case of hospitalization, length of stay, reason, and urgency [urgent/not urgent]).

5.1.3. Safety Objective

– to describe patient incidence and type of adverse events as assessed by adverse drug reactions (ADRs), serious AEs (SAEs), and AEs of special interest (AESIs) to treatment with Vipidia®;

– to describe incidence of newly diagnosed co-morbidities and complications.

5.1.4. Exploratory objectives



5.2 Study endpoints

5.2.1. Primary endpoint

– Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3).

5.2.2. Secondary endpoints

– Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3) in subgroups with different clinical characteristics.

– Proportion (%) of patients with diabetes mellitus type 2 who assessed by glycosylated hemoglobin (HbA1c) level reduction to the goal <7.0% by V3;

– Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy over time (V1-V2-V3);

– Proportion (%) of patients with marked hyperglycemia (V2) (Marked Hyperglycemia is defined as fasting plasma glucose higher than or equal to 11 mmol/L);

– Change from baseline in fasting plasma glucose level on Vipidia® therapy over time (V1-V2-V3);

– Change from baseline in weight during Vipidia® treatment period (V1-V2-V3);

– Change from baseline in metabolic parameters (pre- and postprandial glycemia, total cholesterol triglycerides, low density lipoproteins, high density lipoproteins) during Vipidia® treatment period (V1-V2-V3);

– Proportion (%) of patients with diabetes mellitus type 2 who decrease in HbA1c ≥ 0.3% over time (V1-V2-V3);

– Proportion (%) of patients who used healthcare resources - rate of hospitalization, reasons, emergency, emergency room visits, and physician office visits; in case of hospitalization, length of stay, reason, and urgency (urgent/not urgent).

5.2.3. Safety endpoints

– Patient incidence and type of adverse events as assessed by adverse drug reactions (ADRs), serious AEs (SAEs), and AEs of special interest (AESIs)) to treatment with Vipidia®;

– Incidence of newly diagnosed co-morbidities and complications.

5.2.4. Exploratory endpoints

[redacted]

6 Study Design and Description

6.1 Study Design

This is a local, prospective, multicentre, non-interventional, observational study in adult patients with T2DM diagnosis.

This study is a 'non-interventional study' as defined in Directive 2001/20/EC [4] and will follow the guidelines for GPP, GVP, GEP [2, 3, 12]. 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.

The purpose of this study is to observe clinical response to treatment with Vipidia® utilization patterns in standard clinical practice. No investigational product will be administered in this study.

6.2 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 Patent First Visit) is defined as the date when the last patient sings 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 must be signed within 12 months after the collection of the last data point.

6.3 Justification for the Study Design

The primary study objective is to estimate hypoglycemic effect of Vipidia® therapy on HbA1c level in patients with DM2T in routine clinical practice of DM2T 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 [4] permits to estimate "real life" conditions. Moreover 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.

The population that is planned to include in the study supposed to be heterogeneous in terms of clinical characteristics.

6.4 Premature Termination or Suspension of Study or Investigational Site

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

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.

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

7 Selection and Discontinuation/Withdrawal of patients

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 Russian SmPC of Vipidia® before including patients into the study and get acquainted with the information about dosage and method of administration of the drug, special warnings and precautions regarding the use. The approved Russian SmPC Vipidia® will be included into the documentation on the study.

Approximately 1403 patients should be included into the study in accordance with the inclusion/exclusion criteria below.

7.1 Inclusion criteria

Patient eligibility is determined according to the following criteria prior to start of data collection:

Inclusion criteria:

1. Patient is male and female subjects ≥ 18 years of age;
2. Has a diagnosis of T2DM
3. Patients with:
   - newly diagnosed DM type 2 (drug naïve) or
   - inadequate glycemic control on previously prescribed any oral antidiabetic drug.
4. Vipidia® is prescribed according to the approved label for the Russian Federation
5. The patient's physician decides to prescribe Vipidia®:
   - as monotherapy or
   - as a part of combination therapy.
6. The patient (or, when applicable, the patient's legally acceptable representative) signs and dates a written, informed consent form prior to the start of data collection. Patient 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.

7.2 Exclusion criteria

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

1. Contraindications of respective approved Russian SmPC;

2. In the opinion of the physician, the patient has any reasons of medical and non-medical character, which in the opinion of the physician can prevent patient participation in the study;

3. Patients who had used Dipeptidyl peptidase-4 inhibitors (DPP-IV inhibitors) or Glucagon like peptide-1 agonists (aGLP-1) within the 3 months prior to the start of Vipidia® treatment.

4. The patient is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

7.3 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 alogliptin benzoate clinical trials suggest that this drug provides fast and long term antihyperglycemic effect, so it could be effective as in newly diagnosed DM2T patients and in patients who are on the inadequate glycemic control on previously prescribed monotherapy with metformin or with any other oral antidiabetic drug in achieving HbA1c goals. Comparative study of alogliptin with glipizide have shown the superior efficacy of Vipidia® over comparator [9]. Thus, Vipidia® could be effective in patients with insufficient HbA1c control on other oral antidiabetic drugs in monotherapy or combination therapy.

So, inclusion criteria are designed to provide the inclusion of patients with either newly diagnosed DM2T or inadequate glycemic control mono- or combination therapy, including metformin and other antihyperglicemic drugs.

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 Russian SmPC of Vipidia® and routine practice. Exclusion criteria were designed to prevent inclusion of patients who cannot receive Vipidia® therapy for medical reasons (due to contraindications).

7.4 Patient selection and procedure for avoiding of selection bias

In order to reduce selection bias, each patient who are planned to treat of DM2T by Vipidia® 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 Vipidia® must be enrolled consecutively into the study and documented in the case report form. No eligible Vipidia® 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. Additionally, for each informed consent signed, there will be CRFs recorded with the patient's data.

7.5 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. (Specify)

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 deviation, 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 DM2T treatment by Vipidia® automatically means end of data collection.

Details for the premature termination of the study/sites as a whole are provided in section 6.4 (Premature termination or Suspension of Study or Investigational Site).

7.6 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 7.5. 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.

8 Non-interventional study material management

In accordance with NIS definition and principles of NISs [4] the study medication (Alogliptin benzoate) and concomitant medication cannot be provided by the Sponsor.

9 Study plan

9.1 The study plan (plan of observation)

A physician makes the decision to prescribe Vipidia® 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 [5] and local routine practice. The patients would take Vipidia® according to the Russian 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. Information for the study will be collected from 3 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.

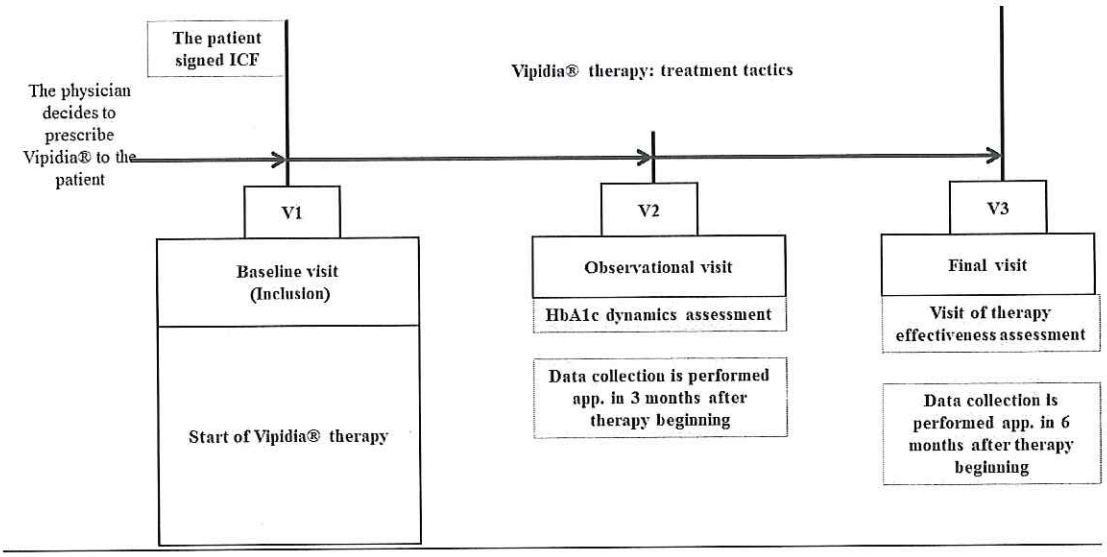
- Visit 2 (Observational visit): assessment the dynamics of HbA1c and glycemia levels Data collection is performed approximately 3 month after therapy beginning

- Visit 3 (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 9.3.5.

Scheme 1. The observational study schematic



9.2 Study Procedures

The following sections describe the study procedures and data to be collected.

9.1.1. Informed Consent Procedure

The requirements of the informed consent are described in Section 14.5.

Informed consent must be obtained prior to the start of data collection. A unique patient identification number (patient number) will be assigned to each patient at the time; this patient number will be used throughout the study.

9.1.2. Treatments to be documented in the study

All medications should be administered according to approved Russian SmPCs.

9.1.2.1. Documentation of the study medication

Due to non-interventional design of the study, the decision about particular DM2T treatment strategy to the patient is taken by attending physician. Treatment of interest is Vipidia®. The study medication is not provided by the Sponsor.

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

- start date of Vipidia® treatment,
- end date of Vipidia® treatment or prolongation of Vipidia® treatment,
- dose, frequency, reason for 12,5 dose (primary one);
- reason(s) for discontinuation of Vipidia® treatment (if applicable).

Vipidia® should be administered according to the official prescribing information (The Russian SmPC).

9.1.2.2. Prior DM2T treatment

Medication taken before start of the study is called prior medication. In case the patient already underwent DM2T treatment during 12 weeks prior to start of Vipidia® treatment, details of the therapy should be recorded in the CRF.

9.1.2.3. Concomitant medication

Concomitant medication is any drug given in addition to the Vipidia® treatment DM2T 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 treatment 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 treatment 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.

DM2T treatment

In case of combination DM2T treatment all co-medications for DM2T 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.

9.1.2.4. Follow-up DM2T treatment

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

9.1.3. 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 (including but not limited DM2T).

Any events which occur after start of Vipidia® treatment and are not related or related to the Vipidia® treatment should be considered as adverse events.

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

9.1.4. Pregnancy

If any patient is found to be pregnant during the study she should be withdrawn. The pregnancy should be reported immediately, using a 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 after the birth of the child will also be conducted.

9.1.5. 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 and up-dates of reference ranges with effective dates for each protocol required lab test performed according to routine practice will be collected as well.

9.3 Data collection

9.3.1. 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.).

9.3.2. 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)	Final visit (V3)
Inclusion/exclusion criteria	X		
Signed Informed consent form	X		
Date of visit	X	X	X
Demographic information	X		
Medical history including history of DM2T	X		
Concurrent medical conditions	X		
Physical examination and vital signs*	X	X	X
Study medication	X	X	X
Laboratory tests and instrumental exams*	X	X	X
Concomitant treatment (including DM2T treatment)	X	X	X
Healthcare resources utilization		X	X
Adverse events		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, analysis of blood glucose self-control measurement (patient's dairy). All examinations should be registered in the CRF only if they are done in routine practice.

9.3.3. Data collected on the Baseline visit

Baseline visit is a visit after physician makes a decision to prescribe Vipidia® for DM2T treatment. It means that investigator inform patient about the study only after taking decision about strategy of DM2T 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, race, region of residence (city, town etc)
- Medical history and concurrent conditions: (condition, start/end date)
  - Smoking status,
  - General medical history – diseases/conditions/, abnormality (ongoing or not at the study entry), date of diagnosis,
  - History of DM2T: - date of diagnosis of diabetes, historical complications of DM (diabetic retinopathy, autonomic neuropathy, diabetic nephropathy – and their date of diagnosis), family history of DM and cardiovascular diseases, previous DM2T treatment (including reason(s) for discontinuation of previous DM2T-treatment (if applicable);
  - History of cardiovascular and related disorders (arterial hypertension, IM, stroke, dyslipidaemia, arrhythmias, chronic heart failure, peripheral artery diseases, etc.)
- Physical examination and vital signs: height (cm), weight (kg), systolic and diastolic blood pressure (position, time, values), heart rate,
- Laboratory data (last available measurements, if done within routine practice):
  - Hb1Ac,
  - FPG,
  - PPG,
  - Lipid profile (total cholesterol, tryglycerides, low-density lipoproteins, high-density lipoproteins),
- The study medication:
  - Vipidia® treatment data (start and stop date, frequency, single dose, primary reason for 12,5 mg dose and primary reason for interruption or change);
- Concomitant treatment:
  - DM2T treatment ,
  - Other concomitant treatment - INN, trade name, dosage regimen (dose taken), duration of treatment, indication for administration

9.3.4. Data collected on the Observational visits 2, 3

Data to be collected:

- Date of visit (day, month, year)
- Physical examination and vital signs: , weight (kg), systolic and diastolic blood pressure (position, time, values), heart rate
- Laboratory data (last available measurements, if done within routine practice):
  - Hb1Ac,

– FPG,

– PPG,

– Lipid panel (total cholesterol, tryglycerides, low-density lipoproteins, high-density lipoproteins)

- Healthcare resources utilization: Type (including: emergency (at home service),, emergency room visits, hospitalization and physician office visits; , reasons, start and end date and urgency (urgent/not urgent)
- The study medication:
  – Vipidia®
- Concomitant treatment:

– DM2T treatment - current DM2T-treatment if applicable,), reason(s) for discontinuation of previous DM2T-treatment (if applicable),

– Other concomitant treatment - I, trade name, dosage regimen (dose taken), duration of treatment, indication for administration

- Adverse events: seriousness, severity, causality, start and stop dates, action, frequency, outcomes

9.3.5. Data collected at the End of observation

The end of observation in this study should be documented for all patients who passed the Baseline visit.

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

- DM2T treatment:
  – Date of the last Vipidia® intake or continuation of Vipidia® treatment,
  – Reason(s) for discontinuation of Vipidia® treatment (insufficient efficacy, contraindications and warnings according to the local SmPC, patients' unwillingness, all reasons mentioned in the section 7.5. of the current protocol),
  – planned non-Vipidia®, Vipidia® or combination Vipidia® DM2T treatment (if applicable) (INN, trade name, dosage regimen (dose taken),
  – assessment of Vipidia® and DM2T treatment by investigator (very satisfied, satisfied, neutral, unsatisfied, very unsatisfied).
- Reason(s) for discontinuation prematurely data collection (if applicable) including all reasons mentioned in the section 7.5. of the current protocol

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

10 Safety Reporting

10.1 Definitions

10.1.1. 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.

10.1.2. 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 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:

- Changes in laboratory values 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 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.

10.1.3. 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. Is 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 Bone marrow failure Disseminated Intravascular Coagulation Haemolytic anaemia Thrombotic Thrombocytopenic Purpura	**Immune system** Anaphylaxis Progressive multifocal leukoencephalopathy (PML) Transplant rejection
Cardiovascular System Cardiac arrest Cardiac failure Cardiomyopathy acute Malignant hypertension Myocardial infarction Ventricular arrhythmias	**Nervous System** Cerebrovascular accident Coma Convulsive seizures Hyperthermia malignant Macular oedema Meningoencephalitis Neuroleptic malignant syndrome Suicidal behaviour
Endocrine System Adrenal crisis	**Musculoskeletal System** Rhabdomyolysis
Gastrointestinal System Acute pancreatitis GI haemorrhage GI perforation GI obstruction Necrotising colitis	**Respiratory System** Acute respiratory failure Pulmonary hypertension Pulmonary thromboembolism

Peritonitis	
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.

10.1.4. 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.

10.1.5. 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.

10.1.6. 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.

10.1.7. Frequency

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

10.1.8. 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.

10.1.9. 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.

10.2. Reporting of Adverse Events

10.2.1. Legislation for Pharmacovigilance in the Russian Federation

Applicable legal base Pharmacovigilance 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»

10.2.2. 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 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".

10.2.3. Collection and reporting of AEs

Any AEs observed during the study should be reported by the investigator to the responsible CRO. Start of AEs collection: AEs must be collected from start of Vipidia® treatment.

Collection of AEs will commence from the time of the first Vipidia® intake (Baseline visit). Routine collection of AEs will continue until Final visit (Visit 3).

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.

10.2.4. Collection and reporting of SAEs and pregnancies

The physician must report all reportable SAEs and pregnancies to CRO

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.

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

All safety-related data on study patient collected in the study database will be summarised in the Non-Interventional Study Report. All SAEs and pregnancy cases will be reported by CRO directly to Takeda within 24 hours.

The Sponsor is responsible for reporting all serious adverse drug reactions (SADRs) 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 or CRO.

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

Periodic Safety Update Report (PSUR) contains drug safety information obtained from spontaneous reports, literature and in clinical trials for a certain reporting period. If the PSUR submission time terms and frequencies for particular drugs are not established by Roszdravnadzor, PSUR submission time terms and frequency shall be calculated from the first drug's worldwide registration date (International Birth Date) and are as follows:

- Every 6 months during first 2 years from International Birth Date;
- Annually during the following 2 years;
- Once in three years – thereafter.

11 Data handling and recordkeeping .

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

11.1 CRFs (Electronic and Paper)

Completed CRFs are required for each patient who signs an informed consent.

The Sponsor or responsible CRO will supply investigative sites with paper CRFs/access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. CRFs must be completed in Russian.

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. AE data reported according to section 11 and data on serious AEs collected according to section 10.2 should be signed off by investigator separately.

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

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

The data will be recorded directly into the CRFs are described in the section 9.3.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. 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. The Sponsor or responsible CRO will supply investigators with paper CRFs if investigator chooses the paper 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 initialed 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 submission of the CRFs to the Sponsor, any change of, modification of or addition to the data on CRFs should be made by the investigator with use of change and modification records of CRFs (Data Clarification Form) provided by the sponsor. The investigator must review the Data Clarification.

Electronic Case Report Form (eCRF)

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

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 or responsible CRO will make arrangements to train investigators in the use of the eCRF.

11.2 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" [12]. 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 Sections14.5, 14.6, 14.8).

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 erroneously included in the study more than once all data will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

If a patient is included in the study in spite of being treated off-label (not according to the Russian 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 14.6)

11.3 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.

11.4 Record Retention

The investigator agrees to keep the records stipulated in Section 11.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, all original signed and dated informed consent forms,, and copies of all paper CRFs and query responses/ electronic copy of eCRFs, including the audit trail to enable evaluations or audits from regulatory authorities, the sponsor or its designees. . In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12 Data Quality Control and Assurance

12.1 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.

12.2 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.

12.3 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. In accordance with NIS definition all examinations and other data should be registered in the CRF only if they are done in routine practice.

Should other unexpected circumstances arise that will require deviation from protocol-specified procedures and data collections rules, the investigator should consult with the Sponsor, responsible CRO or designee (and IRB or IEC, as required) to determine the

appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

12.4 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.

12.5 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.

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 Non-interventional 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 Vipidia® 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 5.2.

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 Sison, C.P and Glaz J. method [14].

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, AEs, 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 glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3). Taking into account inclusion criteria (either newly diagnosed DM type 2 (drug naive) or inadequate glycemic control on previously prescribed any oral antidiabetic drug) as well as non-intervention nature of the study it is proposed to use multifactorial regression model to determine factors related to effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics.

Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3) in subgroups with different clinical characteristics will be summarized using relevant descriptive statistics and analyzed using Multiple Linear Regression with following predictors: prior therapy of DM, sex, age, cardiovascular risk group, therapy type (monotherapy or combined therapy), baseline BMI, initial glycemic control.

In addition, change from baseline in glycosylated hemoglobin (HbA1c) level will be assessed and evaluated using Mixed model repeated measures (MMRM) methodology [14, 15]. 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 glycosylated hemoglobin (HbA1c) level 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 3. 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.

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

- Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy over time (V1-V2-V3) will be summarized using relevant descriptive statistics and analyzed with mixed model with repeated measures using clinical characteristics as independent factors;
- Proportion (%) of patients with marked hyperglycemia (V2) (Marked Hyperglycemia is defined as fasting plasma glucose higher than or equal to 11 mmol/L) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Change from baseline in fasting plasma glucose level on Vipidia® therapy over time (V1-V2-V3) will be summarized using relevant descriptive statistics and analyzed with mixed model with repeated measures using clinical characteristics as independent factors;

- Change from baseline in weight during Vipidia® treatment period (V1-V2-V3) will be calculated and presented in summary tables using descriptive statistics for continuous variables;
- Change from baseline in metabolic parameters (pre- and postprandial glycemia, total cholesterol triglycerides, low density lipoproteins, high density lipoproteins) during Vipidia® treatment period (V1-V2-V3) will be summarized using relevant descriptive statistics and analyzed with mixed model with repeated measures using clinical characteristics as independent factors;
- Proportion (%) of patients with diabetes mellitus type 2 who decrease in HbA1c $\geq$ 0.3% over time (V1-V2-V3) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Healthcare resources utilization: rate of hospitalization, reasons, emergency, emergency room visits, and physician office visits; in case of hospitalization, length of stay, reason, and urgency (urgent/not urgent) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Company Confidential Information [redacted]
- Company Confidential Information [redacted]
- Company Confidential Information [redacted]
- Company Confidential Information [redacted]
- Company Confidential Information [redacted]

13.2.3. Safety Analysis

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 10.2 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 Vipidia® efficacy will not be available. However data regarding dynamics of glycosylated hemoglobin (HbA1c) level in real-life practice will be gathered and analyzed. The inclusion criteria are those that used when administering Vipidia® 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 HbA1c 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 [17] 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

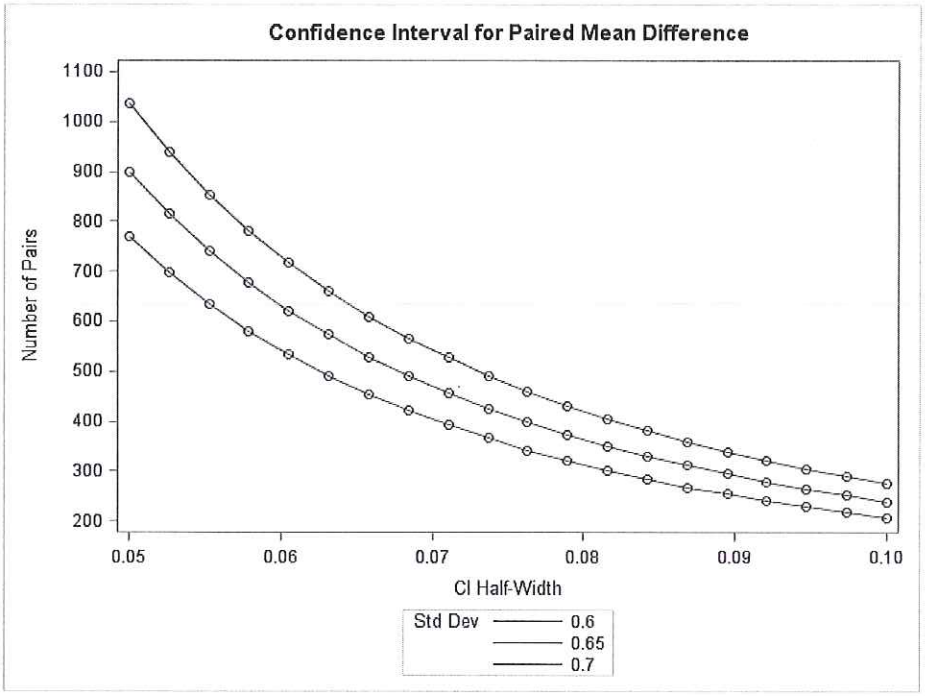
Sample size was calculated for the primary objective of the study: to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3). Sample size was calculated using SAS 9.3 proc power procedure (power for Confidence Interval for Paired Mean Difference as for accuracy of parameter estimation) for following parameters (fixed scenario elements):

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Correlation	0.35
Nominal Prob(Width)	0.9
Number of Sides	2
Alpha	0.05
Prob Type	Conditional

Standard deviation was assessed based on S. Del Prato et. al study [1] and was considered to be at most 0.70% (for glycosylated hemoglobin level dynamics). To determine required number of patients values from 0.60% to 0.70% were taken. Desired half-wide for parameter esimation was set as range between 0.05 – 0.1. Following required number of pairs were calculated:

[1] Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. Diabetes Obes Metab. 2014 Dec;16(12):1239-46.

Computed N Pairs				
Index	**Half-Width**	**Std Dev**	**Actual Prob(Width)**	**N Pairs**
1	0.05	0.60	0.904	770
2	0.05	0.65	0.904	899
3	0.05	0.70	0.900	1037
4	0.06	0.60	0.904	542
5	0.06	0.65	0.903	632
6	0.06	0.70	0.903	729
7	0.07	0.60	0.906	404
8	0.07	0.65	0.902	470
9	0.07	0.70	0.904	542
10	0.08	0.60	0.902	313
11	0.08	0.65	0.907	365
12	0.08	0.70	0.905	420
13	0.09	0.60	0.905	251
14	0.09	0.65	0.906	292
15	0.09	0.70	0.907	336
16	0.10	0.60	0.904	206
17	0.10	0.65	0.902	239
18	0.10	0.70	0.904	275



For worst-case scenario maximum required number of pairs is 1037. Taking into account a possible dropout of 25%, to reach study objectives in regard to this endpoint, it is recommended to enrol at least 1383 patients into the study.

As well as for the primary objective, sample size was calculated for the secondary objective of the study: to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3) in dependence of baseline clinical characteristics. According to concurrent Guidance for Industry for Diabetes Mellitus primary endpoint analysis (change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3) in subgroups with different baseline clinical characteristics) should account for factors with substantial correlation with the outcome and independence from the treatment (e.g. prior therapy of DM, sex, age group, cardiovascular risk group, therapy type (monotherapy or combined therapy) etc.).

Taking into account inclusion criteria (either newly diagnosed DM type 2 (drug naive) or inadequate glycemic control on previously prescribed monotherapy with metformin or inadequate glycemic control on previously prescribed monotherapy with any other oral antidiabetic drug) as well as non-intervention nature of the study it is proposed to use regression model to determine factors related to effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics. Sample size was calculated using SAS 9.3 proc power procedure (power for Multiple Linear Regression) for following parameters (fixed scenario elements):

Fixed Scenario Elements	
Method	Exact
Model	Random X
Number of Predictors in Full Model	7
Number of Test Predictors	1
Partial Correlation	0.1
Nominal Power	0.9
Alpha	0.05

Where the computational method set to exact, assumed distribution of the tested predictors set to joint multivariate normal distribution for the response and tested predictors, number of predictors in the full model, not counting the intercept assumed to be 7 (prior therapy of DM, sex, age, cardiovascular risk group, therapy type (monotherapy or combined therapy), baseline BMI, initial glycemic control), number of predictors in the reduced model, not counting the intercept assumed to be at least 1, level of significance of the statistical test set to 0.05, desired power of the test set to 0.9, partial correlation between the tested

predictors and the response, adjusting for any other predictors in the model assumed to be at least 0.1 (small effect size).

For the denoted scenario, it is required to receive data from at least 1052 patients after the treatment of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics.

Computed N Total	
Actual Power	N Total
0.800	1052

Taking into account a possible dropout of 25%, to reach study objectives in regard to this endpoint, it is recommended to enrol at least 1403 patients into the study. Due to minimal difference between these two endpoints and number of subjects required, it is recommended to take bigger computed number of subjects (1403).

14 Ethical aspects of the study

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.

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki. Each investigator will conduct the study according to applicable local or regional regulatory requirements. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 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 [4]. Epidemiological methods shall be used for the analysis of the collected data [4]. 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 Pharamacovigilance Practice, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline, Good Epidemiological Practice requirements and any local regulations [1, 2, 3,12]. 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 study Sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

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

According to applicable regulations, the responsible CRO or the Investigators (if it's requered) 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 (if it's requered) 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.

14.3 Local Ethics Committee (LEC)

This non-interventional study will be submitted to Local Ethics Committees (LECs) upon the requirements of the particular investigational sites. 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.

14.4 Authorities approval

Non-interventional (observational) studies are not covered by the definition of the «clinical trials» stated in the Directive 2001/20/EC [4]. 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. 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.

14.5 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.

It is the responsibility of the investigator to explain the detailed elements of the informed consent form and patient information sheet to the patient. 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, or the patient's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study and (3) consider and to pose questions. If the patient, or the patient's legally acceptable representative, determines he or she will participate in the study, then the informed consent form must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and prior to the start of data collection. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to start of data collection.

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.). 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.

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

14.6 Patient identification

The Patient Information Sheet and Informed Consent Form will explain that study data will be stored in a 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-2015-101024),

– 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.

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.

14.7 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.

14.8 Patient confidentiality

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" [13]. 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 14.6).

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.g. 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 SAE 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.

14.9 Publication, Disclosure, and the Study Registration Policy

14.9.1. 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

14.9.2. 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.

14.9.3. Study Results Disclosure

Takeda will post the results studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

14.9.4. 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 Archiving of Study Documentation

During the course of the study the investigator must as a minimum file the essential documents (Section 3.3), 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.

16 References

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