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

NCT Number: NCT02756832

SAP Approve Date: 17-Dec-2018

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

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

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

Statistical Analysis Plan

Protocol Number:	Alogliptin-4018 (MACS-2015-101024)
Project code:	15TK02
Protocol Title:	Local, multicentre, observational, non-interventional prospective study of Alogliptin benzoate in patients with Diabetes mellitus type 2
Effective date:	17.12.2018
Version No.:	1.2

CHANGE HISTORY

Версия/ Version	Дата/Date	Описание/Description	Автор/Author
1.0	10.01.2017	Initial version	Personal Protected Data
1.1	09.02.2018	Amendment # 1	Personal Protected Data
1.2	17.12.2018	Amendment # 2	Personal Protected Data

ПОДПИСИ/SIGNATURES

Personal Protected Data

Personal Protected Data

Personal Protected Data

Одобрено/Approved:

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SAP version 1.2 17.12.2018

Personal Protected Data

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Contents

LIST OF ABBREVIATIONS

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

Contacts

1.1 Study sponsor

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Project Manager:	Personal Protected Data
Responsible for statistical processing and statistical analysis:	

1.2 Clinical Research Organization

Name and address:	Personal Protected Data
Project Manager:	Personal Protected Data
Responsible for statistical processing and statistical analysis:	Personal Protected Data

2. PROTOCOL SUMMARY

2.1 Study design and conduct

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

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.

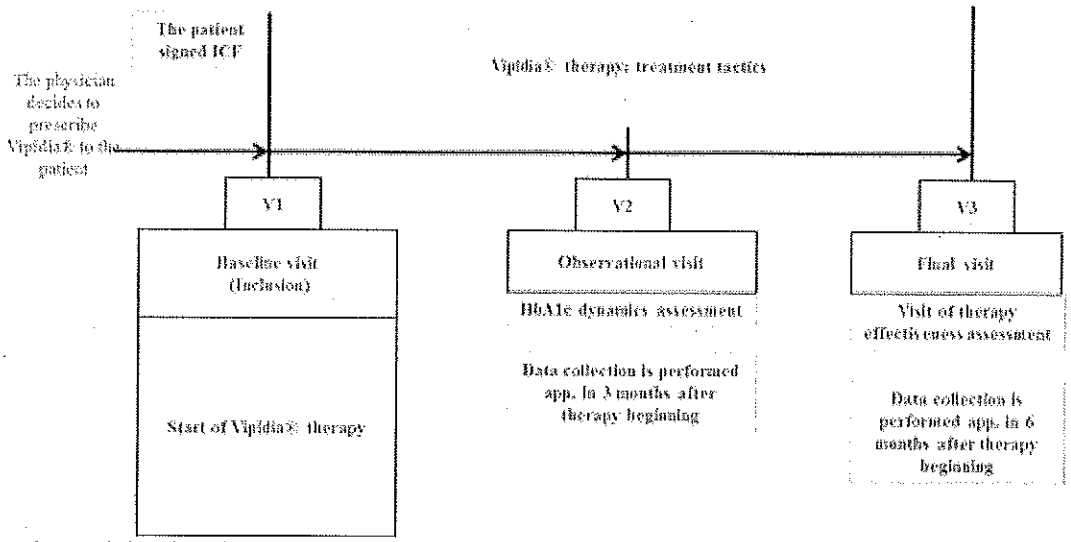
Start of the study is defined as the date of the start of data collection (first patient signed ICF for data collection).

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 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.



It's planned that interim statistical analysis of study data will be performed as soon as 350 first study patients have completed the study by achieving final study visit or discontinuing their participation.

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

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

2.2 Study objectives

2.2.1 Primary objective

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

2.2.2 Secondary objectives

The secondary objectives for this study are as follows:

1. 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
2. To describe the real-world clinical response to treatment with Vipidia® as assessed by glycosylated hemoglobin (HbA1c) level reduction to the goal <7.0%;
3. To evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);
4. To evaluate the proportion of patients with diabetes mellitus type 2 and marked hyperglycemia (V2);
5. To evaluate the effect of Vipidia® on fasting plasma glucose dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);
6. To evaluate changes in weight during Vipidia® treatment period (V1-V2-V3);
7. 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);
8. To estimate proportion of patients with diabetes mellitus type 2 who decrease in HbA1c $\geq$ 0.3%

over time (V1-V2-V3);

9. 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]).

2.2.3 Safety objectives

The safety objectives for this study are as follows:

1. 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®;
2. To describe incidence of newly diagnosed co-morbidities and complications.

2.2.4 Exploratory objectives

The exploratory objectives for this study are as follows:

2.3 Study variables

2.3.1 Efficacy variables

The study has primary endpoint: Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3).

Secondary endpoints of this study will be:

1. Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy (V3) in subgroups with different clinical characteristics.
2. Proportion (%) of patients with diabetes mellitus type 2 who assessed by glycosylated hemoglobin (HbA1c) level reduction to the goal <7.0% by V3;
3. Change from baseline in glycosylated hemoglobin (HbA1c) level on Vipidia® therapy over time (V1-V2-V3);
4. Proportion (%) of patients with marked hyperglycemia (V2) (Marked Hyperglycemia is defined as fasting plasma glucose higher than or equal to 11 mmol/L);
5. Change from baseline in fasting plasma glucose level on Vipidia® therapy over time (V1-V2-V3);
6. Change from baseline in weight during Vipidia® treatment period (V1-V2-V3);
7. 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);
8. Proportion (%) of patients with diabetes mellitus type 2 who decrease in HbA1c $\geq$ 0.3% over time (V1-V2-V3);
9. 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).

2.3.2 Safety variables

The safety outcome measures for this study are as follows:

1. 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®;
2. Incidence of newly diagnosed co-morbidities and complications.

2.3.3 Other variables of interest

Other variables of interest (exploratory endpoints) for this study are:

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[redacted]

2.4 Sample size and power

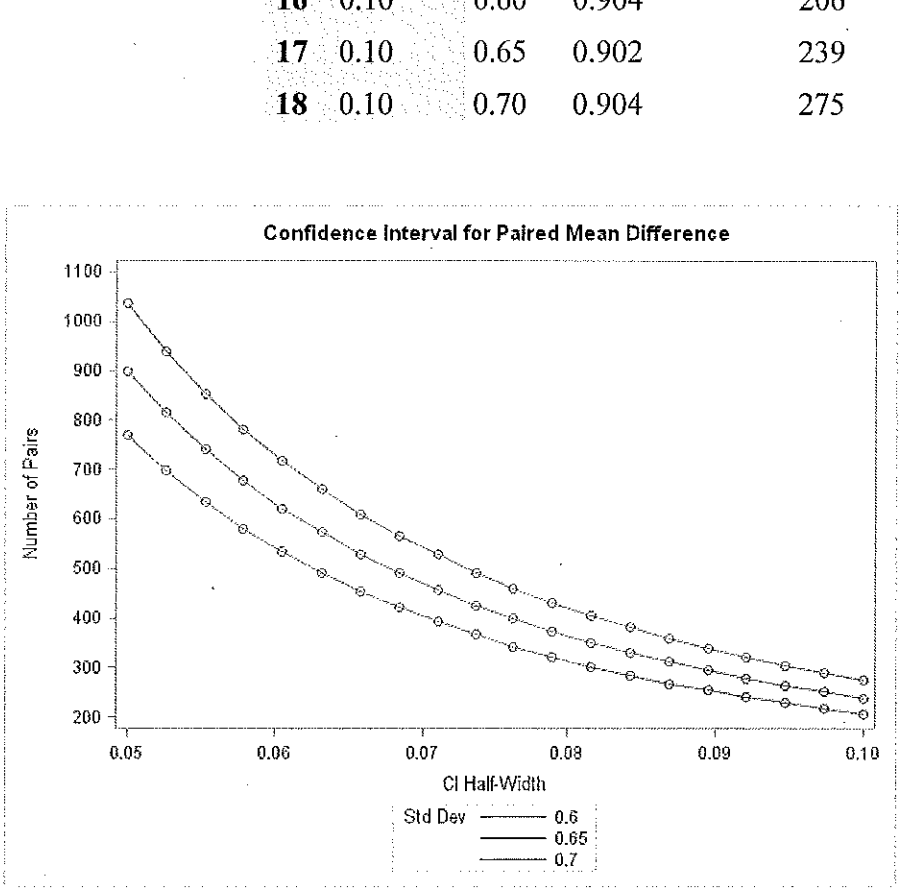
Sample size was calculated for the primary objective of the study: to evaluate the effect of Vipidia® on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3). Sample size was calculated using SAS 9.3 proc power procedure (power for Confidence Interval for Paired 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 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:

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).

3. DATA ANALYSIS CONSIDERATIONS

Overall analysis frame

This study is non-interventional and descriptive methods will be employed for data analyses. Descriptive analysis will be performed of all collected data, i.e. all data listed in section 2.3 ("Study variables"), except data collected only for the purpose of data cleaning.
The primary and secondary outcomes of the study are presented in section 2.3.1 ("Efficacy variables").

Summary of study data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, 25 percentile, 75 percentile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. For variables marked "binary" exact (Clopper-Pearson) 95% confidence intervals will be calculated where appropriate. For categorical variables with more than 2 categories 95% confidence intervals will be calculated using Goodman`s method or other appropriate (e.g. Sison and Glatz) method.
In general, all data will be listed, sorted by site and patient, and when appropriate by visit number within patient. All summary tables will be structured with a column for each cohort in the increasing order and will be annotated with the total population size relevant to that table/dose cohort, including any missing observations.

Baseline data

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, ethnicity, region of residence (city, town etc)

- Medical history and concurrent conditions: (condition, start/end date)
  - Nicotine use,
  - General medical history – body system, 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),
- The study medication:
  - prescribed Vipidia® dosage regimen;
- Concomitant treatment:
  - DM2T treatment - prescribed or current DM2T-treatment (if applicable),
  - Other concomitant treatment - INN, trade name, dosage regimen (dose taken), duration of treatment, indication for administration

All baseline data will be presented using denoted descriptive statistics (see chapter "Summary of study data") and conventional notations. The baseline visit is defined as the last observations collected prior to administration of the study drug.

4. CLINICAL DATABASE

Overall approach to data handling and recordkeeping described in the Protocol of the study.

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.

The study database will be set up and maintained by responsible CRO in accordance with SOPs of responsible CRO.

The full details of procedures for data handling will be documented in the Data Management Plan.

Clinical Database Access Resctrictions

Clinical Database Access Restrictions will be set in accordance with CRO`s Standard Operational.

Database for final analysis

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

Database for interim analysis

As soon as first 350 study patients have completed through final visit of the study or discontinue their participation a snapshot of the clinical database will be generated. The snapshot of the database will be performed in accordance with Standard operating procedures of CRO responsible for Data collection and data management. All tables, figures and listings described in this SAP will be generated on this interim snapshot of the database

5. STATISTICAL / ANALYTICAL ISSUES

Visit windows

In accordance with the protocol, due to the non-interventional study design it's not possible to appoint exact times for the study visits, although it is expected that the period of observation will be approximately 6 months. The frequency of the visits will be assigned by each physician according to their routine practice. It is anticipated that the patients will visit their physician every 3 months and more often at the beginning.
So, for the analysis and summary of clinical laboratory, efficacy, and safety data in case of this analysis/summary performed on "by visit" base. In the event of multiple values for an assessment within an analysis window, the value closest to the scheduled visit date will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected as the analysis value.

Analysis Window	Start	End	Target	Assessment to be used if duplicates
Baseline visit	<1			NA
Month 3 (Visit 2)	0	135	90	Closest to target day, if equidistant use later result.
Month 6 (Visit 3)	136	NA	180	

The definition for the study days included in each study window is defined as below:
Treatment Day prior to first dose = Visit Date – Date of First Dose
Treatment Day on or after first dose = Visit Date – Date of First Dose + 1

Adjustments for Covariates

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

Handling of Dropouts or Missing Data

Missing efficacy outcomes will be assumed to be missing at random (MAR) and thus will not be imputed in the primary analysis. However if greater than 1% of all primary/secondary outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary MAR analysis.
This sensitivity analysis will include an evaluation of the results of models developed under the assumptions of:
1) last observation carried forward;
2) worst extreme case imputation and;
3) regression model imputation using all available information.

Outlier identification

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

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

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

Interim Analyses

An interim analysis is planned to be performed as soon as first 350 patients have completed the study by achieving final study visit or discontinuing the study.

The reasons of performing this interim analysis is an importance of study data for medical society and commitment of the company to disclosure clinically relevant information to medical specialists.

At this level of the analysis study objectives listed in the sections 2.2.1-2.2.4 will be evaluated. The results will be provided according to reporting rules applicable for final statistical analysis and described in the Statistical Analysis Plan.

The interim analysis will be performed according to statistical procedures described in the sections # 05-10 of this Statistical Analysis Plan. No subgroup analyses are to be performed within interim analysis of the study.

The results of the interim analysis should be disclosed to public either through publication in medical scientific journal or within presentation at medical congress/conference.

After study is completed the complete study results are to be considered as prevailing the results of

interim analysis.

Multiple Comparisons/Multiplicity

When needed, corrections for multiplicity will be justified and performed according to Bonferroni. Overall alpha-level will be controlled and will not exceed 0.05. The interim analysis will not be taken into account within multiplicity adjustment procedure.

Examination of Subgroups

Some secondary endpoints will be analyzed in subgroups of patients with different clinical characteristics: demographic information, nicotine use, history of DM2T (see "EFFICACY ANALYSES" chapter).

6. STUDY POPULATION CHARACTERISTICS

Patient Disposition

Data regarding how many patients reached the various stages of the trial, how many dropped out, discontinued the treatment and for what reasons (death, 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.
As an open label study, there is limited opportunity for patients to receive incorrect drug and/or to inadvertently break the blind. However, in order to assess the conduct of the study, major protocol violations will be summarized and listed. Such violations will be defined prior to the first reporting event but will include at least the following:

- Non compliance with inclusion criteria
- Non compliance with exclusion criteria
- Non compliance with study treatment
- Use of disallowed concomitant medication

7. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics

Unless specified otherwise, all demographic and other baseline characteristics will be summarized for the All Patients Enrolled population of subjects.
All demographic and other Baseline characteristics will be summarized for overall analysis population. It's planned to describe all baseline patients characteristics within an interim analysis as well.

Medical History, Concomitant Diseases

Baseline medical conditions (comorbidities) reported in the Medical History Case Report Form (CRF) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by

Dosage cohort group for all treated patients on two levels: event level and subject level. For event level all comorbidities reported on the CRF will be summarized in the first table (by Dosage cohort group), and the second table will summarize only comorbidities that were ongoing on the date of baseline visit.
For subject level reporting, study subjects with at least one comorbidity (by Preferred Term within System Organ Class Term) will be summarized by Dosage cohort group, as well as study subjects with at least one comorbidity that were ongoing on the date of baseline visit will be summarized by Dosage cohort group.

Prior and Concomitant Medications

Prior medications, taken after informed consent is signed, and before the first dose of study drug, will be summarized by Dosage cohort group.
Concomitant medications are medications other than study drug that a patient reports taking between the first dose and last dose of study drug. These include medications that are taken before the first dose of study drug and continue to be taken during study treatment. Concomitant medications will be summarized by Dosage cohort group.
All prior and concomitant medications will be coded using Anatomical Therapeutic Chemical (ATC) dictionary and reported by the 2nd level by Dosage cohort group.

8. MEASUREMENT OF EXPOSURE TO STUDY DRUG

The total duration of exposure is defined as the time interval between the first dose and the last dose, inclusive, of study drug based on the patient study drug dosing information. In case if significant (e.g. >5%) number of subjects will switch doses during the study, additional tabulation by dose will be performed (these subgroups will be defined as dosage cohorts and will be used for data tabulation / presentation purposes). Total duration (weeks) of exposure to study drug in the All Patients Enrolled population will be summarized by descriptive statistics (ie, total number, mean, standard deviation, median, minimum, and maximum) - see "Summary of study data".
Data for study subjects` compliance will be summarized and tabulated by visit.
Area under curve as product of compliance for distinct period (e.g. time between visits) and duration of this period) will be calculated and summarized.
This evaluation will be performed both for overall and for interim analysis of the study.

9. EFFICACY ANALYSES

Unless stated othervise all Patients Enrolled population will be used for the primary, supportive primary, secondary, and exploratory efficacy analyses conducted for the study.
Unless stated otherwise, all efficacy variables will be summarized in convenience with "Summary of study data". All efficacy data, including selected derived data will be included in data listings.
For performing interim analysis data of first 350 enrolled patients will be used for the efficacy analyses listed in this section. For the interim efficacy analyses the methodology listed in this section is planned to be used.

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

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, T2DM duration. No subgroup analyses will be performed within interim analysis of study data.

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 and duration of T2 DM 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.

9.2. Statistical Analysis of the Secondary Efficacy Variables

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

9.2.1. 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;9.2.2. 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;9.2.3. 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;9.2.4. 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;

9.2.5. 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;9.2.6. 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;9.2.7. 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;9.2.8. Company Confidential Information

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All of variables listed above consisting of variable changes between study visits will be additionally analyzed with appropriate statistic tests for repeated measurements (i.e. paired T-test or Wilcoxon test as appropriate).

9.3. Additional exploratory analyses

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9.3.9. Primary and secondary outcomes will be analyzed in the subgroups of the patients with different duration of T2DM (0-3 years, 3-5 years, 5-10 years, >=10 years

9.3.10. Primary and secondary outcomes will be analyzed in the subgroup of patient who didn't receive any therapy within the last 12 weeks before ICF signing.

10. SAFETY ANALYSES

Unless specifically stated otherwise, the Safety population will be used for all safety summaries and

analyses.
All safety data will be included in data listings.
For relevant safety variables, early Withdrawal Visits will be assigned to the closest scheduled visit (after the last non-missing visit value) for the particular assessment that is being summarized.

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).

Interim safety analysis will be based on the data of first 350 patients who either achieved final study visit or discontinued the study.

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

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

Table 1 Mock table for reporting descriptive statistics

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

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

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

Systolic blood pressure	Subgroup A	Subgroup B	Total

(mgHg)	(N=xx)		(N=xx)		(N=xx)	
Visit						
Statistic	Value	Change	Value	Change	Value	Change
Systolic blood pressure (mgHg)						
Baseline						
n	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.xx		xxx.xx		xxx.xx	
Minimum	xxx		xxx		xxx	
Median	xxx.x		xxx.x		xxx.x	
Maximum	xxx		xxx		xxx	
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	
Month 1						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Maximum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	
Month 3						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Maximum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	
Month 6						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Maximum	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
95% CI for mean	xx.x-xx.x		xx.x-xx.x		xx.x-xx.x	

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

Table 3 Mock version of Adverse Event reporting table

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

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

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

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

During statistical analysis report preparation all statistical procedures output (e.g. proc mixed, proc freq) will be included unmodified (original statistical package output) as they have necessary diagnostics to assess validity of results. These diagnostic tables will not be included in Clinical Study Report.
Individual values listing will have subject id included, other data will be presented in listings unmodified.

Table 5 Mock version of individual value listings

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

13. REFERENCES

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