CLINICAL STUDY REPORT

1 TITLE PAGE

A multi-centre, prospective, open-label, single-arm, non- interventional, post marketing surveillance (PMS) study of Ryzodeg™ (insulin degludec/insulin aspart) to evaluate long term safety and efficacy in patients with diabetes mellitus in routine clinical practice in India

Protocol NN5401-4149

Investigational Product:	Ryzodeg™ (Insulin degludec/Insulin aspart)
Indication:	Diabetes Mellitus requiring insulin therapy under normal clinical practice conditions
Sponsor:	Novo Nordisk India Private Ltd. Plot No.32, 47 - 50, EPIP Area, Whitefield, Bangalore - 560 066 India
study Number:	NN5401-4149
Phase of Development:	Post Marketing Surveillance (PMS)/ Post Authorization Safety study (PASS)
study Initiation Date:	24 November 2015
study Completion Date:	01 June 2017
Sponsor's Medical Expert:	Dr. [redacted]
Sponsor Signatory:	Dr. [redacted]
Report Date:	12 Jan 2018

This study was conducted in compliance with Good Clinical Practice

CONFIDENTIALITY STATEMENT

2 SYNOPSIS

Name of Sponsor: Novo Nordisk India Private Ltd., India		*(For National Authority Use Only)*
Name of Investigational Product: Ryzodeg™		
Name of Active Ingredients: Insulin degludec/ Insulin Aspart		

Title and Number of study:

A multi-centre, prospective, open-label, single-arm, non- interventional, post marketing surveillance (PMS) study of Ryzodeg™ (insulin degludec/ insulin aspart) to evaluate long term safety and efficacy in patients with diabetes mellitus in routine clinical practice in India (Study Number: NN5401-4149)

Investigators:

The list of investigators is presented in Section 6.1 (Table 1) and Appendix 16.1.4.

Study Sites:

In this study 40 sites actively enrolled patients. A detailed listing of these sites and the respective Investigators is provided in Table 1.

Publications:

No publication was issued by the time this report was written.

Study Period:

Study Initiation Date: 24 November 2015
Study Completion Date: 01 June 2017

Phase of Development:

Post Marketing Surveillance (PMS)/ Post Authorization Safety study (PASS) (Phase IV)

Objective:

Primary objective

The primary objective of the study was:

- To assess the safety of long-term treatment with insulin degludec/ insulin aspart (Ryzodeg™) in insulin requiring patients with diabetes mellitus, initiating treatment with Ryzodeg™ under routine clinical practice in India.

Secondary objective

The secondary objective of the study was:

- To assess safety and efficacy of long term (1 year) treatment with Ryzodeg™

Methodology:

This was a multi-centre, prospective, single-arm, open-label, non-interventional, PMS/PASS study to evaluate safety and efficacy during long-term treatment (1 year) with Ryzodeg™ in patients with diabetes mellitus (DM) requiring insulin therapy under normal clinical practice conditions in India. A total of 1000 patients were planned to be enrolled in this study to investigate the safety of Ryzodeg™. A total of 1029 patients were enrolled in this study. Based on the clinical judgement of treating physician, patients were started with Ryzodeg™ in their routine clinical practice. The assignment of the patients to Ryzodeg™ was decided in advance in the protocol. The patients were decided to be prescribed with Ryzodeg™, by physicians before the enrolment in the study, based on requirement and clinical judgment in diabetes management.

Data were collected at screening (Visit 1), 3 months (Visit 2), 6 months (Visit 3) and finally at one year (Visit 4).

Name of Sponsor: Novo Nordisk India Private Ltd., India		*(For National Authority Use Only)*
Name of Investigational Product: Ryzodeg™		
Name of Active Ingredients: Insulin degludec/ Insulin Aspart		

The study schedule consisted of the following visits:

- *Visit 1 (Screening visit/0 week):* During this visit, patient's eligibility to participate in the study was determined, voluntary informed consent was obtained, demography details, medical history (DM history, before PMS/PASS was initiated), most recent glycated haemoglobin (HbA1c) (if available), most recent fasting plasma glucose/fasting blood sugar (FPG/FBG) value (if available), details of blood glucose confirmed hypoglycaemia, and details of treatment prescribed during the study. The reason why decision taken to start therapy with Ryzodeg™.
- *Visit 2 (Treatment Visit/3 months ± 2 weeks):* During this visit, DM treatment prescribed since last visit, patient's hypoglycaemic events (since last visit), HbA1c (if available), most recent FPG/FBG value (if available), diabetes treatment during PMS/PASS study, concomitant medications, adverse events/serious adverse events/adverse drug reactions/serious adverse drug reactions (AEs/SAEs/ADRs/SADRs)
- *Visit 3 (Treatment Visit/6 months ± 2 weeks):* During this visit, DM treatment prescribed since last visit, patient's hypoglycaemic events (since last visit), HbA1c (if available), most recent FPG/FBG value (if available), diabetes treatment during PMS/PASS study, concomitant medications, AEs/SAEs/ADRs/SADRs
- *Visit 4 (Treatment Visit/1 year ± 2 weeks)*: During this visit, DM treatment prescribed since last visit, patient's hypoglycaemic events (since last visit), HbA1c (if available), most recent FPG/FBG value (if available), diabetes treatment during PMS/PASS study, concomitant medications, AEs/SAEs/ADRs/SADRs

Visit window period for all visits in the study was ± 2 weeks.

Number of Patients:

Planned: A total of 1000 patients were planned to enrolled in the study
Analysed: A total of 1029 patients who met the eligibility criteria were recruited at 40 sites within India

Inclusion Criteria:

Patients who satisfied the following criteria were included in the Study:

1. Informed consent obtained before any Study-related activities (Study related activities are any procedure related to recording of data according to the protocol). The historical data including the data before informed consent obtained (e.g., HbAlc, FPG, PPG, severe hypoglycemia before the start of Ryzodeg™ therapy) can be used for baseline data.
2. Patients with insulin requiring diabetes mellitus and who were scheduled to start treatment with Ryzodeg™ based on the clinical judgment of their treating physician.
3. More than 18 years old, male/female patients

Exclusion Criteria:

Patients were excluded from the study if they met any of the following criteria:

1. Known or suspected allergy to Ryzodeg™, the active substance or any of the excipients
2. Previous participation in this study
3. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
4. Patients who were or had previously been on Ryzodeg™ therapy
5. Patients who were participating in other studies or clinical trials
6. Patients who were pregnant, breast feeding or have the intention of becoming pregnant within the following 12 months

Name of Sponsor: Novo Nordisk India Private Ltd., India		*(For National Authority Use Only)*
Name of Investigational Product: Ryzodeg™		
Name of Active Ingredients: Insulin degludec/ Insulin Aspart		

Duration of study:

Total duration of this study was 1 year and 6 months.

Each enrolled patient was observed for 1 year.

Dose and Mode of Administration of Test Product:

Being a non-interventional study, patients with DM requiring insulin therapy, who qualified for starting treatment with Ryzodeg™ based on clinical judgment by their treating physician were treated with Ryzodeg™ (insulin degludec/insulin aspart, 100 u/mL FlexTouch™ prefilled pen injector). Dose was adjusted as per the discretion of the treating investigator and mode of administration was subcutaneous.

Dose and Mode of Administration of Reference Products:

No Reference product was used as this was a single-arm study.

Criteria for Evaluation:

Primary Endpoint:

The primary endpoint of the study was:

- Incidence of AEs by preferred term during 1 year of treatment

Secondary Safety Endpoints:

The secondary safety endpoint of the study was:

Incidence of the following events during 1 year of treatment:

- Serious Adverse Events (SAEs) by preferred term
- Serious Adverse Drug Reactions (SADRs) by preferred term
- Adverse Drug Reactions (ADRs) by preferred term
- Severe of Blood glucose (BG) confirmed hypoglycaemia during 1 year of treatment

Secondary Efficacy Endpoints:

The secondary efficacy endpoints of the study were:

- Change from baseline in HbAlc after 1 year of treatment
- Change from baseline in Fasting Plasma Glucose (FPG) & Post Prandial Blood/Plasma Glucose (PPBG/PPPG) after 1 year of treatment

Statistical Methods:

Analysis Populations:

The following populations were defined for the statistical analyses:

- **Safety Analysis Set (SAS) population**: The SAS population was defined as all patients who had received at least one dose of Ryzodeg™ during the PMS/PASS study. The descriptive analysis of AEs and demographic data was also based on the SAS
- **Efficacy Analysis Set (EAS) population**: The EAS population was defined as all patients in the SAS who had at least one post baseline measurement concerning HbA1c, FPG or confirmed hyperglycaemic event(s). The summaries of HbA1c, FPG or confirmed hyperglycaemic event(s) were based on EAS

Sample Size Determination:

The sample size calculation was based on the primary objective to evaluate the safety and tolerability of

Name of Sponsor: Novo Nordisk India Private Ltd., India		*(For National Authority Use Only)*
Name of Investigational Product: Ryzodeg™		
Name of Active Ingredients: Insulin degludec/ Insulin Aspart		

Ryzodeg™. A sample size of 1000 patients, assuming 20% dropouts who had been exposed to the insulin degludec/ insulin aspart (IDeg/ IAsp) during the treatment provided a probability of 80% of detecting at least one event that occurred with an incidence of 2 in 1000 patients or approximately 6 events with an incidence of 1/100 patients.

For an unobserved event, with the above sample size the upper limit of the 95% CI of the rate were 0.375 per year. In other words, for an unobserved event, a rate of 0.375 per year or larger were excluded with 95% probability.

Statistical Analysis:

No formal statistical testing was performed in this study. All continuous and categorical endpoints were analysed using descriptive statistics.

The descriptive statistics for continuous variables were presented with number (n) of observations, number of missing observations, mean, standard deviation (SD), median, minimum, and maximum of range. For categorical data, the descriptive statistics were presented using counts and percentages. Baseline, end of study values and change from baseline values were presented. The descriptive analyses of AEs and demographic data were based on the SAS. The summaries of HbA1c, FPG and confirmed hypoglycaemic events were based on the EAS.

Efficacy Endpoint Analysis:

The HbA1c, FPG, PPBG/PPPG and confirmed hypoglycaemic events were evaluated for efficacy aspect of Ryzodeg™ by means of descriptive statistics. Baseline, end of study values and change from baseline values were presented with number (n) of observations, number of missing observations, mean, standard deviation (SD), median, minimum, and maximum or range. Also, paired-t test was used to evaluate the changes in HbA1c, FPG, PPBG/PPPG and confirmed hypoglycaemic events by visit within the treatment at 5 % level of significance.

Safety Endpoint Analysis:

All AEs/ADRs were coded by system organ class (SOC) and preferred term (PT) using the latest version 20.0 of Medical Dictionary for Drug Regulatory Affairs (MedDRA) body system or later. The number of patients who experienced any AE/ADR were summarized for the treatment arm. AEs were collected, evaluated, and tabulated by causality, seriousness, severity, action taken, outcome, SOC, and PT for each treatment group. SAEs were summarized by SOC and PT. Descriptive statistics for AEs/ADRs/SAEs/SADRs by SOC and PT were presented by number of patients with event, number of events, incidence rate and rate per 100PYE and patient listing were presented for AEs. The information was collected for pregnancies in female patients and AEs in the foetus or new born infant and severe hypoglycaemic episodes.

Summary Results:

- There were 1029 patients enrolled in this study, of which 1003 were included in efficacy evaluation population set. Overall 971 patients completed the study and 58 discontinued the study.
- There were more males (65.2%), compared to females (34.8%)
- The prevalence of Peripheral Neuropathy was 20.8% and Coronary Heart Disease was 7.4% and Nephropathy (7.0%) in the Study Cohort
- Out of total patients, improvement of HbA1c was the most common reason in majority (87.0%) of patients to start insulin degludec/insulin aspart (IDegAsp)
- Improvement in FBG and PPG was the reason in 57.6% and 62.7% patients
- Approximately 40% of patients were shifted to Ryzodeg™ due to high risk of hypoglycaemia with their current treatment strategy and 22.2% of patients shifted due to need for flexibility in timing of injection.
- A decline in HbA1c was observed in study at different time points. The mean ± SD value of

Name of Sponsor: Novo Nordisk India Private Ltd., India		*(For National Authority Use Only)*
Name of Investigational Product: Ryzodeg™		
Name of Active Ingredients: Insulin degludec/ Insulin Aspart		

HbA1c (%) was significantly reduced from 9.5 ± 1.78 at Visit 1, to 7.7 ± 1.07 at Visit 4 (p <0.0001)

- A decline in HbA1c was also noted in cohort of patients receiving OAD previously. In those patients, mean ± SD HbA1c was significantly reduced from 9.3 ± 1.70 at Visit 1 to 7.6 ± 1.03 at Visit 4 (p <0.0001)
- A decline in HbA1c was also noted in cohort of patients receiving insulin previously. In those patients, mean ± SD HbA1c was significantly reduced from 9.9 ± 1.93 at Visit 1 to 8.1 ± 1.11 Visit 4 (p <0.0001)
- A decline in FPG was observed in all efficacy evaluable patients at different time points. The mean ± SD FPG in was significantly reduced from 180.4 ± 59.70 at Visit 1 to 130.0 ± 33.05 at Visit 4 (p <0.0001)
- A decline in FPG was also noted in cohort of patients receiving OAD previously. In those patients, mean ± SD FPG was significantly reduced from 181.1 ± 56.74 (Visit 1) to 128.6 ± 32.37 (Visit 4) (p <0.0001)
- A decline in FPG was also noted in cohort of patients receiving insulin previously. In those patients, mean ± SD FPG was significantly reduced from 178.3 ± 67.58 (Visit 1) to 133.9 ± 34.63 (Visit 4) (p <0.0001)
- A decline in PPG levels were observed at corresponding timepoints during each visit. The reduction in PPG levels were found to be significant (p <0.0001)
    - The mean ± SD of Post breakfast PPG levels were reduced from 266.9 ± 77.81 at Visit 1 to 184.4 ± 47.22 at visit 4
    - The mean ± SD of Post lunch PPG levels were reduced from 254.8 ± 84.02 at Visit 1 to 180.6 ± 40.08 at visit 4
    - The mean ± SD of Post dinner PPG levels were reduced from 216.3 ± 57.99 at Visit 1 to 164.88 ± 36.21 at visit 4
- A decline in mean PPG levels was also noted in patients, previously on OAD and insulin, at different time points
    - The mean ± SD Post breakfast PPG value was reduced 277.7 ± 73.62 at Visit 1 to 183.8 ± 47.51 at Visit 4 in patients previously on OAD
    - The mean ± SD Post breakfast PPG value was reduced from 247.0 ± 81.54 at Visit 1 to 185.6 ± 46.74 at visit 4 in patients previously on insulin
    - The mean ± SD Post lunch PPG value was reduced from 257.6 ± 86.60 at Visit 1 to 179.6 ± 38.47 at visit 4 in patients previously on OAD
    - The mean ± SD Post lunch PPG value was reduced from 200.2 at Visit 1 to 170.3 ± 37.98 at visit 4 in patients previously on insulin
    - The mean ± SD Post dinner PPG value was reduced from 200.0 at Visit 1 to 141.8 ± 4.19 at Visit 4 in patients previously on OAD
    - The mean ± SD Post dinner PPG value was reduced from 224.5 ± 79.55 at Visit 1 to 180.3 ± 40.43 at visit 4 in patients previously on insulin
- A decrease in confirmed hypoglycaemic events were noted from Visit 1 (176 events reported in 67 patients) to subsequent follow up visits (28 events reported in 12 patients at Visit 2 and no event reported at Visit 3 and Visit 4) with respect to both number of subjects and number of events
- A total of 30 AEs were reported during the Study period
- Among total AEs, there were 2 serious and 28 non-serious AEs presented in 2 (0.2%) and 21

Name of Sponsor: Novo Nordisk India Private Ltd., India		*(For National Authority Use Only)*
Name of Investigational Product: Ryzodeg™		
Name of Active Ingredients: Insulin degludec/ Insulin Aspart		

(2.0%) patients, respectively.

- Both SAEs were fatal
- Majority of AEs were mild [25 AEs in 19 (1.9 %) patients] in nature
- Four AEs were severe in nature
- 19 AEs in 16 (1.6%) patient got recovered/resolved during study period
- Causality assessment showed 23 of 30 AEs were unlikely related to the study drug, 2 were possibly and 5 AEs were probably related to study drug
- By action taken to study drug due to AE, dose of study drug was reduced in 2 patients with 2 AEs. In 2 patients study drug was withdrawn. Study drug dose was not changed in 7 patients
- A total of 8 (0.8%) patients were encountered with 9 AEs in the class of General disorders and administration site conditions. This was followed by Metabolism and nutrition disorders [3 (0.3%)] with 4 AEs and Infections and infestations [3 (0.3%)] with 3 AEs. Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, Nervous system disorders, and vascular disorders each reported in 2 (0.2%) patients with 2 AEs. Cardiac disorders, injury poisoning and procedural complications, investigations, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorder, and skin and subcutaneous tissue disorders each SOC reported in 1 (0.1%) patient with 1 AE
- A total of 7 ADRs were reported in 5 (0.5%) Subjects during the Study.
- 4(0.4%) patients had reported 1 ADR each and 1 (0.1%) had reported 3 ADRs
- No ADRs were serious in nature
- 5 ADRs, in 3 (0.3%) patients, were mild, 1 was moderate, and 1 was severe.
- Of all reported ADRs 3 were not Recovered/resolved during the course of Study
- In 2 (0.2%) patients, the dose of Study drug was withdrawn, and in one patient dose was reduced while in 1 (0.1%) patient no change was observed
- Of the total ADR reported, 1 (0.1%) patient reported with one ADR in each SOC general disorders and administration site conditions, injury, poisoning and procedural complications investigations, and nervous system disorders. Two [2 (0.2%)] patients reported 3 ADRs of metabolism and nutrition disorders
- A total of 24 events of Severe Hypoglycemic Episodes were recorded in 17 (1.7%) patients at Baseline Visit
- No further Severe Hypoglycemic Episodes were noted at any follow Up Visit during the Study period

Conclusion:

In conclusion, IDeg/IAsp was shown to be a promising treatment option for subjects with DM inadequately controlled with OADs and other Insulin. In this study IDeg/IAsp demonstrated the long-term safety profile for 1 year in routine clinical practice. IDeg/IAsp was safe and well tolerated and provided overall glycaemic control at a lower rate of confirmed hypoglycaemia. It is possible that these advantages of IDeg/IAsp, in-particular low rates of hypoglycaemic events while effectively lowering HbA1c, FPG and PPG values might encourage physicians and patients to titrate insulin regimens more rigorously to reach glycaemic target.

Date of Report: 12 Jan 2018

3 TABLE OF CONTENTS

List of Tables

List of Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations	Expanded Form
ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CCDS	Company Core Data Sheet
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DM	Diabetes Mellitus
DPP	Dipeptidyl Peptidase
EAS	Efficacy Analysis Set
EC	Ethics Committee
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
HbA1c	Glycosylated Haemoglobin
IAsp	Insulin aspart
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDeg	Insulin Degludec
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Drug Regulatory Affairs
OAD	Oral Antidiabetic Drug
PASS	Post Authorization Safety study
PMS	Post Marketing Surveillance
PPBG	Postprandial Blood Glucose
PPPG	Postprandial Plasma Glucose
PT	Preferred Term
PYE	Patient-year of exposure
SADR	Serious Adverse Drug Reactions
SAE	Serious Adverse Event
SAR	Statistical Analytical Report
SAS	Safety Analysis Set
SC	Subcutaneous
SD	Standard Deviation

SMBG	Self-Monitoring of Blood Glucose
SOC	System Organ Class
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes mellitus
WHO	World Health Organization

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This study was initiated after protocol version 1.0, dated 20 April 2014, was reviewed and approved by competent authorities and the local independent ethics committee (IEC)/ institutional review board (IRB) of the respective sites per local regulations. The study was carried out in conformity with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP). The original protocol (version 1.0, dated 20 April 2014) is provided in Appendix 16.1.1.

The investigative site's IRB/IEC was provided with the following but not limited to:

- Case Report Form (CRF)
- Informed consent document
- Clinical study protocol
- Relevant curricula vitae

All Ethics Committees were compliant to regulations laid down by Schedule-Y and had followed the ICH GCP guidelines.

The study was initiated at 40 sites in India. The study was conducted only after getting the approval from the IEC/IRB. The details of the study site, along with the participating investigator, can be found in Section 6.1. The study dossier was submitted according to the IEC/IRB requirements for all sites. During the course of the study, all relevant events, such as changes to essential documents and any information regarding patient safety, were reported to the IEC/IRB. A list of all IECs/IRBs is provided in Appendix 16.1.3

5.2 Ethical Conduct of the study

The study was conducted in conformity with the principles of the Declaration of Helsinki, ICH-GCP guidelines, Indian Council of Medical Research, Indian GCP guidelines, and as per the protocol version 1.0 dated 20 April 2014, submitted to IEC/IRB. All patient related documents like informed consent form (ICF) were used only after the review and approval from the ethics committee. No change was made in study documents or study conduct during the execution of this study.

5.3 Patient Information and Consent

Patients were asked to participate in the study if they had voluntarily chosen to take part in the study. Consent forms were designed to assure the protection of patient's rights. Patients were provided with adequate verbal and written information in their local language. Either the study investigator/designee provided the verbal explanation to the patient. The verbal explanation covered all the elements specified in the written information provided for the patient. The study investigator informed the patient of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it entailed. The patient was given every opportunity to clarify any points the patient did not understand and if necessary asked for more information. At the end of the interview the patient was given time to reflect, if this was appropriate. It was emphasized that the patient was at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the patient was otherwise entitled. The study investigator was responsible for obtaining the patients' freely given consent. The written consent form provided to the patient was signed and dated by the patient as well as the investigator immediately after the patient had verbally consented for study participation. The patient was given a copy of the document, which included the name and phone number of the person to contact in case of an emergency. The consent was kept on file by the investigator for possible inspection, monitoring and audit by regulatory authorities and/or sponsor professional persons. The signature confirmed the consent, which was based on information that was understood by the patient. If the patient was ≤ 18 years of age a legally acceptable representative provided consent on behalf of the patient by signing and dating the informed consent form. A sample of the IEC approved ICF (English) is provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators

The study was conducted at 40 sites in India. The following investigators participated in the study:

Table 1 List of Investigators

Sr. No.	Site no	Investigator Name	Site Name and Address
1	[redacted]	Dr. [redacted]	[redacted]
2	[redacted]	Dr. [redacted]	[redacted]
3	[redacted]	Dr. [redacted]	[redacted]
4	[redacted]	Dr. [redacted]	[redacted]
5	[redacted]	Dr. [redacted]	[redacted]
6	[redacted]	Dr [redacted]	[redacted]
7	[redacted]	Dr. [redacted]	[redacted]
8	[redacted]	Dr. [redacted]	[redacted]
9	[redacted]	Dr. [redacted]	[redacted]
10	[redacted]	Dr. [redacted]	[redacted]
11	[redacted]	Dr. [redacted]	[redacted]
12	[redacted]	Dr. [redacted]	[redacted]
13	[redacted]	Dr. [redacted]	[redacted]
14	[redacted]	Dr. [redacted]	[redacted]
15	[redacted]	Dr. [redacted]	[redacted]
16	[redacted]	Dr. [redacted]	[redacted]
17	[redacted]	Dr. [redacted]	[redacted]
18	[redacted]	Dr. [redacted]	[redacted]

Sr. No.	Site no	Investigator Name	Site Name and Address
19	[redacted]	Dr. [redacted]	[redacted]
20	[redacted]	Dr. [redacted]	[redacted]
21	[redacted]	Dr. [redacted]	[redacted]
22	[redacted]	Dr. [redacted]	[redacted]
23	[redacted]	Dr. [redacted]	[redacted]
24	[redacted]	Dr. [redacted]	[redacted]
25	[redacted]	Dr. [redacted]	[redacted]
26	[redacted]	Dr. [redacted]	[redacted]
27	[redacted]	Dr. [redacted]	[redacted]
28	[redacted]	Dr. [redacted]	[redacted]
29	[redacted]	Dr. [redacted]	[redacted]
30	[redacted]	Dr. [redacted]	[redacted]
31	[redacted]	Dr. [redacted]	[redacted]
32	[redacted]	Dr. [redacted]	[redacted]
33	[redacted]	Dr. [redacted]	[redacted]
34	[redacted]	Dr. [redacted]	[redacted]
35	[redacted]	Dr. [redacted]	[redacted]
36	[redacted]	Dr [redacted]	[redacted]
37	[redacted]	Dr. [redacted]	[redacted]
38	[redacted]	Dr. [redacted]	[redacted]
39	[redacted]	Dr. [redacted]	[redacted]

Sr. No.	Site no	Investigator Name	Site Name and Address
40	[redacted]	Dr. [redacted]	[redacted]

6.2 Central Laboratories

Not applicable

6.3 Sponsor

Novo Nordisk India Private Limited was the sponsor for this study and was responsible for oversight of the study and medical monitoring. The contact details of Novo Nordisk India Private Limited are as follows:

Novo Nordisk India Private Limited
Plot No. 32, 47-50
EPIP Area, Whitefield
Bangalore 560 066, India

Project Manager: Dr. [redacted]

Medical Advisor: Dr. [redacted]

Pharmacovigilance: Dr. [redacted] / Dr. [redacted]

Study Monitor: [redacted]

6.4 Contract Research Organizations

[redacted] ([redacted], a contract research organization) provided study management, biostatistics, and medical writing services. The address is as follows:

[redacted]

The following were the relevant study personnel at [redacted]:

Study Management	Dr. [redacted]
Site Management	Dr. [redacted]
Biostatistics	[redacted]
Data Management	[redacted]
Medical Writing	[redacted]

7 INTRODUCTION

7.1 Background

Diabetes is on the rise all over the world and countries are struggling to keep pace. Worldwide, there are 425 million people, aged 20-79 years are living with diabetes in 2017. Based on IDF Atlas 8th edition, the number of people with diabetes is predicted to rise to 629 million by 2045. In 2017, India has approximately 72.9 million patients living with diabetes, which will reach up to 134.3 million by 2045 (1). Like type 2 diabetes mellitus (T2DM), type 1 diabetes mellitus (T1DM) is also increasing, with a trend of 3–5% increase/year. According to a recent report, India has three new cases of T1DM/100,000 children of 0–14 years (3). In other words, diabetes prevalence, deaths attributable to diabetes, and health expenditure due to diabetes continue to rise across the globe with important social, financial and health system implications (2)

Insulin is recommended as a mainstay treatment in patients with T2DM with and an initial HbA1c > 9%, or if diabetes is uncontrolled despite optimal oral glycaemic therapy (3). Basal insulin is an important element in the treatment of T1DM, and the use of long-acting insulin analogues as part of a basal–bolus injection regimen has resulted in significantly improved glycaemic control. Current basal insulins can be administered once daily; however, the duration of the glucose-lowering effect can vary between patients, resulting in a requirement for twice-daily injections in many patients, particularly in patients with T1DM (4, 5).

To reduce the burden insulin regimen, in recent years research is focussed on improved of properties of Insulin. Which have simple therapeutic regimen, lower risk of hypoglycaemia, long-term glycaemic control to improve the adherence with treatment. Till date, three basal insulin analogues have been approved for clinical use i.e. insulin glargine, insulin detemir, and insulin degludec (IDeg) (6). IDeg offers longer duration of action of more than 42 hours developed for once-daily administration with a distinct mechanism of action. Studies demonstrated that IDeg has glucose lowering potential, reduced hypoglycaemic events and lower nocturnal hypoglycaemia rates than IGlar ((7-9)).

IAsp is a rapid acting insulin analogue developed using amino acid substitution of human insulin to reduce the propensity for insulin. It provides faster absorption of insulin in bloodstream and rapidly achieve maximum plasma concentrations (6).

The chemical properties of IDeg facilitates the development of a soluble co-formulation with IAsp in order to maintain the insulin level for 24 hours. This novel formulation (IDeg/IAsp) leads improvement in adherence and safety of DM patients. IDeg/IAsp (Ryzodeg™) is a new co-formulation available as subcutaneous injection developed by Novo Nordisk (10). Previous phase II and III studies have demonstrated that IDeg/IAsp provide effective reduction in HbA1c and blood glucose levels with lower risk of hypoglycaemia (11-14).

7.2 Rationale

This study is conducted as a primary regulatory requirement by the Indian health authority to expand the safety assessment in a larger Indian population for all medicinal products approved for clinical use in India. In addition, although marketing approval for Ryzodeg™ has been granted in India, there is a continuous need to monitor the safety of medicinal products as post-approval surveillance, while they are used under normal clinical practice. Spontaneous reporting helps detect signals of safety concern and is a part of continuous safety surveillance. However, more formal studies or surveys constitute a proactive approach to planned collection of safety information and will in some instances identify unexpected ADRs (Adverse Drug Reaction).

The purpose of this PMS/post authorization safety study (PASS) was to assess long-term (1 year) safety and efficacy of Ryzodeg™ in patients with diabetes mellitus requiring insulin therapy under normal clinical practice conditions.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study was:

- To assess the safety of long-term treatment with insulin degludec/ insulin aspart (Ryzodeg™) in insulin requiring patients with diabetes mellitus, initiating treatment with Ryzodeg™ under routine clinical practice in India

8.2 Secondary Objective

The secondary objective of the study was

- To assess safety and efficacy of long term (1 year) treatment with Ryzodeg™

8.3 study Endpoints

8.3.1 Primary Endpoint

- Incidence of AEs by preferred term during 1 year of treatment

8.3.2 Secondary Safety Endpoints:

Incidence of the following events during 1 year of treatment:

- Serious Adverse Events (SAEs) by preferred term
- Serious Adverse Drug Reactions (SADRs) by preferred term
- Adverse Drug Reactions (ADRs) by preferred term
- Severe or Blood glucose (BG) confirmed hypoglycaemia during 1 year of treatment

8.3.3 Secondary Efficacy Endpoints:

- Change from baseline in HbAlc after 1 year of treatment
- Change from baseline in Fasting Plasma Glucose (FPG) & Post Prandial Blood/Plasma Glucose (PPBG/PPPG) after 1 year of treatment

9 INVESTIGATIONAL PLAN

9.1 Overall study Design and Plan-Description

9.1.1 Description of study Design and Plan

This was a multi-centre, prospective, single-arm, open-label, non-interventional, post marketing surveillance study/ post authorization safety study (PMS/ PASS) to evaluate safety and efficacy during long-term treatment (1-year) with Ryzodeg™ in patients with DM requiring insulin therapy under normal clinical practice conditions in India. A total of 1000 patients were planned to be enrolled to investigate safety of Ryzodeg™. Data were collected at baseline (Visit 1), 3 months (Visit 2), 6 months (Visit 3) and finally at 1-year (Visit 4).

The protocol, and a case report form (CRF) are included as Appendices 16.1.1 and 16.1.2, respectively. The assignment of the patient to Ryzodeg™ was not decided in advance of this the protocol but it was a part of current practice. Hence, the prescription of Ryzodeg™ was clearly separated from the decision to include the patient in the study.

9.1.2 Description of study Visits

A patient who met all inclusion criteria and none of exclusion criteria was enrolled in the study and assigned a patient number. Patients enrolled in the study was provided with contact addresses and telephone number(s) of the physician and/or site staff. The Flow chart of study visits is depicted in Table 2.

The details of each study visit are as follows:

9.1.2.1 Visit 1 ***(Screening visit/0 week)***

The physician gathered the following information from either the patient's medical record, patient recall or patient's diary (If available).

Following assessments were made during this visit:

- Patient informed consent
- Patient eligibility
- Demographic data
  - Date of birth
  - Gender
  - Race
- Body measurements
  - Weight
  - Height
  - Waist and Hip Circumference
  - Systolic and diastolic blood pressure measured in sitting posture
- DM history
  - Date of diagnosis of DM
  - Type of diabetes (Type I or Type II)
  - Diabetic macro-vascular complications (peripheral vascular disease, coronary heart disease, stroke)
  - Diabetic micro-vascular complications (diabetic retinopathy, diabetic nephropathy, diabetes neuropathy)
- DM treatment before PMS/PASS study initiated (follow any physician recommended diet plan and exercise for diabetes management, metformin, sulphonylureas, metiglinides, alpha-glucosidase inhibitors, thiazolidinediones, DPP-IV inhibitor, basal insulin, premix insulin, bolus insulin, exenatide, liraglutide, etc).
- Most recent FPG/FBG value and date of measurement prior to starting Ryzodeg™ treatment (if available)
- DM treatment prescribed during PMS/PASS study
- Reasons why decision was taken to start therapy with Ryzodeg™
  - To improve the patient’s glycaemic control

- Unacceptable hypoglycaemia profile/ pattern on current anti-diabetic treatment
- The patient had fear of hypoglycaemia
- The patient wished to try another anti-diabetic treatment available
- The patient wished to try another pen-device available
- The patient required high insulin doses, therefore needing to inject more than once
- The patient had difficulties in complying with timing of injection(s) on current anti-diabetic treatment
- The patient experienced high day to day variability on current anti-diabetic treatment.
- The patients had eating habits that fits to the pharmacokinetic profile
- Other

- Starting date of Ryzodeg™ therapy
- Concomitant medications excluding diabetes medication

9.1.2.2 Visit 2 *(Treatment Visit/3 months ± 2 weeks)*, Visit 3 *(Treatment Visit/6 months ± 2 weeks)* & Visit 4 *(Treatment Visit/1 Year ± 2 weeks)*

The physician gathered the following information from either the patient's medical record, patient recall, and/or the patient's Self-Monitoring of Blood Glucose (SMBG) diary:

Following assessments were made during this visit:

- All AEs/SAEs/ ADRs/SADR.s reported by the patient since last visit
- Reasons for early termination (lost to follow-up, ADR, meeting withdrawal criteria), if Applicable
- Number of all confirmed hypoglycaemic episodes experienced since last visit
- Number of all episodes of severe or BG confirmed hypoglycaemia experienced since last visit
- Date and value of most recent HbAlc since last visit (if applicable)
- Most recent FPG/FBG value and date of measurement since last visit (if applicable)
- DM treatment prescribed since the last visit
- Change in Ryzodeg™ treatment (date of change and the prescribed dose)
- Any other anti-diabetic treatment (metformin, sulphonylureas, metiglinides, alpha-glucosidase inhibitors, thiazolidinediones, DPP-IV inhibitor, basal insulin, premix insulin, bolus insulin, etc)
- Concomitant medications
- Reason for intensifying Ryzodeg™ from OD to BID if applicable

9.2 Discussion of study Design, including Choice of Control Groups

This was a multi-centre, prospective, single-arm, open-label, non-interventional, PMS/ PASS to evaluate safety and efficacy during long-term treatment (1 year) with Ryzodeg™ in patient with DM requiring insulin therapy under normal clinical practice conditions in India.

The study assessed the safety profile of Ryzodeg™ used in patients under normal clinical practice conditions without any active intervention and without a comparator. The study is a regulatory requirement following approval with a primary objective to assess safety; therefore, no comparator was required in the study. The 1 year observation period was expected to be sufficient to capture untoward medical occurrences that are likely to be associated with long-term use of Ryzodeg™. The frequency and timing of visit were based on normal clinical practice for patients with DM requiring insulin therapy in India. The PMS/PASS study was conducted in a real-life setting and without extensive monitoring of the data collected. Hence there was a risk that complete data stated in the protocol were not always collected from all patients. However, data included routine clinical measurements which need to be recorded and analysed for measuring safety and efficacy of Ryzodeg™.

In agreement with its observational nature, there were no interventions in standard care for this study. Any procedure ordered by the physician during this study was according to routine practice. The patient was not called in for premature discontinuation or for a missed visit. The primary reason (adverse drug reaction or other) for discontinuation was specified in the CRF. Patients were instructed to maintain a diary to record AEs, hypoglycaemic episodes and concomitant medications, and these data were entered the paper CRF. The patient was asked about AEs during each contact (visit or telephone) with the physician or study site staff. This was done by posing a simple question such as "have you experienced any problems so the last contact?"

9.3 Selection of study Population

Patients with DM where the treating physician decided to start Ryzodeg™ according to routine clinical practice qualified to participate in the study. Ryzodeg™ prescribed by the physician under normal clinical practice conditions and was obtained/ purchased from the chemist based on physician prescription. The physician determined the starting dose, as well as later changes to dose, if any. Ryzodeg™ was used in accordance with the package insert.

Patients were excluded if they had known or suspected allergy to Ryzodeg™ or any of the excipients or in case of previous participation in this study. Patients were allowed to withdraw from the study at their will at any time. Also, a patient might withdraw from this study at the discretion of the physician due to a safety concern

9.3.1 Inclusion Criteria

Patients who satisfied the following criteria were included in the Study:

1. Informed consent obtained before any study-related activities (study-related activity were any procedure related to recording of data according to the protocol). The historical data including the data before informed consent obtained (e.g., HbAlc, FPG, PPPG, severe hypoglycaemia before the start of Ryzodeg™ therapy) used for baseline data
2. Patients with insulin requiring diabetes mellitus and who were scheduled to start treatment with Ryzodeg™ based on the clinical judgment of their treating physician
3. More than 18 years old, male/ female patients

9.3.2 Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

1. Known or suspected allergy to Ryzodeg™, the active substance or any of the excipients
2. Previous participation in this study
3. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
4. Patients who were or had previously been on Ryzodeg™ therapy
5. Patients who were participating in other studies or clinical trials
6. Patients who were pregnant, breast feeding or have the intention of becoming pregnant within the following 12 months

9.3.3 Removal of patients from therapy or assessment

The investigator made every effort to keep each patient in the study. But following were the justifiable reasons for removing a patient from the study:

1. The patient withdrew at will at any time
2. The patient withdrew from this PMS/PASS study at the discretion of the physician due to a safety concern

9.4 Treatments

9.4.1 Treatments Administered

Not applicable as this was a non-interventional study.

9.4.2 Identity of Investigational Products

Not applicable as this was a non-interventional study.

9.4.3 Method of Assigning Patients to Treatment Groups

The assignment of the patient to Ryzodeg™ was not decided in advance by the protocol but fell within current practice and the prescription of Ryzodeg™ was clearly separated from the decision to include the patient in the study.

9.4.4 Selection of Doses in the study

Not applicable, all eligible patients enrolled in this study were treated as in routine practice. The Ideg/IAsp, marketed as Ryzodeg™ FlexTouch™ prefilled pen injector (100 u/mL), was available in the market by prescription and purchase/supply as in routine practice and according to local regulations was used in our study.

9.4.5 Selection and timing of Dose for each patient in the study

Not applicable.

9.4.6 Blinding

Not Applicable.

9.4.7 Prior and Concomitant Therapy

Concomitant medication was defined as any medication other than Ryzodeg™ and other anti-diabetic medications that were taken during the study. Details of all concomitant medications were recorded at study entry (i.e. at the first visit [Visit 1]). The information collected for each concomitant medication included at a minimum, start date, stop date or continuing and indication.

9.4.7.1 Concomitant Medication Restrictions

Being PMS/PASS in nature and study was conducted in a real-life setting, there was no concomitant medication restriction during the study.

9.4.8 Treatment Compliance

Not applicable.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The study evaluation schedule is presented in Table 2.

Table 2 Evaluation Schedule for Safety and Efficacy

	Visit 1 (0 Week)	Visit 2 (3 months ± 2 weeks)	Visit 3 (6 months ± 2 weeks)	Visit 4 (1 year ± 2 weeks)
Patient informed consent	X			
Patient eligibility	X			
Early termination		X	X	X
Demographic data[1]	X			
Diabetes history	X			
History of hypoglycaemia with previous treatments	X			
Confirmed Hypoglycaemic events since last visit[2]		X	X	X
Most recent HbA1c value and date of measurement (if available)[3]	X	X	X	X
Most recent PPBG/PPPG value and date of measurement (if available)[3]				
Most recent FPG/PBG value and date of measurement (if available)[3]	X	X	X	X
Diabetes treatment before the Ryzodeg™ was initiated	X			
Diabetes treatment during the PMS/PASS study		X	X	X
Concomitant medications	X	X	X	X
AEs/SAEs/ ADRs/SADRs[4]		X	X	X
Reason for initiating or intensifying treatment with Ryzodeg ™	X			

[1] Including body weight, height, waist and hip circumference, systolic and diastolic blood pressure measured in sitting posture (if available)

[2] Confirmed hypoglycaemia: In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level off 3.1 mmol/L (56 mg/dL). Therefore, Novo Nordisk included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.

Confirmed hypoglycaemic episodes were defined as episodes that are severe (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) Biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia."

[3] For Visit 1, the term recent means "over the past 4 weeks before starting on insulin degludec/ insulin aspart"

[4] Each AE/SAE was recorded on a separate AE Form according to existing reporting procedures. If the AE was serious then a Safety Information Form was also completed and the sponsor or their designee were notified within the specified period. Severe hypoglycaemic episodes (according to definition in footnote #2) always qualify for AE/SAE reporting

ADR: Adverse Drug Reaction; AE: Adverse Events; FPG: Fasting Plasma Glucose; HbA1c: Glycated Haemoglobin; PPG: Post Prandial Plasma Glucose: PMS/PASS: Post Marketing Surveillance/ Post Authorization Safety study: SADR: Serious Adverse Drug Reaction;

Source: protocol NN5401-4149 version 1.0 dated 20 April 2014

9.5.1.1 Efficacy Parameters

- Change from baseline in HbA1c after 1 year of treatment
- Change from baseline in Fasting Plasma Glucose (FPG) & Post Prandial blood/Plasma Glucose (PPBG/PPPG) after 1 year of treatment

9.5.1.2 Safety Parameters

In this study, the following safety information was systematically collected during one year of study period:

- Incidence of Adverse events (AEs) by preferred term (PT)
- Incidence of Serious adverse events (SAEs) by PT
- Incidence of Adverse drug reactions (ADRs) by PT
- Incidence of Serious adverse drug reactions (SADRs) by PT
- Severe or blood glucose (BG) confirmed hypoglycaemia during 1 year of treatment

9.5.1.2.1 Adverse Drug Reaction

An ADR was an untoward medical occurrence in a patient administered the study product for which a causal relationship between the product and the occurrence was suspected, i.e. judged possible or probable (for definitions, see below) by the reporter or by Novo Nordisk India Private Ltd. An ADR can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study product, which was considered related to the product. An ADR was either a SADR or a non-serious ADR (for definitions, see below).

This includes ADRs which arise from:

- A worsening of a concomitant illness
- Occupational exposure to the study product

Pre-existing conditions and procedures where the reason for the procedure was known should not be reported as ADRs or AEs.

9.5.1.2.2 Adverse Events

An adverse event was any untoward medical occurrence in a patient administered the study product, which does not necessarily have a causal relationship with the product.

Terms used to describe causal relationship to the study product:

- Probable: good reasons and sufficient documentation to assume a causal relationship
- Possible: a causal relationship was conceivable and cannot be dismissed
- Unlikely: the event was most likely related to an aetiology other than the study product

9.5.1.2.3 Serious Adverse Event

An adverse drug reaction or adverse event was a SADR or SAE, respectively, if the reaction or event results in any of the following seriousness criteria:

- Death
- A life-threatening experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that did not result in death, were life-threatening or require hospitalization[b] were considered a serious adverse event - when based upon appropriate medical judgement - they may jeopardise the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition[d]. This also included suspected transmission of an infectious agent via a study product.

[a]The term "life threatening" referred to an event in which the patient was at risk of death at the time of the event. It did not refer to an event which hypothetically might have caused death if it was more severe.

[b]The term "hospitalization" was used when a patient was: admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stayed at the hospital for treatment or observation for more than 24 hours. Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalization. Hospitalizations for administrative, study related and social purposes did not constitute adverse reactions or events and should therefore not be reported as ADRs or AEs including SADRs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to study inclusion were not considered ADR reactions or AEs including SAEs or SADRs.

[c]A substantial disruption of a patient's ability to conduct normal life functions, e.g. following the event or clinical investigation the patient had significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life.

[d]For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that did not result in hospitalization, or development of drug dependency or drug abuse.

9.5.1.2.4 Non-Serious Adverse Drug Reaction or Adverse Event

An ADR or AE that did not meet a seriousness criteria was considered to be non-serious.

9.5.1.2.5 Severity Assessment Definitions

Mild: No or transient symptoms, no interference with the patient's daily activities
Moderate: Marked symptoms, moderate interference with the patient's daily activities
Severe: Considerable interference with the patient's daily activities, unacceptable

9.5.1.2.6 Outcome Categories and Definitions

Recovered/resolved: The patient had fully recovered from the condition, or by medical or surgical treatment the condition had returned to the level observed at the first study related activity after the patient had signed the informed consent.

Recovering/resolving: The condition was improving and the patient was expected to recover from the condition/event.

Recovered/resolved with sequelae: The patient had recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If the sequelae met a seriousness criterion, the ADR or AE must be reported as a SADR or SAE.

Not recovered/not resolved: The condition of the patient had not improved and the symptoms were unchanged, or the outcome was not known at the time of reporting.

Fatal: (only applicable if the patient died from a condition related to the reported ADR or AE. Outcomes of other reported ADR or AE in a patient before he/she died were assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An ADR or AE with fatal outcome was reported as a SADR or SAE).

Unknown: This term should only be used in cases where the patient is lost to follow-up.

9.5.1.2.7 Medication Errors

- Administration of wrong product
- Wrong route of administration, such as intramuscular instead of subcutaneous
- Administration of an overdose with the intention to cause harm, eg suicide attempt
- Administration of an accidental overdose; e.g. dose which may lead to significant health consequences, as judged by the physician, irrespective of whether the SAE/SADR criteria were fulfilled or not.

9.5.1.2.8 Collection and Reporting of Safety Information

At each contact with the site the patient was asked about AEs. This was done by posing a simple question such as "have you experienced any problems since the last contact?"

All AEs/reactions, either observed by the physician or reported by the patient, were recorded by the physician and evaluated.

AEs/reactions were reported by the physician on the applicable AE form. One single AE form was used per AE/reaction from start to resolution.

In addition to this, for SADRs/SAEs, further information was reported by the physician on the applicable safety information form.

Medication errors were reported by use of the medication error form. For other safety information, i.e. safety information which was not collected as part the systematic collection, a customer complaint form was used.

The physician reported to Novo Nordisk India Private Ltd. within the following timelines:

For SADRs/SAEs:

- Initial information was reported **within 24 hours** of the physician's knowledge of the event
- Further information was reported **within 5 calendar days** of the physician's knowledge of the event
- If the initial reporting was made by any other means (e.g. phone call within 24 hours), initial and further safety information was provided **within 5 calendar days** of the physician's knowledge of the event on the forms, as described above.

For non-serious adverse events/reactions:

The AE form was signed and sent to Novo Nordisk India Private Ltd. when the event was resolved or at the end of study

Initial and further information was reported on the applicable AE form within **14 calendar days** of the physician's knowledge of the event.

The physician completed and forwarded electronically, fax or courier copies of the applicable forms within the above specified timelines of obtaining knowledge about the event(s). The information was provided by telefax or telephone to:

Novo Nordisk India Pvt. Ltd.
Plot # 32, 47-50, EPIP Area, Whitefield, Bangalore-560066
Ph: +91-080-40303225

Fax: +91-080-41123517
Email: INAgree@novonordisk com

The physician recorded the diagnosis, if available. If no diagnosis was available, the physician recorded each sign and symptom as individual AEs or ADRs. Once the patient get diagnosed, the diagnosis was reported and the signs and symptoms covered by the diagnosis were described.

If more than one sign or symptom was reported, a separate form for each sign and symptom was used. However, if several symptoms or diagnoses occurred as part of the same clinical picture, only one safety information form was used to describe all the SAR or SAE.

Sponsor's assessment of expectedness was done according to the reference documents: Company core data sheet (CCDS) for IDeg, current version or any updates hereof.

In accordance with regulatory requirements, including GVP, the sponsor informed the regulatory authorities of study product related SADR. In addition, the sponsor or external CRO informed the IECs/IRBs of study product related SADRs, in accordance with the local requirements in force. The sponsor or CRO notified the physician of study product related suspected SADRs, in accordance with the local requirements.

9.5.1.2.9 Follow-up of safety information

Follow-up information concerning previously reported SADR/SAE, were reported by the physician within 24 hours of the physician's knowledge of the follow-up information.

All follow-up information requested by Novo Nordisk India Private Ltd. were forwarded to Novo Nordisk India Private Ltd. **within 14 calendar days** from the date specified on the request, unless otherwise specified in the follow-up information request.

The physician ensured that the worst-case severity and seriousness was kept consistent through the series of forms used for safety reporting. The follow up information should only include new (updated and/or additional) information that reflected the situation at the time of the physician's signature.

All serious and non-serious AEs/ADRs classified as severe or possibly/probably related to the study product were followed until the outcome of the reaction or event was “recovered", "recovered with sequelae" or "fatal" and until all queries had been resolved. Cases of chronic conditions, cancer, SAEs/SADRs ongoing at the time of the death (i.e. the patient dies from another SAE/SADR) were closed with the outcome of "recovering" or "not recovered". Cases were closed with an outcome of "recovering" when the patient had completed the last visit (as stated in this protocol) and was expected by the physician to recover.

All other non-serious adverse events were followed until the outcome of the event was "recovering", "recovered" or "recovered with sequelae" or until the last visit whichever came first, and until all queries related to these AEs were resolved. AEs ongoing at time of death (i.e. patient died from another AE) were closed with an outcome of "recovering" or "not recovered".

9.5.1.2.10 Collection and reporting of pregnancies in female patients

In female patients, pregnancy was reported using pregnancy forms **within 14 calendar days** of the physician's first knowledge of the pregnancy. Follow-up information on the foetus or new-born infant from pregnancy in a patient were collected at 1 month of age at the earliest. Information was reported **within 14 calendar days** of the physician's first knowledge of the pregnancy outcome. All AEs experienced by the foetus or new-born infant were collected and reported regardless of causality assessment.

Reporting of ADRs or AEs in foetus, new-born infant or in connection with the pregnancy was done on the same forms as described for reporting of ADRs and events. It was clearly stated in the diagnosis field on the form if the event occurred in the patient, foetus or new-born infant. The reporting timelines were as described for other AEs or reactions and other SAEs or SADRs.

9.5.2 Appropriateness of Measurements

All efficacy and safety assessments were standard procedures and were generally recognized as reliable, accurate, and relevant.

9.5.3 Efficacy variables

- Change from baseline in HbA1c after 1 year of treatment
- Change from baseline in Fasting Plasma Glucose (FPG) & Post Prandial Blood/ Plasma Glucose (PPBG/PPPG) after 1 year of treatment

9.5.4 Safety Variables

9.5.4.1 Primary Safety Variable

- Incidence of AEs by PT during 1 year of treatment

9.5.4.2 Secondary Safety Variable

- Incidence of following events during 1 year of treatment:
    - SAEs by PT
    - SADRs by PT
    - ADRs by PT
    - Severe or BG confirmed hypoglycaemia

9.5.5 Other Variables

The reason for initiating or intensifying treatment with Ryzodeg™

9.5.6 Drug Concentration Measurements

Not Applicable.

9.6 Data Quality Assurance

Quality assurance and quality control systems were implemented and maintained using written standard operating procedures to ensure that the study was conducted and data were generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control was applied to each stage of data handling to ensure that all data were reliable and had been processed correctly. Novo Nordisk India Private Ltd. ensured a quality check on the functioning of CRO, their data management flow and procedures, site monitoring, check lab accreditations, to ensure the quality control of overall study. Novo Nordisk India Private Ltd. reserved the right to conduct monitoring on a case-to-case basis when need was determined.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

No formal statistical testing was done in this non-interventional study. All continuous and categorical endpoints were analysed using descriptive statistics

The descriptive statistics for continuous variables were presented with number (n) of observations, no. of missing observations, mean, standard deviation (SD), median, minimum, and maximum or range. For categorical data, the descriptive statistics were presented using counts and percentages. Baseline, end of study values and change from baseline values were presented.

The descriptive analyses of AEs were based on the SAS (Safety Analysis Set). Also, demographic data was presented using SAS. The summaries of HbA1c, FPG and confirmed hypoglycaemic events were based on the EAS (Efficacy Analysis Set).

9.7.1.1 Study Populations

There were two analysis populations: efficacy analysis population, and the safety analysis population. Following are the details of analysis population.

9.7.1.1.1 Safety Analysis Population

The Safety Analysis Set (SAS) population was defined as all patients who had received at least one dose of Ryzodeg™ during the PMS/PASS study.

The descriptive analysis of AE's was based on the SAS. The demographic data were also presented using SAS.

9.7.1.1.2 Efficacy Analysis Population

The Efficacy Analysis Set (EAS) population was defined as all patients in the SAS who had at least one post baseline measurement concerning HbA1c, FPG or confirmed hyperglycaemic events.

The summaries of HbA1c, FPG or confirmed hyperglycaemic event(s) were based on EAS.

9.7.1.2 Demographics and Other Baseline Characteristics

9.7.1.2.1 Demographics

Demographic variables include age, gender, body measurements and vital signs (weight, height, waist circumference, hip circumference and blood pressure) and DM history. All efficacy and safety parameters which were collected at baseline were summarized.

All the continuous variables were presented with number (n) of observations, no. of missing observations, mean, standard deviation (SD), median, minimum, and maximum or range, while the categorical data was presented using counts and percentages.

9.7.1.3 Efficacy Analysis

HbA1c, FPG, PPBG/PPPG and confirmed hypoglycaemic events were evaluated for efficacy aspect of Ryzodeg™ by means of descriptive statistics. Baseline, end of study values and change from baseline values were presented with number (n) of observations, no. of missing observations, mean, standard deviation (SD), median, minimum, and maximum or range. Also, paired-t test was used to evaluate the changes in HbA1c, FPG, PPBG/PPPG and confirmed hypoglycaemic events by visit wise within the treatment. Test was carried out as two-sided on a 5% level of significance.

9.7.1.4 Safety Analysis

9.7.1.4.1 Adverse Events/ Adverse Drug Reactions

The AEs/ADRs were coded by system organ class (SOC) and preferred term (PT) using the latest version 20.0 of Medical Dictionary for Drug Regulatory Affairs (MedDRA) body system or later. The number of patients who experienced any AEs/ADRs were summarized for the treatment arm. AEs were collected, evaluated, and tabulated by causality, seriousness, severity, action taken, outcome, SOC, and PT for each treatment group. SAEs were summarized by SOC and PT. Descriptive statistics for AEs/ADRs/SAEs/SADRs by SOC and PT were presented by number of patients with event, number of events, incidence rate and rate per 100PYE and patient listing was presented for AEs.

In this study, the following safety information was systematically collected:

- Adverse events
- Adverse drug reactions
- Serious adverse events
- Serious adverse drug reactions

Besides these, information was collected for

- Pregnancies in female patients and adverse events in the foetus or new-born infant
- Severe hypoglycaemic episodes

9.7.1.4.2 Pregnancies in female patients and adverse events in the foetus or new-born infant

All the continuous variables were presented with number (n) of observations, no. of missing observations, mean, SD, median, minimum, and maximum or range, while the categorical data were presented using counts and percentages.

9.7.1.4.3 Severe Hypoglycaemic Episodes

Severe Hypoglycaemic Episodes for each visit were represented as event, number of events, incidence rate and rate per 100PYE.

9.7.2 Determination of Sample Size

The sample size calculation was based on the primary objective to evaluate the safety and tolerability of Ryzodeg™. A sample size of 1000 patients, assuming 20% dropout rate who had been exposed to the IDeg/IAsp during the treatment provided a probability 80% of detecting at least one event that occurred with an incidence of 2 in 1000 patients or approximately 6 events with an incidence of 1/100 patients.

9.8 Changes in the Conduct of study or Planned Analyses

9.8.1 Changes in the Conduct of study

No Changes were made in the conduct of study

9.8.2 Changes in Planned Analysis

No changes were made in the planned analysis

10 STUDY PATIENTS

10.1 Disposition of Patients

In this study, a total of 1029 DM patients were screened, of which all were found eligible for analysis (Table 3). Of 1029 enrolled patients, 1003 patients were included in efficacy evaluable population and 971 patients completed the study. Study was discontinued by 58 patients (lost to follow-up in 41 patients, IDeg/IAsp discontinued in 12 patients, and 6 patients discontinued due to other reasons). One patient might have discontinued the study for more than one reason.

Table 3 Summary of Analysis Population and study Completion-All Population (N = 1029)

Category, n (%) [1]	Screened/Enrolled Population (N = 1029)
Patients in Safety Population	1029 (100)
Patients in Efficacy Population	1003 (97.5)
Patients Completed study	971 (94.4)
Patients Discontinued study	58 (5.6)
Reason for Discontinuation [2][3]	
Lost to follow-up	41 (70.7)
Adverse Drug Reaction	-
Insulin degludec/Aspart discontinued	12 (20.7)
Other	6 (10.3)

Source Data: Listing 16.2.1, 16.2.2, 16.2.3; Table: 14.1.1.2
N: Total number of patients; n: number of patients in specified criteria
Note:
[1] Respective column header count was used as denominator for percentage calculation.
[2] Total number of Patients Not Completed study were used as denominator for percentage calculation.
[3] One patient may discontinue for more than one reason.
General Note:
Zero frequencies are presented by '-'.

10.2 Protocol Deviations

The were no protocol deviations observed during the study.

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Safety Analysis Set (SAS) Population: All enrolled 1029 patients received at least one dose of Ryzodeg™ during the PS/PASS study, and were included in SAS population.

Efficacy Analysis Set (EAS) Population: The 1003 (97.5%) of all enrolled patients in the SAS who had at least one post baseline measurement concerning HbA1c, FPG or confirmed hyperglycaemic events were included in EAS population.

11.2 Demographic and Other Baseline Characteristics

The demographic details of all eligible patients are presented in Table 4. Among total patients, 671 (65.2%) were males and 358 (34.8%) were females. The mean ± SD age of all patients were 55.0 ± 12.16 years. The mean ± SD Weight (kg), Waist Circumference (cm) and Hip Circumference (cm) of patients were 73.2 ± 12.46, and 95.2 ± 11.59, and 98.7 ±12.50, respectively.

Table 4 Summary of Patient Demographics at Screening visit-SAS Population (N = 1029)

Parameters	Statistic/Category, n (%) [1]	Overall (N = 1029)
Age (completed years)	n	1027
	Missing	2
	Mean	55.0
	SD	12.16
	Median	55.0
	Range (Min.: Max.)	(17:90)
Gender	Male	671(65.2)
	Female	358(34.8)
Hip Circumference (cm)	n	474
	Missing	555
	Mean	98.7
	SD	12.50
	Median	98.0
	Range (Min.: Max.)	(44:155)
Waist Circumference (cm)	n	682
	Missing	347
	Mean	95.2
	SD	11.59
	Median	94.0
	Range (Min.: Max.)	(58:154)
Weight (kg)	n	1028
	Missing	1
	Mean	73.2
	SD	12.46
	Median	73.0
	Range (Min.: Max.)	(32:127.5)

Source Data: Listing 16.2.4.1; Table: 14.1.2.1
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation
Note:
[1] Respective column header count was used as denominator for percentage calculation.
General Note:
[1] Zero frequencies are presented by "- "
[2] The unavailable data shown in 'Missing' category.

11.2.1 Other Baseline Medical History

Summary of Diabetes Mellitus History

Complications due to Diabetes Mellitus

The DM is associated with both microvascular and macrovascular complication affecting several organs. Table 5 summarised the details of complications due to DM. The results revealed that among microvascular complications, peripheral neuropathy was the most common (20.8%), followed by nephropathy (7.2%), autonomous neuropathy (7.0%), and retinopathy (6.1%). Among the macrovascular complications, coronary heart disease (7.4%) was relatively higher, followed by Stroke (2.1%) and macroangiopathy (including peripheral vascular disease) (1.9%).

Table 5 Summary of complications due to Diabetes Mellitus-SAS population (N = 1029)

Parameters	Statistic/Category, n (%)) [1]	Overall (N = 1029)
Micro-vascular complications		
Autonomic Neuropathy	Yes	72(7.0)
	No	957(93.0)
Peripheral Neuropathy	Yes	214(20.8)
	No	815(79.2)
Nephropathy	Yes	74(7.2)
	No	955(92.8)
Retinopathy	Yes	63(6.1)
	No	966(93.9)
Macro-vascular complications		
Macroangiopathy including Peripheral Vascular Disease	Yes	20(1.9)
	No	1009(98.1)
Coronary Heart Disease	Yes	76(7.4)
	No	953(92.6)
Stroke	Yes	22(2.1)
	No	1007(97.9)

Source Data: Listing 16.2.4.2; Table 14.2.3.1
N: Total number of patients; n: number of patients in specified criteria
Note:
[1] Percentage were calculated by taking respective column header count as denominator.

Reason(s) to Start Therapy with Ryzodeg™

In our study, improvement of HbA1c was the most common reason in majority of patients [895 (87.0%)] to start Ryzodeg™. Improvement of HbA1c contributes 28.3% of total reasons reported. This was followed by improvement in PPG [645 (62.7%)] and FPG [593 (57.6%)], which contributes 20.4% and 18.8% of total reason reported, respectively. In addition to this, approximately 40% of patients were shifted to Ryzodeg™ due to high risk of hypoglycaemia which contributed 13.1% of total reasons reported. The summary of reasons to start therapy with Ryzodeg™ by patients and reason was mentioned in Table 6.

Table 6 Summary of reason(s) to Start Therapy with Insulin degludec by patients - SAS population (N = 1029)

Reasons /Category, n (%) [1]	Overall (N = 1029)	Overall Reason (Total reason count = 3150)
Improve HbA1c	895 (87.0)	(28.3)
Improve FBG	593 (57.6)	(18.8)
Improve PPG	645 (62.7)	(20.4)
Side effects from previous therapy	27 (2.6)	(0.9)
Reduce risk of hypoglycaemia	413 (40.1)	(13.1)
Patients dissatisfaction with previous therapy	153 (14.9)	(4.8)
Improve beta cell function	73 (7.1)	(2.3)
Improve weight control	126 (12.2)	(4.0)
Need for flexibility in timing of injection	228 (22.2)	(7.2)
Other	6 (0.6)	(0.2)

Source Data: Listing 16.2.4.3; Table 14.1.2.3.2
FPG: Fasting Plasma Glucose; HbA1c: Glycated Haemoglobin; N: Total Number of Patients; n: number of patients in specified criteria; PPG: Post Prandial Glucose
Note:
[1] Percentage was calculated by taking respective column header count as denominator.

11.3 Treatment Compliance

Not applicable

11.4 Efficacy Results and Tabulation of Individual Patient Data

11.4.1 Analysis of Efficacy

The efficacy parameters included the change in HbA1c, FPG, and PPBG/PPPG.

Glycated Haemoglobin (HbA1c)

The mean HbA1c level was decreased from 9.5 ± 1.78 at Visit 1, to 8.3 ± 1.28 at Visit 2, 8.1 ± 1.29 at Visit 3, and 7.7 ± 1.07 at Visit 4 in efficacy evaluable patients (Table 7 and

Figure 1). The mean reduction in HbA1c level at each visit was presented in Table 8 and

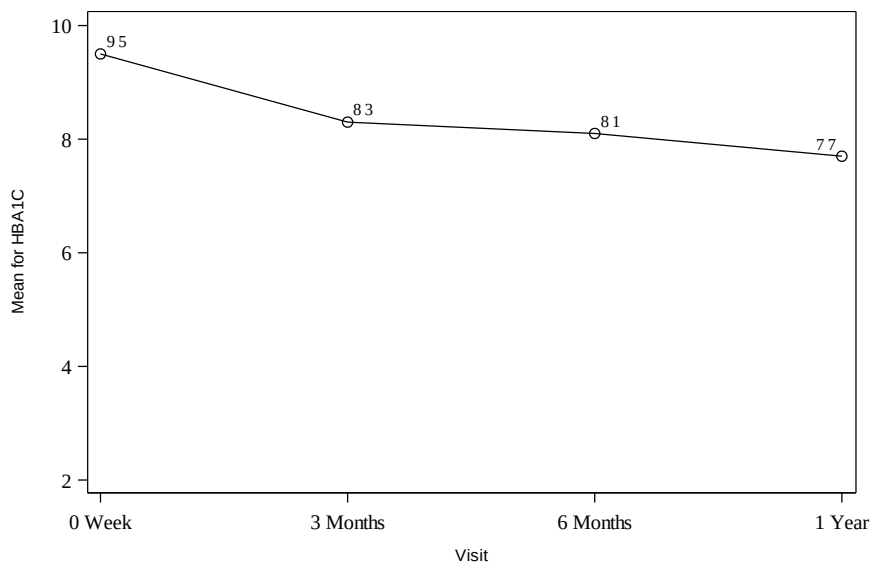
Figure 2. The mean reduction at Visit 2 from Visit 1 was -1.0 ± 1.22, at Visit 3, -1.4 ± 1.48, and at Visit 4, -1.7 ± 1.58. The change in HbA1c from Visit 1 was statistically significant (p<0.0001) at each visit.

Table 7 Visit wise Summary of HbA1c-EAS population (N = 1003)

Visit	Statistic	Overall (N = 1003)
Visit 1	N	903
	Missing	100
	Mean	9.5
	SD	1.78
	Median	9.3
	Range (Min.: Max.)	(5.1 :19.0)
Visit 2	N	629
	Missing	362
	Mean	8.3
	SD	1.28
	Median	8.1
	Range (Min.: Max.)	(4.0 :14.5)
Visit 3	N	705
	Missing	279
	Mean	8.1
	SD	1.29
	Median	7.9
	Range (Min.: Max..)	(0.0 :13.9)
Visit 4	N	892
	Missing	78
	Mean	7.7
	SD	1.07
	Median	7.5
	Range (Min.: Max..)	(3.7 :13.2)

Source Data: Listing 16.2.4.4; Table: 14.2.1.1
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in specified criteria; SD: Standard deviation

Figure 1 Line Diagram for mean for HbA1c at each visit



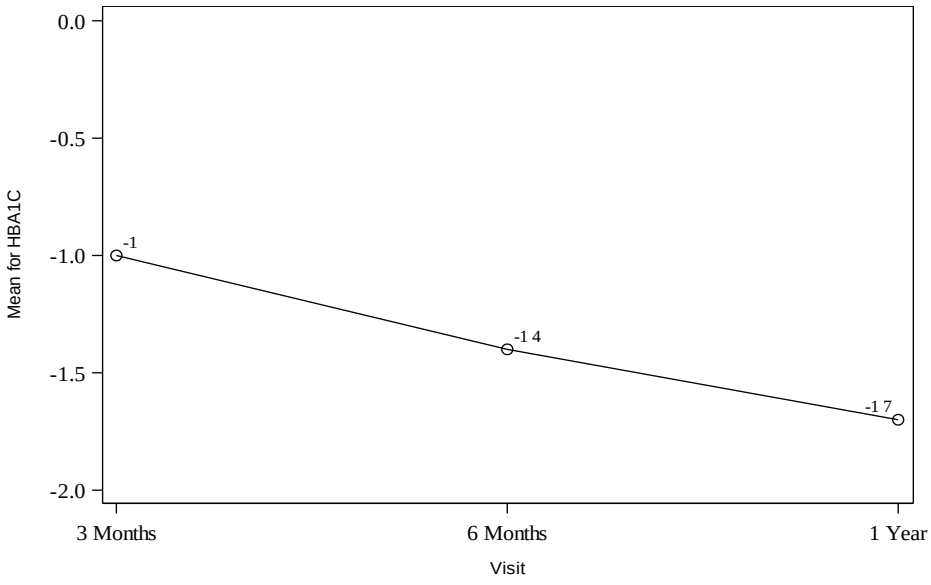
Source: Figure 14.2.1.1

Table 8 Summary of change in HbA1c for EAS population from Visit 1(Baseline) - EAS population (N = 1003)

Visit	Statistic	Overall (N = 1003)
Visit 4	N	818
	Missing	152
	Mean	-1.7
	SD	1.58
	Median	-1.5
	Range (Min.: Max..)	(-10.7 :3.7)
	p-value [1]	<.0001
Visit 3	N	677
	Missing	307
	Mean	-1.4
	SD	1.48
	Median	-1.1
	Range (Min.: Max..)	(-8.1 :4.5)
	p-value [1]	<.0001
Visit 2		
	N	600
	Missing	391
	Mean	-1.0
	SD	1.22
	Median	-0.7
	Range (Min.: Max..)	(-8.4 :2.5)
	p-value [1]	<.0001

Source Data: Listing16.2.4.4; Table 14.2.2.1
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in specified criteria; SD: Standard deviation
Note:
[1] p-value were calculated by using one sample t- test.

Figure 2 Line Diagram for mean change for HbA1C at each follow-up visit



Source: Figure 14.2.2.1

Of all efficacy, evaluable patients, 678 were previously on oral anti diabetic drugs (OAD) and 225 were previously on insulin. The mean ± SD HbA1c in OAD treated patients was reduced from 9.3 ± 1.70 at Visit 1 to 7.6 ± 1.03 at Visit 4. Similarly, mean ± SD HbA1c was reduced from 9.9 ± 1.93 (Visit 1) to 8.1 ± 1.11 (Visit 4) in patients receiving insulin previously (Table 9). The mean reduction in HbA1c level at each visit presented in Table 10. The mean ± SD reduction in HbA1c was -1.0 ± 1.24, -1.4 ± 1.55, and -1.7 ± 1.48 at Visit 2, Visit 3, and Visit 4, respectively from Visit 1 in patients received OAD previously. In the patients treated with insulin the mean reduction in HbA1c was -0.9 ± 1.15 at Visit 2, -1.1 ± 1.20 at Visit 3, and -1.7 ± 1.85 at Visit 4. The mean reduction in HbA1c from Visit 1 to each visit was found to be statistical significant (p<0.0001).

Table 9 Visit wise Summary of HbA1c-EAS population by Previous Medication (N = 1003)

Visit	Statistic	Previous Medication	
		OAD	Insulin
Visit 1	n	678	225
	Missing	52	48
	Mean	9.3	9.9
	SD	1.70	1.93
	Median	9.1	9.7
	Range (Min.: Max..)	(5.1 :16.7)	(5.8 :19.0)
Visit 2	n	498	131
	Missing	220	142
	Mean	8.2	8.7
	SD	1.29	1.16
	Median	8.0	8.6
	Range (Min.: Max..)	(4.0 :14.5)	(5.7 :12.1)
Visit 3	n	534	171
	Missing	181	98
	Mean	7.9	8.7
	SD	1.20	1.35
	Median	7.6	8.5
	Range (Min.: Max..)	(0.0 :12.0)	(5.8 :13.9)
Visit 4	n	650	242
	Missing	59	19
	Mean	7.6	8.1
	SD	1.03	1.11
	Median	7.4	8.0
	Range (Min.: Max..)	(5.6 :12.2)	(3.7 :13.2)

Source Data: Listing 16.2.4.4; Table 14.2.1.1.1
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

Table 10: Summary of change in HbA1c for EAS population from Visit 1(Baseline) - EAS population by previous medication (N = 1003)

Visit	Statistic	Previous Medication	
		OAD	Insulin
Visit 4	n	611	207
	Missing	98	54
	Mean	-1.7	-1.7
	SD	1.48	1.85
	Median	-1.5	-1.6
	Range (Min.: Max..)	(-8.1 :3.5)	(-10.7 :3.7)
	p-value [1]	<.0001	<.0001
Visit 3	n	516	161
	Missing	199	108
	Mean	-1.4	-1.1
	SD	1.55	1.20
	Median	-1.1	-1.1
	Range (Min.: Max..)	(-8.1 :4.5)	(-5.3 :2.5)
	p-value [1]	<.0001	<.0001
Visit 2			
	n	481	119
	Missing	237	154
	Mean	-1.0	-0.9
	SD	1.24	1.15
	Median	-0.8	-0.6
	Range (Min.: Max..)	(-7.1 :2.5)	(-8.4 :1.9)
	p-value [1]	<.0001	<.0001

Source Data: Listing16.2.4.4; Table 14.2.2.1.1
Note:
[1] p-value were calculated by using one sample t- test.
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

FPG-EAS population

The mean FPG value at Visit 1 of all efficacy evaluable patients was 180.4 ± 59.70 mg/dL. At Visit 2 FPG was reduced to 143.7 ± 37.84; at Visit 3, 134.8 ± 35.15; and at Visit 4, 130.0 ± 33.05. This decline in mean FPG is presented in Table 11 and

Figure 3.

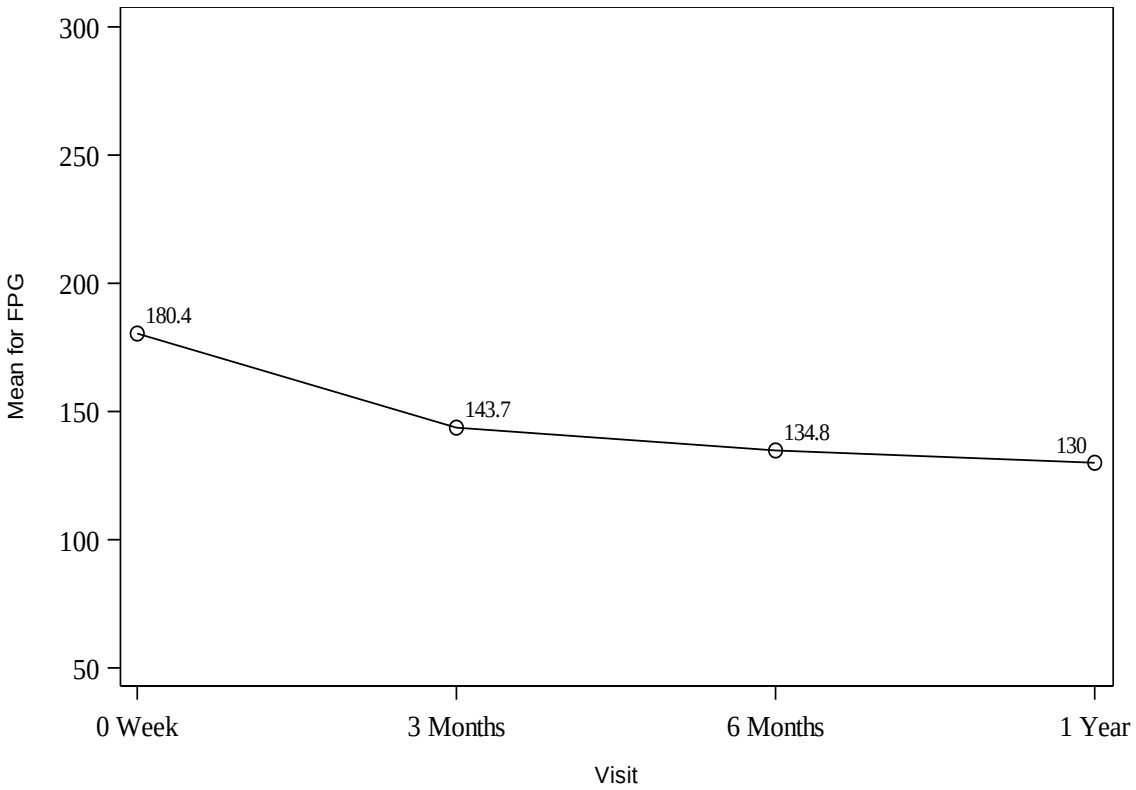
The mean reduction in FPG value at Visit 2 from Visit 1 was -35.6 ± 51.18, at Visit 3, -42.7 ± 55.99, and at Visit 4, -52.3 ± 60.09. This reduction in FPG level during the study was found to be statistical significant (p<0.0001) (Table 12 and Figure 4).

Table 11 Visit wise Summary of FPG-EAS population (N = 1003)

Visit	Statistic	Overall (N = 1003)
Visit 1	N	792
	Missing	211
	Mean	180.4
	SD	59.70
	Median	172.8
	Range (Min.: Max..)	(66.0 :594.0)
Visit 2	n	748
	Missing	243
	Mean	143.7
	SD	37.84
	Median	138.0
	Range (Min.: Max..)	(66.0 :306.0)
Visit 3	n	768
	Missing	216
	Mean	134.8
	SD	35.15
	Median	128.0
	Range (Min.: Max..)	(67.0 :320.0)
Visit 4	n	896
	Missing	74
	Mean	130.0
	SD	33.05
	Median	121.0
	Range (Min.: Max..)	(46.0 :324.0)

Source Data: Listing 16.2.4.4; Table: 14.2.1.2
FPG: Fasting plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

Figure 3 Line Diagram for mean for FPG at each visit



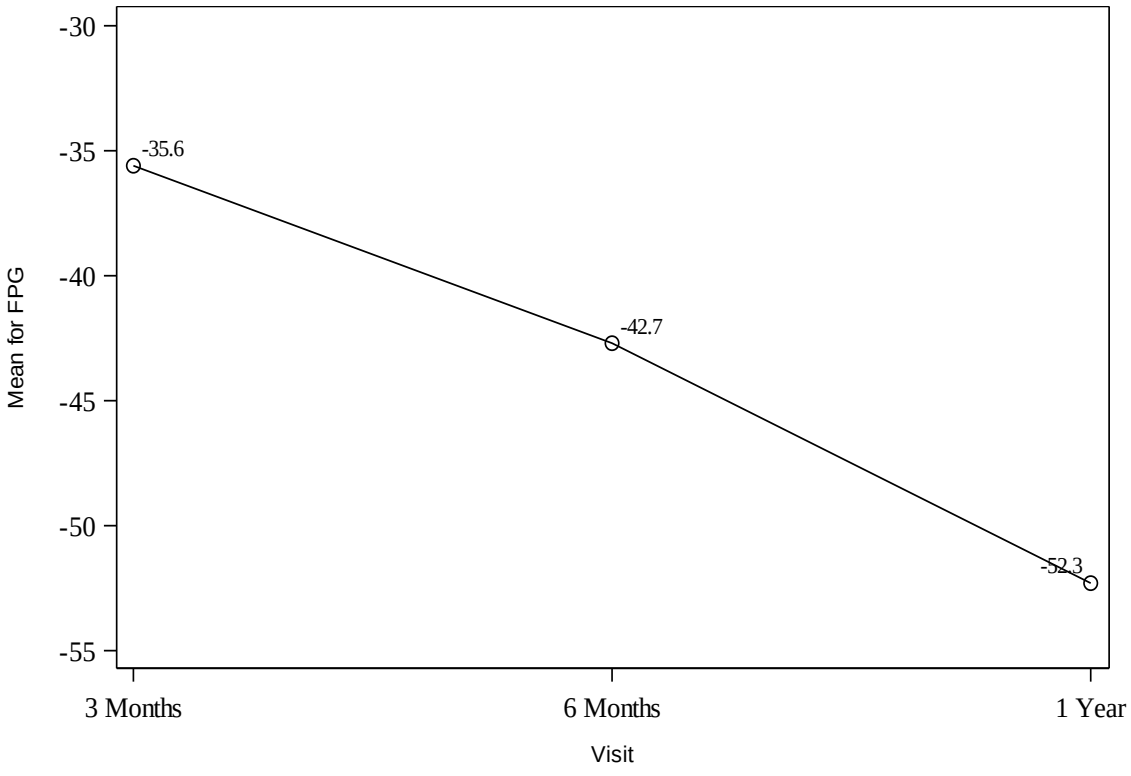
Source: Figure 14.2.1.2

Table 12 Summary of change in FPG for EAS population from Visit 1(Baseline) - EAS population (N = 1003)

Parameter/visit	Statistic	Overall (N = 1003)
Visit 4	n	734
	Missing	236
	Mean	-52.3
	SD	60.09
	Median	-46.5
	Range (Min.: Max..)	(-384 :145.0)
	p-value [1]	<.0001
Visit 3	n	697
	Missing	287
	Mean	-42.7
	SD	55.99
	Median	-37.0
	Range (Min.: Max..)	(-380 :148.0)
	p-value [1]	<.0001
Visit 2	n	683
	Missing	308
	Mean	-35.6
	SD	51.18
	Median	-29.0
	Range (Min.: Max..)	(-338 :181.0)
	p-value [1]	<.0001

Source Data: Listing16.2.4.4; Table 14.2.2.2
FPG: Fasting plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation
Note:
[1] p-values were calculated by using one sample t- test.
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

Figure 4 Line Diagram for mean change for FPG at each follow-up visit



Source: Figure 14.2.2.2

A decline in FPG was also noted in patients who were previously on OAD and insulin, at different time points. The mean ± SD FPG was reduced from 181.1 ± 56.74 (Visit 1) to 128.6 ± 32.37 (Visit 4) in patients receiving OAD previously. Similarly, mean ± SD FPG was reduced from 178.3 ± 67.58 (Visit 1) to 133.9 ± 34.63 (Visit 4) in patients previously on insulin (Table 13). Table 14 presented the change in FPG for efficacy evaluable patients by previous medication. In patients treated with OAD maximum reduction was observed at Visit 4 (-53.0 ± 57.31) in patients treated with Insulin maximum reduction was observed at Visit 4 (-50.3 ± 67.90). The reduction in FPG levels was statistical significant (p <0.0001) in both patients treated with OAD and Insulin.

Table 13 Visit wise Summary of FPG-EAS population by Previous Medication (N = 1003)

Visit	Statistic	Previous Medication	
		OAD	Insulin
Visit 1	n	587	205
	Missing	143	68
	Mean	181.1	178.3
	SD	56.74	67.58
	Median	173.0	170.0
	Range (Min.: Max..)	(66.0 :398.0)	(70.0 :594.0)
Visit 2	n	560	188
	Missing	158	85
	Mean	144.7	140.7
	SD	37.93	37.49
	Median	140.0	130.5
	Range (Min.: Max..)	(66.0 :306.0)	(73.0 :265.0)
Visit 3	n	579	189
	Missing	136	80
	Mean	133.4	139.2
	SD	32.10	42.98
	Median	127.0	131.0
	Range (Min.: Max..)	(67.0 :320.0)	(76.0 :312.0)
Visit 4	n	659	237
	Missing	50	24
	Mean	128.6	133.9
	SD	32.37	34.63
	Median	120.0	126.0
	Range (Min.: Max..)	(46.0 :324.0)	(62.0 :265.0)

Source Data: Listing16.2.4.4; Table 14.2.1.2.1
FPG: Fasting plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

Table 14 Summary of change in FPG for EAS population from Visit 1(Baseline) - EAS population by Previous Medication (N = 1003)

Visit	Statistic	Previous Medication	
		OAD	Insulin
Visit 4	n	551	183
	Missing	158	78
	Mean	-53.0	-50.3
	SD	57.31	67.90
	Median	-49.0	-40.0
	Range (Min.: Max..)	(-256 :138.0)	(-384 :145.0)
	p-value [1]	<.0001	<.0001
Visit 3	n	527	170
	Missing	188	99
	Mean	-44.6	-36.6
	SD	52.46	65.56
	Median	-40.0	-28.9
	Range (Min.: Max..)	(-236 :148.0)	(-380 :124.0)
	p-value [1]	<.0001	<.0001
Visit 2	n	513	170
	Missing	205	103
	Mean	-36.1	-34.0
	SD	49.13	57.06
	Median	-29.0	-29.5
	Range (Min.: Max..)	(-272 :180.0)	(-338 :181.0)
	p-value [1]	<.0001	<.0001

Source Data: Listing16.2.4.4; Table 14.2.2.2.1
FPG: Fasting plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation
Note:
[1] p-value were calculated by using one sample t- test.

PPG - EAS population

Table 15 summarised the details of decline in mean PPG observed at corresponding timepoints during each visit in overall population. The mean ± SD of post breakfast PPG was reduced from 266.9 ± 77.81 at Visit 1 to 212.7 ± 54.75, 199.0 ± 51.74 and 184.4 ± 47.22 at Visit 2, Visit 3 and Visit 4, respectively. Similarly, mean ± SD of Post lunch PPG were reduced from 254.8 ± 84.02 at Visit 1 to 182.3 ± 46.56, 187.7 ± 49.19

and 180.6 ± 40.08 at Visit 2, Visit 3 and Visit 4, respectively. The mean ± SD of Post dinner PPG was reduced from 216.3 ± 57.99 at Visit 1 to 160.0 ± 28.55, 192.3 ± 32.55 and 164.88 ± 36.21 at Visit 2, Visit 3 and Visit 4, respectively (Table 15 and Figure 5). This reduction in PPG at post breakfast and post lunch timepoint was found to statistically significant (p<0.0001) at all visits (Table 16 and Figure 6).

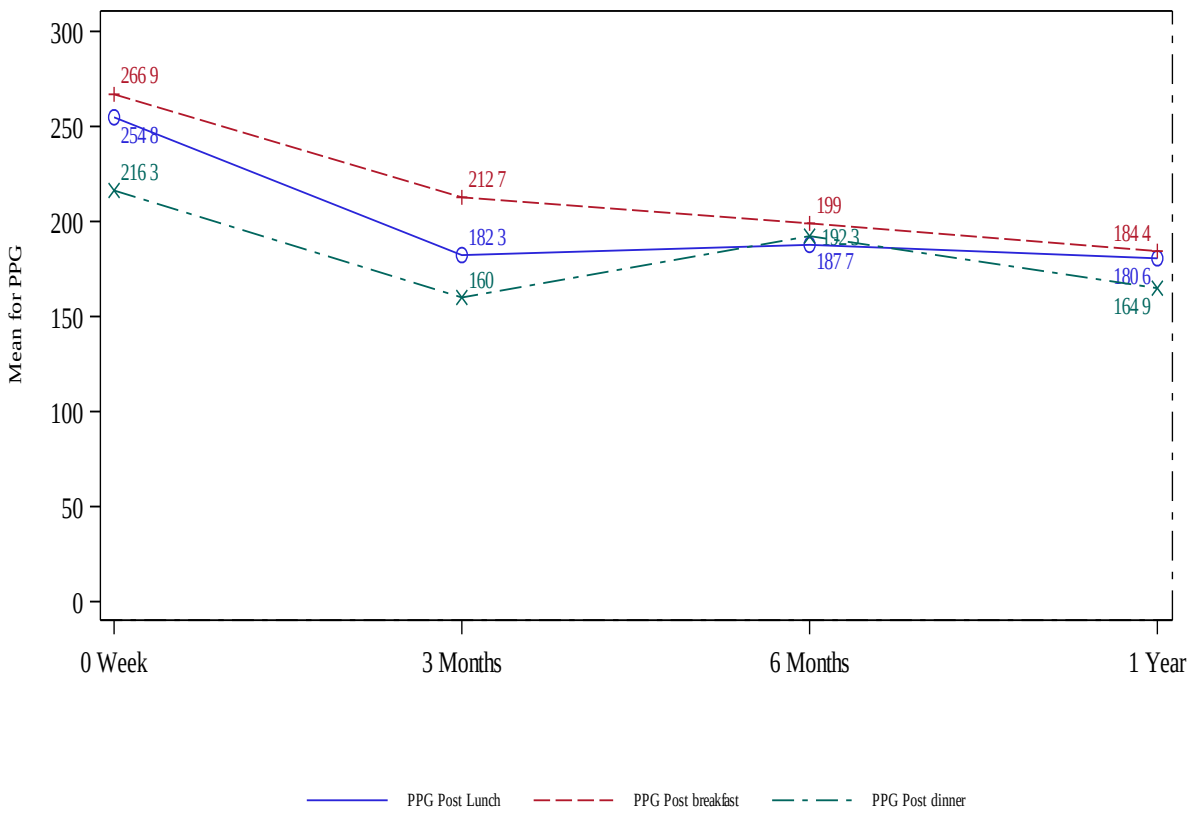
Table 15 Visit wise Summary of PPG - EAS population (N = 1003)

Parameter/Time point	Statistic	Overall (N = 1003)
Visit 1		
Post breakfast	n	476
	Missing	527
	Mean	266.9
	SD	77.81
	Median	260.0
	Range (Min.: Max..)	(86.4 :603.0)
Post lunch	n	175
	Missing	828
	Mean	254.8
	SD	84.02
	Median	247.5
	Range (Min.: Max..)	(116.0 :671.0)
Post dinner	n	3
	Missing	1000
	Mean	216.3
	SD	57.99
	Median	200.0
	Range (Min.: Max..)	(168.2 :280.7)
Visit 2		
Post breakfast	n	461
	Missing	530
	Mean	212.7
	SD	54.75
	Median	203.0
	Range (Min.: Max..)	(78.0 :557.0)
Post lunch	n	161
	Missing	830
	Mean	182.3
	SD	46.56
	Median	178.0
	Range (Min.: Max..)	(87.7 :383.0)
Post dinner	n	17
	Missing	974
	Mean	160.0
	SD	28.55
	Median	170.0
	Range (Min.: Max..)	(111.0 :200.0)
Visit 3		
Post breakfast	n	468
	Missing	516
	Mean	199.0
	SD	51.74
	Median	190.0
	Range (Min.: Max..)	(92.0 :458.0)
Post lunch	n	175
	Missing	809
	Mean	187.7
	SD	49.19
	Median	180.0
	Range (Min.: Max..)	(100.0 :356.0)
Post dinner	n	12
	Missing	972
	Mean	192.3
	SD	32.55
	Median	181.5
	Range (Min.: Max..)	(146.0 :248.0)
Visit 4		
Post breakfast	n	515
	Missing	455
	Mean	184.4
	SD	47.22

Parameter/Time point	Statistic	Overall (N = 1003)
	Median	179.0
	Range (Min.: Max..)	(64.0 :384.0)
Post lunch	n	253
	Missing	717
	Mean	180.6
	SD	40.08
	Median	179.0
	Range (Min.: Max..)	(69.0 :312.0)
Post dinner	n	10
	Missing	960
	Mean	164.9
	SD	36.21
	Median	147.0
	Range (Min.: Max..)	(139.0 :250.0)

Source Data: Listing 16.2.4.4; Table 14.2.1.3
PPG: post prandial plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

Figure 5 Multiple Line Diagram for mean for PPG at each visit for multiple time point



Source Figure 14.2.1.3

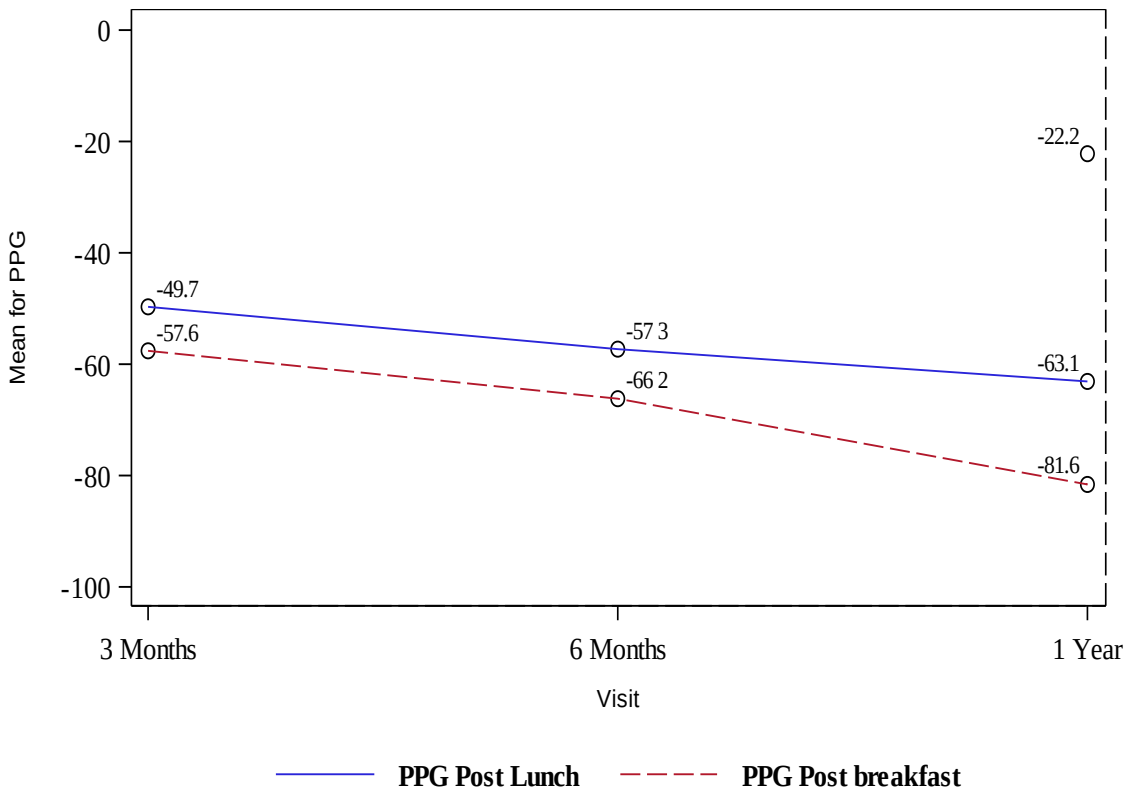
Table 16 Summary of change in PPG for EAS population from Visit 1(Baseline) EAS population (N = 1003)

Parameter/visit	Statistic	Overall (N = 1003)
Visit 4		
Post breakfast	n	410
	Missing	560
	Mean	-81.6
	SD	85.31
	Median	-76.8
	Range (Min.: Max..)	(-375 :180.0)
	p-value [1]	<.0001
Post lunch	n	124
	Missing	846
	Mean	-63.1
	SD	73.13
	Median	-61.0
	Range (Min.: Max..)	(-283 :117.0)
	p-value [1]	<.0001
Post dinner	n	1
	Missing	969
	Mean	-22.2
	SD	-
	Median	-22.2
	Range (Min.: Max..)	(-22.2: -22.2)
	p-value [1]	.
Visit 3		
Post breakfast	n	406
	Missing	578
	Mean	-66.2
	SD	82.00
	Median	-62.9
	Range (Min.: Max..)	(-344 :176.0)
	p-value [1]	<.0001
Post lunch	n	123
	Missing	861
	Mean	-57.3
	SD	71.99
	Median	-30.0
	Range (Min.: Max..)	(-461 :117.0)
	p-value [1]	<.0001
Post dinner	n	0
	Missing	984
	Mean	-
	SD	-
	Median	-
	Range (Min.: Max..)	-
	p-value [1]	.
Visit 2		
Post breakfast	n	401
	Missing	590
	Mean	-57.6
	SD	74.93
	Median	-53.0
	Range (Min.: Max..)	(-350 :227.0)
	p-value [1]	<.0001
Post lunch	n	102
	Missing	889
	Mean	-49.7
	SD	66.18
	Median	-24.5
	Range (Min.: Max..)	(-401 :76.9)
	p-value [1]	<.0001
Post dinner	n	0
	Missing	991
	Mean	-
	SD	-
	Median	-
	Range (Min.: Max..)	-

Parameter/visit	Statistic	Overall (N = 1003)
	p-value [1]	.

Source Data: Listing 16.2.4.4; Table 14.2.2.3
PPG: Post prandial plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation
Note:
[1] p-value were calculated by using one sample t- test.

Figure 6 Line Diagram for mean change for PPG at each follow-up visit



Source: Figure 14.2.2.3

Of all efficacy evaluable patients, 678 were previously on oral anti diabetic drugs (OAD) and 225 were previously on insulin. Table 17 presented the summary of PPG in patient treated with OAD and Insulin. The PPG in OAD treated patients at different timepoints at post breakfast was reduced from 277.7 ± 73.62 at Visit 1 to 183.8 ± 47.51 at Visit 4; at post lunch was reduced from 257.6 ± 86.60 at Visit 1 to 179.6 ± 38.47 at Visit 4; and at post dinner PPG was reduced from 200.0 at Visit 1 to 141.8 ± 4.19. Similar trends in decline of PPG was observed in patients receiving insulin previously (Table 17). The mean change in PPG at different timepoints is presented in Table 18. This reduction in PPG at post breakfast and post lunch timepoint was found to be in patient treated with OAD and insulin statistically significant ($p<0.0001$) at all visits.

Table 17 Visit wise Summary of PPG-EAS population by Previous Medication (N = 1003)

Parameter/Time point	Statistic	Previous Medication	
		OAD	Insulin
Visit 1			
Post breakfast	n	309	167
	Missing	421	106
	Mean	277.7	247.0
	SD	73.62	81.54
	Median	272.0	239.0
	Range (Min.: Max..)	(100.0 :534.0)	(86.4 :603.0)
Post lunch	n	147	28
	Missing	583	245
	Mean	257.6	240.1
	SD	86.60	68.36
	Median	247.5	246.6
	Range (Min.: Max..)	(118.6 :671.0)	(116.0 :450.0)
Post dinner	n	1	2
	Missing	729	271
	Mean	200.0	224.5
	SD	-	79.55

Parameter/Time point	Statistic	Previous Medication	
		OAD	Insulin
	Median	200.0	224.5
	Range (Min.: Max..)	(200.0 :200.0)	(168.2 :280.7)
Visit 2			
Post breakfast	n	298	163
	Missing	420	110
	Mean	211.6	214.6
	SD	56.56	51.38
	Median	199.5	210.0
	Range (Min.: Max..)	(78.0 :557.0)	(91.0 :396.0)
Post lunch	n	122	39
	Missing	596	234
	Mean	187.8	165.1
	SD	47.11	40.74
	Median	180.0	166.0
	Range (Min.: Max..)	(87.7 :383.0)	(100.0 :280.0)
Post dinner	n	4	13
	Missing	714	260
	Mean	169.5	157.1
	SD	17.00	31.23
	Median	173.0	158.0
	Range (Min.: Max..)	(146.0 :186.0)	(111.0 :200.0)
Visit 3			
Post breakfast	n	301	167
	Missing	414	102
	Mean	196.8	203.0
	SD	48.68	56.79
	Median	188.0	198.0
	Range (Min.: Max..)	(92.0 :452.0)	(99.0 :458.0)
Post lunch	n	138	37
	Missing	577	232
	Mean	188.5	184.9
	SD	52.07	36.95
	Median	179.1	192.0
	Range (Min.: Max..)	(100.0 :356.0)	(119.0 :310.0)
Post dinner	n	3	9
	Missing	712	260
	Mean	170.7	199.4
	SD	2.31	34.97
	Median	172.0	205.0
	Range (Min.: Max..)	(168.0 :172.0)	(146.0 :248.0)
Visit 4			
Post breakfast	n	348	167
	Missing	361	94
	Mean	183.8	185.6
	SD	47.51	46.74
	Median	178.0	182.0
	Range (Min.: Max..)	(64.0 :384.0)	(70.7 :369.0)
Post lunch	n	178	75
	Missing	531	186
	Mean	179.6	182.7
	SD	38.47	43.85
	Median	177.5	179.0
	Range (Min.: Max..)	(89.0 :312.0)	(69.0 :289.0)
Post dinner	n	4	6
	Missing	705	255
	Mean	141.8	180.3
	SD	4.19	40.43
	Median	140.0	172.5
	Range (Min.: Max..)	(139.0 :148.0)	(144.0 :250.0)

Source Data: Listing16.2.4.4; Table: 14.2.1.3.1
PPG: Post prandial plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation

Table 18 Summary of change in PPG for EAS population from Visit 1(Baseline) - EAS population by Previous Medication (N = 1003)

Visit /Time point	Statistic	Previous Medication	
		OAD	Insulin
Visit 4			

Visit /Time point	Statistic	Previous Medication	
		OAD	Insulin
Post breakfast	n	268	142
	Missing	441	119
	Mean	-88.3	-68.9
	SD	83.45	87.63
	Median	-90.5	-54.8
	Range (Min.: Max..)	(-347 :180.0)	(-375 :113.0)
	p-value [1]	<.0001	<.0001
Post lunch	n	107	
	Missing	602	17
	Mean	-64.7	244
	SD	76.72	-53.2
	Median	-61.0	44.76
	Range (Min.: Max..)	(-283 :117.0)	-43.0
	p-value [1]	<.0001	(-118 :27.0)
			0.0002
Post dinner	n	0	1
	Missing	709	260
	Mean	-	-22.2
	SD	-	-
	Median	-	-22.2
	Range (Min.: Max..)	-	(-22.2: -22.2)
	p-value [1]	.	.
Visit 3			
Post breakfast	n	260	146
	Missing	455	123
	Mean	-75.3	-49.9
	SD	79.55	84.01
	Median	-73.0	-41.0
	Range (Min.: Max..)	(-344 :167.0)	(-325 :176.0)
	p-value [1]	<.0001	<.0001
Post lunch	n	106	17
	Missing	609	252
	Mean	-57.5	-55.7
	SD	75.31	47.96
	Median	-26.8	-44.0
	Range (Min.: Max..)	(-461 :117.0)	(-121 :19.0)
	p-value [1]	<.0001	0.0002
Post dinner	n	0	0
	Missing	715	269
	Mean	-	-
	SD	-	-
	Median	-	-
	Range (Min.: Max..)	-	-
	p-value [1]	.	.
Visit 2			
Post breakfast	n	258	143
	Missing	460	130
	Mean	-67.7	-39.4
	SD	73.95	73.49
	Median	-69.0	-30.0
	Range (Min.: Max..)	(-350 :224.0)	(-301 :227.0)
	p-value [1]	<.0001	<.0001
Post lunch	n	88	14
	Missing	630	259
	Mean	-49.1	-53.4
	SD	69.29	43.42
	Median	-20.2	-50.5
	Range (Min.: Max..)	(-401 :76.9)	(-163: -5.0)
	p-value [1]	<.0001	0.0005
Post dinner	n	0	0
	Missing	718	273
	Mean	-	-
	SD	-	-
	Median	-	-
	Range (Min.: Max..)	-	-

Visit /Time point	Statistic	Previous Medication	
		OAD	Insulin
	p-value [1]	.	.

Source Data: Listing16.2.4.4; Table 14.2.2.3.1
PPG: Post prandial plasma glucose; Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation
Note:
[1] p-value were calculated by using one sample t- test.

11.4.2 Statistical/analytical issues

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Not applicable

11.4.2.3 Interim Analyses and Data Monitoring

The statistical analysis report (SAR) was made available to sponsor following database lock and prior to completion of the final CSR.

11.4.2.4 Multicentre Studies

The data from all 40 sites were pooled for analyses (Section 6).

11.4.2.5 Multiple Comparisons/Multiplicity

Not applicable.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of individual response data

Not applicable.

11.4.4 Drug dose, drug concentration, and relationships to response

Not applicable.

11.4.5 Drug-drug and drug-disease interactions

Not applicable.

11.4.6 By-Patient Displays

Not applicable.

11.4.7 Efficacy Conclusions

The Ryzodeg™ (IDeg/ IAsp) provides effective long-term improvements in efficacy parameters of DM patients. Efficacy parameters included in change in HbA1c, FPG, and PPG. Prior to study enrolment of 1003 efficacy evaluable patients 678 patients were on OAD and 225 patients were on Insulin therapy. The most common reasons to start Ryzodeg™ treatment by patients were improvement in HbA1c (87.0%), improvement in glucose levels (PPG 62.7% and FPG 57.6%) and need for flexibility in timings of injection. In some cases, patients were switched to Ryzodeg™ due to risk of hypoglycaemia and side effects from previous therapies. There was a statistically significant reduction in all efficacy parameters, i.e. HbA1c, FPG and PPD was observed between Visit 1 and 1 year [HbA1c: -1.7% ± 1.58; FPG: -52.3 ± 60.09; PPG: -81.6 ± 85.31(post breakfast), -63.1 ± 73.13 (post lunch), -22.2 (post dinner) all p value < 0.0001]. A decrease in hypoglycaemic event was observed in this study. Considering the results, it can be concluded that these

advantages with Ryzodeg™ in efficacy of lowering of HbA1c, FPG and PPG values could encourage physicians and patients to titrate insulin regimens more rigorously to reach glycaemic target values.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Being a non-interventional study, patients with DM requiring insulin therapy, and qualified for starting treatment with Ryzodeg™, based on clinical judgment by their treating physician, were treated with Ryzodeg™. Safety analysis of was done on 1029 patients.

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

Adverse Events

A total of 30 AEs were reported in 23 patients form the date of singing the informed consent and until Visit 4. Of all enrolled patients, a total of 18 (1.7%) patients reported at least 1 AEs and 5 (0.5%) reported more than 1 AEs. Of all reported AEs, 2 AEs were found to be serious reported in 2 patients. By severity, of 30 reported AEs, 25 were mild reported in 19 patients, 1 was moderate in 1 patient, and 4 were severe reported in 3 patients. By outcome, 19 AEs reported in 16 patients were recovered, 8 AEs in 5 patients were not recovered, 2 were fatal and outcome of 1 reported AE was unknown.

Twenty-three of 30 AEs were unlikely related to the study drug, 2 were possibly and 5 AEs were probably related to study drug.

By action taken to study drug due to AE: dose of study drug was reduced in 2 patients with 2 AEs. In 2 patients study drug was withdrawn. study drug dose was not changed in 7 patients and not applicable in 12 patients.

Table 19 Summary of Adverse Event - SAS Population (N = 1029)

Category, n (%)) [1]	Overall (N = 1029)
Total number of AEs reported	30
Patients reporting any AEs	23(2.2)
Patients reporting 1 AE	18 (1.7) [18]
Patients reporting >1 AEs	5 (0.5) [12]
AE is serious	
Yes	2 (0.2) [2]
No	21 (2.0) [28]
If Yes, is it life threatening [2]	
Yes	2 (100.0) [2]
No	-
Severity	
Mild	19 (1.8) [25]
Moderate	1 (0.1) [1]
Severe	3 (0.3) [4]
Outcome of AE	
Recovered / Resolved	16 (1.6) [19]
Not Recovered / Not Resolved	5 (0.5) [8]
Recovering/resolving	
Fatal	2 (0.2) [2]
Recovered/resolved with sequelae	
Unknown	1 (0.1) [1]
Causality	
Probable	3 (0.3) [5]
Possible	2 (0.2) [2]
Unlikely	20 (1.9) [23]
Action taken to study product(s) due to AE	
Drug interrupted	-
Drug Withdrawn	2 (0.2) [3]
Dose Reduced	2 (0.2) [2]
Dose increased	-
Dose Not Changed	7 (0.7) [12]
Unknown	-
Not Applicable	12 (1.2) [13]

Source Data: Listing 16.2.7; Table 14.3.1.1
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator.
[2] Percentage were calculated by taking count of 'Yes' from 'AE is serious' as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events are presented as: number of patients (percent of patients) (number of events).
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

12.2.2 Display of adverse events

Adverse events by System Organ Class and Preferred Term - SAS Population (N = 1029)

All reported AEs were coded using MedDRA 20.0. All AEs were categorized by System Organ Class (SOC) and summarized by Preferred Term (PT). A total of 8 (0.8%) patients were encountered with 9 AEs in the class of General disorders and administration site conditions. This was followed by Metabolism and nutrition disorders [3 (0.3%)] with 4 AEs and Infections and infestations [3 (0.3%)] with 3 AEs. Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, Nervous system disorders, and vascular disorders each reported in 2 (0.2%) patients with 2 AEs. Cardiac disorders, injury poisoning and procedural complications, investigations, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorder, and skin and subcutaneous tissue disorders each SOC reported in 1 (0.1%) patient with 1 AE.

The AEs by SOC and PT are provided in Table 20. Of all AEs, the following AEs were present in $\geq$ 2 patients:
Pyrexia, and Fatigue (SOC: General disorders and administration site conditions) were observed in 5 and 2 patients, respectively.
Upper respiratory tract infection (SOC: infection and infestation); Muscle spasm (SOC: Musculoskeletal and connective tissue disorders); Dizziness (SOC: Nervous system disorders) each was observed in 2 patients.

Table 20 Summary of adverse events by System Organ Class and Preferred Term - SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Overall (N = 1029)
Total number of patients with at least one adverse event	23 (2.2)
Total number of adverse events, n	30
Cardiac disorders	1 (0.1) [1]
Cardiogenic shock	1 (0.1) [1] (0.0003)
Gastrointestinal disorders	2 (0.2) [2]
Constipation	1 (0.1) [1] (0.0003)
Diarrhoea	1 (0.1) [1] (0.0003)
General disorders and administration site conditions	8 (0.8) [9]
Death	1 (0.1) [1] (0.0003)
Fatigue	2 (0.2) [2] (0.0006)
Gait disturbance	1 (0.1) [1] (0.0003)
Pyrexia	5 (0.5) [5] (0.0014)
Infections and infestations	3 (0.3) [3]
Skin bacterial infection	1 (0.1) [1] (0.0003)
Upper respiratory tract infection	2 (0.2) [2] (0.0006)
Injury, poisoning and procedural complications	1 (0.1) [1]
Road traffic accident	1 (0.1) [1] (0.0003)
Investigations	1 (0.1) [1]
Weight increased	1 (0.1) [1] (0.0003)
Metabolism and nutrition disorders	3 (0.3) [4]
Hyperglycaemia	1 (0.1) [1] (0.0003)
Hypoglycaemia	1 (0.1) [1] (0.0003)
Increased appetite	1 (0.1) [2] (0.0006)
Musculoskeletal and connective tissue disorders	2 (0.2) [2]
Muscle spasms	2 (0.2) [2] (0.0006)
Nervous system disorders	2 (0.2) [2]
Dizziness	2 (0.2) [2] (0.0006)
Renal and urinary disorders	1 (0.1) [1]
Urinary incontinence	1 (0.1) [1] (0.0003)
Respiratory, thoracic and mediastinal disorders	1 (0.1) [1]
Dyspnoea exertional	1 (0.1) [1] (0.0003)
Skin and subcutaneous tissue disorders	1 (0.1) [1]
Swelling face	1 (0.1) [1] (0.0003)
Vascular disorders	2 (0.2) [2]
Accelerated hypertension	1 (0.1) [1] (0.0003)
Hypertension	1 (0.1) [1] (0.0003)

Source Data: Listing 16.2.7; Table 14.3.1.2
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

Adverse events by System Organ Class and Preferred Term by severity- SAS Population (N = 1029)

Majority of AEs in each SOC were mild and moderate in nature. However cardiogenic shock (SOC cardiac disorders), Death (SOC General disorders and administration site conditions), and hyperglycaemia was found to be severe in 1 patient each.

Table 21 Summary of Adverse events by System Organ Class and Preferred Term by severity- SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Severity	Overall (N = 1029)
Total number of patients with at least one adverse event		23 (2.2)
Total number of adverse events, n		30
Cardiac disorders		1 (0.1) [1]
Cardiogenic shock		1 (0.1) [1] (0.0003)
	Mild	-
	Moderate	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Severity	Overall (N = 1029)
	Severe	1 (0.1) [1]
Gastrointestinal disorders		2 (0.2) [2]
Constipation		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Diarrhoea		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
General disorders and administration site conditions		8 (0.8) [9]
Death		1 (0.1) [1] (0.0003)
	Mild	-
	Moderate	-
	Severe	1 (0.1) [1]
Fatigue		2 (0.2) [2] (0.0006)
	Mild	1 (0.1) [2]
	Moderate	-
	Severe	-
Gait disturbance		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Pyrexia		5 (0.5) [5] (0.0014)
	Mild	1 (0.1) [5]
	Moderate	-
	Severe	-
Infections and infestations		3 (0.3) [3]
Skin bacterial infection		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Upper respiratory tract infection		2 (0.2) [2] (0.0006)
	Mild	1 (0.1) [2]
	Moderate	-
	Severe	-
Injury, poisoning and procedural complications		1 (0.1) [1]
Road traffic accident		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Investigations		1 (0.1) [1]
Weight increased		1 (0.1) [1] (0.0003)
	Mild	-
	Moderate	1 (0.1) [1]
	Severe	-
Metabolism and nutrition disorders		3 (0.3) [4]
Hyperglycaemia		1 (0.1) [1] (0.0003)
	Mild	-
	Moderate	-
	Severe	1 (0.1) [1]
Hypoglycaemia		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Increased appetite		1 (0.1) [2] (0.0006)
	Mild	1 (0.1) [2]
	Moderate	-
	Severe	-
Musculoskeletal and connective tissue disorders		2 (0.2) [2]
Muscle spasms		2 (0.2) [2] (0.0006)
	Mild	1 (0.1) [2]
	Moderate	-
	Severe	-
Nervous system disorders		2 (0.2) [2]
Dizziness		2 (0.2) [2] (0.0006)
	Mild	1 (0.1) [2]
	Moderate	-
	Severe	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Severity	Overall (N = 1029)
Renal and urinary disorders		1 (0.1) [1]
Urinary incontinence		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Respiratory, thoracic and mediastinal disorders		1 (0.1) [1]
Dyspnoea exertional		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Skin and subcutaneous tissue disorders		1 (0.1) [1]
Swelling face		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-
Vascular disorders		2 (0.2) [2]
Accelerated hypertension		1 (0.1) [1] (0.0003)
	Mild	-
	Moderate	-
	Severe	1 (0.1) [1]
Hypertension		1 (0.1) [1] (0.0003)
	Mild	1 (0.1) [1]
	Moderate	-
	Severe	-

Source Data: Listing 16.2.7; Table 14.3.1.3
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Zero frequencies were presented by "- ".

Adverse events by System Organ Class and Preferred Term by Causality- SAS Population (N = 1029)

Majority of AEs in all SOC were Unlikely associated with study drug. Amongst the General disorders and administration site conditions, 1 AE (fatigue)was found to be probably related to study drug. Similarly, weight gain (SOC: investigations), and increased appetite (SOC: metabolism and nutrition disorders) were found to be probably related to study drug.

During the course of study, only one event of hyperglycaemia (SOC metabolism and nutrition disorders) was found to be possibly related to study drug. Further details are provided in Table 22

Table 22 Summary of Adverse events by System Organ Class and Preferred Term by Causality- SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Causality	Overall (N = 1029)
Total number of patients with at least one adverse event		23 (2.2)
Total number of adverse events, n		30
Cardiac disorders		1 (0.1) [1]
Cardiogenic shock		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Gastrointestinal disorders		2 (0.2) [2]
Constipation		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Diarrhoea		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
General disorders and administration site conditions		8 (0.8) [9]
Death		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Causality	Overall (N = 1029)
	Unlikely	1 (0.1) [1]
Fatigue		2 (0.2) [2] (0.0006)
	Possible	-
	Probable	1 (0.1) [1]
	Unlikely	1 (0.1) [1]
Gait disturbance		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Pyrexia		5 (0.5) [5] (0.0014)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [5]
Infections and infestations		3 (0.3) [3]
Skin bacterial infection		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Upper respiratory tract infection		2 (0.2) [2] (0.0006)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [2]
Injury, poisoning and procedural complications		1 (0.1) [1]
Road traffic accident		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	1 (0.1) [1]
	Unlikely	-
Investigations		1 (0.1) [1]
Weight increased		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	1 (0.1) [1]
	Unlikely	-
Metabolism and nutrition disorders		3 (0.3) [4]
Hyperglycaemia		1 (0.1) [1] (0.0003)
	Possible	1 (0.1) [1]
	Probable	-
	Unlikely	-
Hypoglycaemia		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Increased appetite		1 (0.1) [2] (0.0006)
	Possible	-
	Probable	1 (0.1) [2]
	Unlikely	-
Musculoskeletal and connective tissue disorders		2 (0.2) [2]
Muscle spasms		2 (0.2) [2] (0.0006)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [2]
Nervous system disorders		2 (0.2) [2]
Dizziness		2 (0.2) [2] (0.0006)
	Possible	1 (0.1) [1]
	Probable	-
	Unlikely	1 (0.1) [1]
Renal and urinary disorders		1 (0.1) [1]
Urinary incontinence		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Respiratory, thoracic and mediastinal disorders		1 (0.1) [1]
Dyspnoea exertional		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Skin and subcutaneous tissue disorders		1 (0.1) [1]
Swelling face		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Causality	Overall (N = 1029)
	Unlikely	1 (0.1) [1]
Vascular disorders		2 (0.2) [2]
Accelerated hypertension		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]
Hypertension		1 (0.1) [1] (0.0003)
	Possible	-
	Probable	-
	Unlikely	1 (0.1) [1]

Source Data: Listing 16.2.7; 14.3.1.4
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Zero frequencies were presented by "- ".

Adverse events by System Organ Class and Preferred Term by Action taken- SAS Population (N = 1029)

The AEs by SOC and PT with the reference of action taken are summarised in Table 23. In majority of patients' dose of drug was not changed. However, the drug was withdrawn in one patient with each of the following AEs: weight increased (SOC: investigation); hyperglycaemia (SOC: Metabolism and nutrition disorders); and accelerated hypertension (SOC: vascular disorders).

Table 23 Summary of adverse events by System Organ Class and Preferred Term by Action taken- SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Action Taken	Overall (N = 1029)
Total number of patients with at least one adverse event		23 (2.2)
Total number of adverse events, n		30
Cardiac disorders		1 (0.1) [1]
Cardiogenic shock		1 (0.1) [1] (0.0003)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [1]
	Unknown	-
Gastrointestinal disorders		2 (0.2) [2]
Constipation		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Diarrhoea		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
General disorders and administration site conditions		8 (0.8) [9]
Death		1 (0.1) [1] (0.0003)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Action Taken	Overall (N = 1029)
	Drug withdrawn	-
	Not Applicable	1 (0.1) [1]
	Unknown	-
Fatigue		2 (0.2) [2] (0.0006)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [1]
	Unknown	-
Gait disturbance		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Pyrexia		5 (0.5) [5] (0.0014)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [5]
	Unknown	-
Infections and infestations		3 (0.3) [3]
Skin bacterial infection		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Upper respiratory tract infection		2 (0.2) [2] (0.0006)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [1]
	Unknown	-
Injury, poisoning and procedural complications		1 (0.1) [1]
Road traffic accident		1 (0.1) [1] (0.0003)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [1]
	Unknown	-
Investigations		1 (0.1) [1]
Weight increased		1 (0.1) [1] (0.0003)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug Withdrawn	1 (0.1) [1]
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Metabolism and nutrition disorders		3 (0.3) [4]
Hyperglycaemia		1 (0.1) [1] (0.0003)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Action Taken	Overall (N = 1029)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug Withdrawn	1 (0.1) [1]
	Drug interrupted	-
	Drug withdrawn	-
	Not applicable	-
	Unknown	-
Hypoglycaemia		1 (0.1) [1] (0.0003)
	Dose Reduced	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not applicable	-
	Unknown	-
Increased appetite		1 (0.1) [2] (0.0006)
	Dose Not Changed	1 (0.1) [2]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Musculoskeletal and connective tissue disorders		2 (0.2) [2]
Muscle spasms		2 (0.2) [2] (0.0006)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [2]
	Unknown	-
Nervous system disorders		2 (0.2) [2]
Dizziness		2 (0.2) [2] (0.0006)
	Dose Reduced	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	1 (0.1) [1]
	Unknown	-
Renal and urinary disorders		1 (0.1) [1]
Urinary incontinence		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Respiratory, thoracic and mediastinal disorders		1 (0.1) [1]
Dyspnoea exertional		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Skin and subcutaneous tissue disorders		1 (0.1) [1]
Swelling face		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Action Taken	Overall (N = 1029)
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Vascular disorders		2 (0.2) [2]
Accelerated hypertension		1 (0.1) [1] (0.0003)
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug Withdrawn	1 (0.1) [1]
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-
Hypertension		1 (0.1) [1] (0.0003)
	Dose Not Changed	1 (0.1) [1]
	Dose increased	-
	Dose not changed	-
	Dose reduced	-
	Drug interrupted	-
	Drug withdrawn	-
	Not Applicable	-
	Unknown	-

Source Data: Listing 16.2.7; Table: 14.3.1.5
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[3] Zero frequencies were presented by "- ".

Adverse events by System Organ Class and Preferred Term by Outcome- SAS Population (N = 1029)

Majority of patients reported AEs during the study were recovered/resolved (Table 24).

An event of cardiogenic shock (SCO: cardiac disorders) in a patient and death (SOC: general disorders and administration site conditions) occurred with fatal outcome. One patient each with following AEs: constipation (SOC: gastrointestinal disorders); fatigue (SOC: general disorders and administration site conditions); upper respiratory tract infection (SOC: infection); and increased appetite (SOC: Metabolism and nutrition disorders) were not recovered/not resolved. Outcome of an event of weight gain in a patient was unknown.

Table 24 Summary of Adverse events by System Organ Class and Preferred Term by Outcome- SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Outcome	Overall (N = 1029)
Total number of patients with at least one adverse event		23 (2.2)
Total number of adverse events, n		30
Cardiac disorders		1 (0.1) [1]
Cardiogenic shock		1 (0.1) [1] (0.0003)
	Fatal	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Gastrointestinal disorders		2 (0.2) [2]
Constipation		1 (0.1) [1] (0.0003)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [1]
	Not recovered/not resolved	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Outcome	Overall (N = 1029)
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Diarrhoea		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
General disorders and administration site conditions		8 (0.8) [9]
Death		1 (0.1) [1] (0.0003)
	Fatal	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Fatigue		2 (0.2) [2] (0.0006)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Gait disturbance		1 (0.1) [1] (0.0003)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Pyrexia		5 (0.5) [5] (0.0014)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [5]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Infections and infestations		3 (0.3) [3]
Skin bacterial infection		1 (0.1) [1] (0.0003)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Upper respiratory tract infection		2 (0.2) [2] (0.0006)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Injury, poisoning and procedural complications		1 (0.1) [1]
Road traffic accident		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Outcome	Overall (N = 1029)
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Investigations		1 (0.1) [1]
Weight increased		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	1 (0.1) [1]
Metabolism and nutrition disorders		3 (0.3) [4]
Hyperglycaemia		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Hypoglycaemia		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Increased appetite		1 (0.1) [2] (0.0006)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [2]
	Not recovered/not resolved	-
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Musculoskeletal and connective tissue disorders		2 (0.2) [2]
Muscle spasms		2 (0.2) [2] (0.0006)
	Fatal	-
	Not Recovered / Not Resolved	1 (0.1) [1]
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Nervous system disorders		2 (0.2) [2]
Dizziness		2 (0.2) [2] (0.0006)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [2]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Renal and urinary disorders		1 (0.1) [1]
Urinary incontinence		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Respiratory, thoracic and mediastinal disorders		1 (0.1) [1]
Dyspnoea exertional		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Outcome	Overall (N = 1029)
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Skin and subcutaneous tissue disorders		1 (0.1) [1]
Swelling face		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Vascular disorders		2 (0.2) [2]
Accelerated hypertension		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-
Hypertension		1 (0.1) [1] (0.0003)
	Fatal	-
	Not recovered/not resolved	-
	Recovered / Resolved	1 (0.1) [1]
	Recovered/resolved	-
	Recovered/resolved with Sequelae	-
	Recovering/resolving	-
	Unknown	-

Source Data: Listing 16.2.7; Table: 14.3.1.6
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[3] Zero frequencies were presented by "- ".

No AEs in any of the SOC had shown a relation to a technical complaint as presented in Table14.3.1.7. (Not included in text).

Serious Adverse Events

A total of 2 SAEs were recorded in two patients during the study. Both Patients reported with 1 SAE each. Both SAEs were severe in nature and proved to be fatal (Table 25). The reported SAEs were found to be unlikely related to study drug as study drug was not given to these patients prior to the onset of SAE. Both SAEs resulted in death of the patients.

Table 25 Summary of Serious Adverse Event - SAS Population (N = 1029)

Category, n (%) [1]	Overall (N = 1029)
Total number of SAEs reported	2
Patients reporting any SAEs	2 (0.2)
Patients reporting 1 SAE	2 (0.2) [2]
Patients reporting >1 SAEs	-
Severity	
Mild	-
Moderate	-
Severe	2 (0.2) [2]
Outcome of AE	
Recovered/resolved	-
Not recovered/not resolved	-
Recovering/resolving	-
Fatal	2 (0.2) [2]

Category, n (%) [1]	Overall (N = 1029)
Recovered/resolved with sequelae	-
Unknown	-
study product(s) given at or prior to onset of SAE	
Yes	-
No	-
Causality	
Probable	-
Possible	-
Unlikely	2 (0.2) [2]
Action taken to study product(s) due to AE	
Drug interrupted	-
Drug withdrawn	-
Dose reduced	-
Dose increased	-
Dose not changed	-
Unknown	-
Not applicable	2 (0.2) [2]
The AE related to a Technical Complaint	
Yes	-
No	2 (0.2) [2]
Was the condition recorded at baseline	1 (0.1) [1]
If Yes did the symptoms increase or exacerbate	-
Did the patient receive any treatment for the event	1 (0.1) [1]
Seriousness category	
Death	2 (0.2) [2]
In-patient hospitalization/prolongation of existing hospitalization	-
Congenital anomaly or birth defect	-
Life threatening	-
Persistent or significant disability or incapacity	-
Important medical event	-
If Death, was an autopsy performed or planned	
Yes	
No	-

Source Data: Listing 16.2.7, 16.2.7.1; Table: 14.3.2.3.1
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Serious adverse events were coded using MedDRA version 20.0 or later.
[2] All Serious adverse events were presented as: number of patients (percent of patients) (number of events).
[3] Patients may had reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

Serious Adverse Events by System Organ Class and Preferred Term

A total of 2 (0.2%) patients reported one SAE [1 (0.1%)] in each patient during study period. Of these SAEs, 1 (0.1%) patient had cardiogenic shock and one died during the study (Table 26).

Table 26 Summary of Serious Adverse Events by System Organ Class and Preferred Term - SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1029)
Total number of patients with at least one serious adverse event	2 (0.2)
Total number of serious adverse events, n	2
Cardiac disorders	1 (0.1) [1]
Cardiogenic shock	1 (0.1) [1] (0.0003)
General disorders and administration site conditions	1 (0.1) [1]
Death	1 (0.1) [1] (0.0003)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1029)

Source Data: Listing 16.2.7; Table: 14.3.2.3.2
AE: Adverse Events; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

Adverse Drug Reaction

A total of 7 ADRs were reported, in 5 (0.5%) patients during the study. 4(0.4%) patients had reported 1 ADR each and 1 (0.1%) had reported 3 ADRs. No ADRs were serious in nature. On the severity scale, 5 ADRs, in 3 (0.3%) patients, were mild, 1 was moderate and 1 was severe. 3 of 7 ADRs were Recovered/resolved, 3 of 7 were not recovered/ not resolved, and outcome of 1 ADR was unknown. In 2 (0.2%) patients, the drug was withdrawn and 1 (0.1%) patient dose was reduced. No dose was changed in 1 (0.1%) patient (Table 27).

Table 27 Summary of Adverse Drug Reaction - SAS Population (N = 1029)

Category, n (%) [1]	**Overall (N = 1029)**
Total number of ADRs reported	5 (0.5) [7]
Patients reporting any AEs	5 (0.5) [7]
Patients reporting 1 ADR	4 (0.4) [4]
Patients reporting >1 ADRs	1 (0.1) [3]
ADR is serious	
Yes	-
No	5 (0.5) [7]
If Yes, is it life threatening [2]	
Yes	-
No	-
Severity	
Mild	3 (0.3) [5]
Moderate	1 (0.1) [1]
Severe	1 (0.1) [1]
Outcome of ADR	
Recovered / Resolved	3 (0.3) [3]
Not Recovered / Not Resolved	1 (0.1) [3]
Recovering/resolving	-
Recovered/resolved with sequelae	-
Unknown	1 (0.1) [1]
study product(s) given at or prior to onset of ADR	
Action taken to study product(s) due to ADR	
Drug interrupted	-
Drug Withdrawn	2 (0.2) [2]
Dose Reduced	1 (0.1) [1]
Dose increased	-
Dose Not Changed	1 (0.1) [3]
Unknown	-
Not Applicable	1 (0.1) [1]

Source Data: Listing 16.2.7, 16.2.7.1; Table 14.3.2.2.1
ADR: Adverse Drug Reaction; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse Drug Reaction were coded using MedDRA version 20.0 or later.
[2] All Adverse Drug Reaction were presented as: number of patients (percent of patients) (number of events).
[3] Patients may had reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

Adverse drug reaction by Organ Class and Preferred Term - SAS Population (N = 1029)

Of the total ADR reported, 1 (0.1%) patient reported with one ADR in each SOC general disorders and administration site conditions, injury, poisoning and procedural complications investigations, and nervous system disorders. Two [2 (0.2%)] patients reported 3 ADRs of metabolism and nutrition disorders (Table 28).

Table 28 Summary of Adverse drug reaction by Organ Class and Preferred Term - SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Overall (N = 1029)
Total number of patients with at least one Adverse Drug Reaction	5 (0.5)
Total number of Adverse Drug Reaction, n	7
General disorders and administration site conditions	1 (0.1) [1]
Injury, poisoning and procedural complications	1 (0.1) [1]
Road traffic accident	1 (0.1) [1] (0.0003)
Investigations	1 (0.1) [1]
Weight increased	1 (0.1) [1] (0.0003)
Metabolism and nutrition disorders	2 (0.2) [3]
Hyperglycaemia	1 (0.1) [1] (0.0003)
Increased appetite	1 (0.1) [2] (0.0006)
Nervous system disorders	1 (0.1) [1]
Dizziness	1 (0.1) [1] (0.0003)

Source Data: Listing 16.2.7; Table: 14.2.2.2
ADR: Adverse Drug Reaction; N: Total number of patients; n: total number of patients in specified criteria; SAS: safety analysis set; SOC: System Organ Class.
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse drug reaction were coded using MedDRA version 20.0 or later.
[2] All adverse drug reaction except System Organ Class were presented as: number of patients (percent of patients) (number of events) [incidence rate] (rate per 100 PYE).System Organ Class were presented as: number of patients (percent of patients) (number of events) [incidence rate].
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

No Serious Adverse Drug Reaction noted during the study.

Severe Hypoglycaemic Episodes - SAS Population

A total of 24 events of Severe Hypoglycaemic Episodes were recorded in 17 (1.7%) patients at Visit 1. No further Severe Hypoglycaemic Episodes were noted at any follow Up Visit during the study period (Table 29).

Table 29 Summary of Severe Hypoglycaemic Episodes - SAS Population (N = 1029)

Visit/ Parameter [1], n (%))	Overall (N = 1029)
Visit 1 Baseline Visit	
Severe hypoglycaemic episodes	17(1.7) (24)
Visit 2 Follow Up Visit	
Severe hypoglycaemic episodes	-
Visit 3 Follow Up Visit	
Severe hypoglycaemic episodes	-
Visit 4 Final Visit	
Severe hypoglycaemic episodes	-

Source Data: Listing 16.2.6; Table: 14.3.2.4
Note:
[1] Percentage was calculated using respective column header count as denominator.
General Note:
[1] All Severe hypoglycaemic episodes were presented as: number of patients (percent of patients) (number of events) (rate per 100 PYE).
[2] Zero frequencies were presented by "- ".

Confirmed Hypoglycaemic Events

Analysis of blood glucose confirmed hypoglycaemic events was based on EAS.

A decrease in confirmed hypoglycaemic events were noted from Visit 1 to subsequent follow up visits with respect to both number of patients and number of events. At Visit 1, 67 (6.7%) patients presented with 176 confirmed hypoglycaemic events. These events were reduced to 28 hypoglycaemic events reported in 12 patients at Visit 2. No confirmed hypoglycaemic event was reported in later visits (Visit 3 & Visit 4).

Table 30 Summary of Confirmed Hypoglycaemic Events - EAS Population (N = 1003)

Visit/ Parameter	Overall (N = 1003)
Visit 1 Baseline Visit	
Confirmed hypoglycaemic events	67(6.7) (176)
Visit 2 Follow Up Visit	
Confirmed hypoglycaemic events	12(1.2) (28) [10.62]
Visit 3 Follow Up Visit	
Confirmed hypoglycaemic events	-
Visit 4 Final Visit	
Confirmed hypoglycaemic events	-

Source Data: Table: 14.2.3, Listing 16.2.6
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Notes:
[1] Confirmed hypoglycaemic events were presented as: number of patients (percent of patients) (number of events) [rate per 100 PYE] in post baseline visits.
[2] Zero frequencies were presented by "- ".

12.2.3 Analysis of adverse events

12.2.3.1 Frequency of Treatment Emergent Adverse Events

A summary of TEAEs for the Safety Population is presented in Section 12.2.1.

12.2.3.2 Adverse Events by Severity

A summary of AEs by Severity for the Safety Population is presented in Section 12.2.1.

12.2.3.3 Adverse Events by Relationship to study Treatment

A summary of AEs by Relationship to study Treatment for the Safety Population is presented in Section 12.2.1.

12.2.3.4 Adverse Events by Action Taken

A summary of AEs by Action Taken for the Safety Population is presented in Section 12.2.2.

12.2.3.5 Adverse Events by Outcome

A summary of AEs by Outcome for the Safety Population is presented in Section 12.2.2.

12.2.4 Listing of adverse events by patient

All AEs by patient are listed in Listing16.2.7.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A total of 2 SAEs were reported in 2 patients. During this study, 2 patients died, both the deaths were found to be unrelated to study drug.

12.3.1 Listing of deaths, other serious adverse events, and other significant adverse events

Listing of death and SAE is provided Appendices 16.2.7.

12.3.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

Not applicable.

12.3.3 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

Not applicable.

12.4 Clinical Laboratory Parameters

The visit wise summary of Laboratory parameters for different variables were presented in Table 31. The mean ± SD (Min: Max) of Total Cholesterol (mg/dL) and triglyceride for each visit were within the Desirable range. No visit wise data on free fatty acid was available. The mean ± SD of Serum Creatinine level was within the normal range at all visits. Visit wise summary of change from Baseline of lab parameters in SAS Population (N = 1029) was presented in (Not included in text).

Table 31 Visit Wise Summary of lab parameters- SAS Population (N = 1029)

Visit/Parameter	Statistic	Overall (N = 1029)
Visit 1		
Total Cholesterol	n	498
	Missing	531
	Mean	173.1
	SD	45.91
	Median	172
	Range (Min.: Max..)	(4.6:358)
High Density Lipoprotein-Cholesterol	n	480
	Missing	549
	Mean	44.6
	SD	12.16
	Median	42.6
	Range (Min.: Max..)	(14.0:94.0)
Low Density Lipoprotein-Cholesterol	n	478
	Missing	551
	Mean	97.9
	SD	37.65
	Median	98.0
	Range (Min.: Max..)	(10.0:213)
Triglyceride	n	494
	Missing	535
	Mean	164.2
	SD	103.79
	Median	140
	Range (Min.: Max..)	(36.5:990)
Free Fatty Acid	n	0
	Missing	1029
	Mean	.
	SD	.
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	n	498
	Missing	531
	Mean	1.6
	SD	7.13
	Median	0.9
	Range (Min.: Max..)	(0.1:143)
Urine albumin	n	43
	Missing	986
	Mean	135.1
	SD	617.64
	Median	26.0
	Range (Min.: Max..)	(0.2:4065)
Visit 2		
Total Cholesterol	n	259
	Missing	736
	Mean	160.9
	SD	36.70
	Median	159
	Range (Min.: Max..)	(87.0:270)
High Density Lipoprotein-Cholesterol	n	249
	Missing	746
	Mean	46.2
	SD	11.07
	Median	45.0
	Range (Min.: Max..)	(24.0:91.0)
Low Density Lipoprotein-Cholesterol	n	249
	Missing	746
	Mean	88.9
	SD	30.97

Visit/Parameter	Statistic	Overall (N = 1029)
	Median	87.0
	Range (Min.: Max..)	(21.1:186)
Triglyceride	n	252
	Missing	743
	Mean	127.2
	SD	46.64
	Median	120
	Range (Min.: Max..)	(46.0:299)
Free Fatty Acid	n	0
	Missing	995
	Mean	.
	SD	.
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	n	234
	Missing	761
	Mean	1.0
	SD	0.71
	Median	0.9
	Range (Min.: Max..)	(0.1:8.0)
Urine albumin	n	12
	Missing	983
	Mean	128.8
	SD	353.24
	Median	27.0
	Range (Min.: Max..)	(2.0:1250)
Visit 3		
Total Cholesterol	n	305
	Missing	681
	Mean	156.0
	SD	34.98
	Median	151
	Range (Min.: Max..)	(93.0:271)
High Density Lipoprotein-Cholesterol	n	282
	Missing	704
	Mean	45.6
	SD	12.33
	Median	42.3
	Range (Min.: Max..)	(20.0:110)
Low Density Lipoprotein-Cholesterol	n	283
	Missing	703
	Mean	82.5
	SD	31.26
	Median	78.0
	Range (Min.: Max..)	(26.0:196)
Triglyceride	n	300
	Missing	686
	Mean	128.9
	SD	48.92
	Median	123
	Range (Min.: Max..)	(32.0:379)
Free Fatty Acid	n	0
	Missing	986
	Mean	.
	SD	.
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	n	284
	Missing	702
	Mean	1.0
	SD	0.58
	Median	0.9
	Range (Min.: Max..)	(0.5:9.0)
Urine albumin	n	9
	Missing	977
	Mean	25.9
	SD	6.09
	Median	26.0
	Range (Min.: Max..)	(15.0:39.0)

Visit/Parameter	Statistic	Overall (N = 1029)
Visit 4		
Total Cholesterol	n	364
	Missing	607
	Mean	148.0
	SD	35.36
	Median	138
	Range (Min.: Max..)	(78.0:270)
High Density Lipoprotein-Cholesterol	n	354
	Missing	617
	Mean	47.2
	SD	14.05
	Median	44.0
	Range (Min.: Max..)	(20.0:99.0)
Low Density Lipoprotein-Cholesterol	n	353
	Missing	618
	Mean	77.7
	SD	29.78
	Median	71.0
	Range (Min.: Max..)	(21.0:200)
Triglyceride	n	352
	Missing	619
	Mean	119.0
	SD	50.97
	Median	110
	Range (Min.: Max..)	(35.0:543)
Free Fatty Acid	n	0
	Missing	971
	Mean	.
	SD	.
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	n	314
	Missing	657
	Mean	1.2
	SD	1.64
	Median	0.8
	Range (Min.: Max..)	(0.1:10.0)
Urine albumin	n	13
	Missing	958
	Mean	17.9
	SD	24.87
	Median	1.2
	Range (Min.: Max..)	(0.4:80.0)

Source Data: Listing 16.2.8; Table: 14.3.6.1.1
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation SAS: safety analysis set.

12.4.1 Listing of individual laboratory measurements by patient (16.2.8) and each abnormal laboratory value (14.3.4)

Not applicable.

12.4.2 Evaluation of each laboratory parameter

The Summary of laboratory parameters were presented in Section 12.4.

12.4.3 Laboratory Values Over Time

The Summary of Change in Laboratory values was presented in Section 14.3. (Table 14.3.6.1.2).

12.4.4 Individual Patient Changes

Not applicable.

12.4.5 Individual Clinically Significant Abnormalities

Not applicable.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

The summary of Body Measurements (Weight, Waist and Hip Circumference) and vital signs (systolic BP, diastolic BP,) across visits is provided in Table 32. The Body Measurements and vital signs of the patients in the SAS population were comparable at Visit 1, Visit 2, Visit 3, and Visit 4 (Table 14.3.4.1)

Visit wise Summary of change in Body Measurements and Vital Signs in SAS Population (N = 1029) was presented in Table 14.3.4.2 (Not included in text)

Table 32 Visit wise Summary of Body Measurements and Vital Signs at - SAS Population (N = 1029)

Visit	Parameter	Statistic/Category, n (%) [1]	Overall (N = 1029)
Visit 1	Weight(kg)	n	1028
		Missing	1
		Mean	73.2
		SD	12.46
		Median	73
		Range (Min.: Max.)	(32:127.5)
	Waist(cm)	n	682
		Missing	347
		Mean	95.2
		SD	11.59
		Median	94
		Range (Min.: Max.)	(58:165)
	Hip(cm)	n	474
		Missing	555
		Mean	98.7
		SD	12.5
		Median	98
		Range (Min.: Max.)	(44:155)
	Systolic Blood Pressure(sitting)(mmHg)	n	1018
		Missing	11
		Mean	130.6
		SD	14.82
		Median	130
		Range (Min.: Max.)	(86:206)
	Diastolic Blood Pressure(sitting)(mmHg)	n	1018
		Missing	11
		Mean	79
		SD	9.02
		Median	80
		Range (Min.: Max.)	(50:119)
Visit 2	Weight(kg)	n	1005
		Missing	3
		Mean	73.4
		SD	12.32
		Median	73
		Range (Min.: Max.)	(32:126)
	Waist(cm)	n	415
		Missing	593
		Mean	94.3
		SD	11.81
		Median	93
		Range (Min.: Max.)	(58:165)
	Hip(cm)	n	381
		Missing	627
		Mean	97.7
		SD	12.69
		Median	97
		Range (Min.: Max.)	(59:167)
	Systolic Blood Pressure(sitting)(mmHg)	n	1000
		Missing	8
		Mean	128.3
		SD	12.06
		Median	130
		Range (Min.: Max.)	(92:189)
	Diastolic Blood Pressure(sitting)(mmHg)	n	1000
		Missing	8
		Mean	79.3
		SD	7.39
		Median	80
		Range (Min.: Max.)	(48:110)
Visit 3	Weight(kg)	n	982
		Missing	8
		Mean	73.3
		SD	12.11
		Median	73
		Range (Min.: Max.)	(32.3:126.4)
	Waist(cm)	n	403
		Missing	587

Visit	Parameter	Statistic/Category, n (%) [1]	Overall (N = 1029)
		Mean	93.7
		SD	12.11
		Median	93
		Range (Min.: Max.)	(41:167)
	Hip(cm)	n	367
		Missing	623
		Mean	96.9
		SD	12.98
		Median	96.5
		Range (Min.: Max.)	(8.9:160)
	Systolic Blood Pressure(sitting)(mmHg)	n	977
		Missing	13
		Mean	127.8
		SD	10.77
		Median	128
		Range (Min.: Max.)	(100:180)
	Diastolic Blood Pressure(sitting)(mmHg)	n	977
		Missing	13
		Mean	79.4
		SD	6.55
		Median	80
		Range (Min.: Max.)	(59:100)
Visit 4	Weight(kg)	n	935
		Missing	41
		Mean	73.5
		SD	12.48
		Median	73
		Range (Min.: Max.)	(5:153)
	Waist(cm)	n	391
		Missing	585
		Mean	93.3
		SD	11.29
		Median	92
		Range (Min.: Max.)	(40:165)
	Hip(cm)		
		n	363
		Missing	613
		Mean	97
		SD	11.55
		Median	97
		Range (Min.: Max.)	(45:137)
	Systolic Blood Pressure(sitting)(mmHg)	n	927
		Missing	49
		Mean	124.8
		SD	9.43
		Median	123
		Range (Min.: Max.)	(96:190)
	Diastolic Blood Pressure(sitting)(mmHg)	n	926
		Missing	50
		Mean	79
		SD	6.63
		Median	80
		Range (Min.: Max.)	(20:100)

Source Data: Listing 16.4.4; Table: 14.3.4.2.
Min: Max: minimum: maximum; N: number of total patients; n: number of patients in a specified criterion; SD: Standard deviation SAS: safety analysis set.

12.5.1 Concomitant Medications

The concomitant medications are summarized in Table 33. The most common concomitant medication in this study were lipid modifying agents (56.1%), followed by agents acting on the renin-angiotensin system (41.4.1%), vitamins (33.7%), antithrombotic agents (12.7%), beta blocking agents (11.8%), thyroid therapy (11.2%), calcium channel blockers (10.2%), and antianemic preparations (9.1%). Further, details are provided in Table 33 below.

Visit wise Summary of DM treatment at each visit in SAS Population (N = 1029) was mentioned in Table 37, respectively.

Visit wise Summary of Antihypertensive Medications and its change during different visits in SAS Population (N = 1029) was mentioned in Table 38 and Table 40, respectively.

Visit wise Summary of lipid-lowering Medications and its change during different visits in SAS Population (N = 1029) was mentioned in Table 39and Table 41 Table 14.3.3.4 (Not included in text) and Table 14.3.3.4.1, respectively.

Table 33 Summary of Concomitant Medication - SAS Population (N = 1029)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
Agents acting on the renin-angiotensin system		426 (41.4)
	Amlodipine besilate, Hydrochlorothiazide, Olmesartan medoxomil	1 (0.1)
	Amlodipine besilate, Perindopril erbumine	1 (0.1)
	Amlodipine besilate, Ramipril	7 (0.7)
	Amlodipine, Hydrochlorothiazide, Telmisartan	1 (0.1)
	Amlodipine, Losartan	1 (0.1)
	Amlodipine, Olmesartan	4 (0.4)
	Amlodipine, Telmisartan	14 (1.4)
	Atorvastatin calcium, Telmisartan	1 (0.1)
	Benazepril hydrochloride	3 (0.3)
	Captopril	3 (0.3)
	Chlortalidone, Cilnidipine, Olmesartan	3 (0.3)
	Chlortalidone, Losartan potassium	1 (0.1)
	Chlortalidone, Olmesartan medoxomil	2 (0.2)
	Chlortalidone, Telmisartan	3 (0.3)
	Cilnidipine, Olmesartan medoxomil	1 (0.1)
	Cilnidipine, Telmisartan	3 (0.3)
	Enalapril	12 (1.2)
	Hydrochlorothiazide, Losartan	3 (0.3)
	Hydrochlorothiazide, Olmesartan	5 (0.5)
	Hydrochlorothiazide, Telmisartan	29 (2.8)
	Levamlodipine besilate, Telmisartan	1 (0.1)
	Losartan	30 (2.9)
	Metoprolol, Olmesartan	1 (0.1)
	Metoprolol, Telmisartan	2 (0.2)
	Olmesartan	44 (4.3)
	Perindopril	1 (0.1)
	Ramipril	51 (5.0)
	Telmisartan	209 (20.3)
	Valsartan	1 (0.1)
Anabolic agents for systemic use		5 (0.5)
	Nandrolone decanoate	5 (0.5)
Analgesics		54 (5.2)
	Acetylsalicylic acid	8 (0.8)
	Ambroxol hydrochloride, Levocetirizine, Paracetamol, Phenylephrine hydrochloride	1 (0.1)
	Cetirizine hydrochloride, Paracetamol, Phenylpropanolamine hydrochloride	1 (0.1)
	Duloxetine	2 (0.2)
	Flunarizine dihydrochloride	1 (0.1)
	Gabapentin	5 (0.5)
	Gabapentin, Nortriptyline	6 (0.6)
	Levomefolic acid, Mecobalamin, Pregabalin, Pyridoxal phosphate, Thioctic acid	1 (0.1)
	Mecobalamin, Pregabalin	8 (0.8)
	Paracetamol	2 (0.2)
	Paracetamol, Tramadol	1 (0.1)
	Pregabalin	20 (1.9)
Anesthetics		1 (0.1)
	Oxetacaine	1 (0.1)
Anti-inflammatory and antirheumatic products		5 (0.5)
	Aceclofenac, Diacerein	2 (0.2)
	Diclofenac deanol	2 (0.2)
	Indomethacin	1 (0.1)
Anti-parkinson drugs		2 (0.2)
	Pramipexole dihydrochloride	1 (0.1)
	Trihexyphenidyl hydrochloride	1 (0.1)
Antianemic preparations		94 (9.1)
	Ascorbic acid, Folic acid, Iron, Mecobalamin, Pyridoxine	4 (0.4)
	Benfotiamine, Biotin, Folic acid, Mecobalamin, Pyridoxine, Thioctic acid	3 (0.3)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
	Benfotiamine, Cobamamide, Folic acid, Mecobalamin, Pyridoxine hydrochloride	3 (0.3)
	Benfotiamine, Folic acid, Inositol, Mecobalamin, Pyridoxine, Thioctic acid	3 (0.3)
	Benfotiamine, Inositol, Mecobalamin, Pyridoxine hydrochloride, Thioctic acid	4 (0.4)
	Benfotiamine, Inositol, Mecobalamin, Thioctic acid	1 (0.1)
	Biotin, Folic acid, Mecobalamin, Pyridoxine, Thioctic acid	3 (0.3)
	Cyanocobalamin	2 (0.2)
	Cyanocobalamin, Ferric ammonium citrate, Glycyrrhiza glabra liquid extract, Liver extract, Nicotinic acid, Pyridoxine, Thiamine, Yeast	2 (0.2)
	Ferric citrate	1 (0.1)
	Ferric hydroxide polymaltose complex	1 (0.1)
	Ferrous ascorbate	3 (0.3)
	Ferrous ascorbate, Folic acid	1 (0.1)
	Ferrous bisglycinate, Folic acid, Mecobalamin, Zinc bis glycinate chelate	1 (0.1)
	Ferrous fumarate	1 (0.1)
	Ferrous sulfate exsiccated, Folic acid	1 (0.1)
	Folic acid	7 (0.7)
	Folic acid, Iron, Zinc	1 (0.1)
	Folic acid, Mecobalamin	1 (0.1)
	Folic acid, Mecobalamin, Proanthocyanidin, Pyridoxine hydrochloride, Thioctic acid	1 (0.1)
	Folic acid, Mecobalamin, Pyridoxine, Thiamine, Thioctic acid	10 (1.0)
	Folic acid, Mecobalamin, Pyridoxine, Thioctic acid	7 (0.7)
	Iron	2 (0.2)
	Mecobalamin	29 (2.8)
	Mecobalamin, Nicotinamide, Pyridoxine	13 (1.3)
	Mecobalamin, Pregabalin	5 (0.5)
	Mecobalamin, Thioctic acid	6 (0.6)
Antibacterials for systemic use		16 (1.6)
	Amoxicillin trihydrate, Bacillus coagulans	1 (0.1)
	Azithromycin	1 (0.1)
	Benzylpenicillin potassium	1 (0.1)
	Cefixime	1 (0.1)
	Cefpodoxime proxetil	1 (0.1)
	Ciprofloxacin	3 (0.3)
	Clarithromycin	1 (0.1)
	Doxycycline	1 (0.1)
	Levofloxacin	1 (0.1)
	Metronidazole	1 (0.1)
	Nitrofurantoin	2 (0.2)
	Ofloxacin	1 (0.1)
	Roxithromycin	1 (0.1)
	Tinidazole	1 (0.1)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents		7 (0.7)
	Attapulgite	4 (0.4)
	Bacillus coagulans	1 (0.1)
	Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium Infantis, Fructooligosaccharides, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus Plantarum, Lactobacillus rhamnosus, Saccharomyces boulardii, Streptococcus thermophilus	1 (0.1)
	Rifaximin	1 (0.1)
Antiepileptics		29 (2.8)
	Carbamazepine	2 (0.2)
	Gabapentin, Mecobalamin, Thioctic acid	6 (0.6)
	Lamotrigine	1 (0.1)
	Lorazepam	1 (0.1)
	Nicotinamide, Pregabalin, Pyridoxine, Thioctic acid	2 (0.2)
	Nortriptyline, Pregabalin	4 (0.4)
	Oxcarbazepine	11 (1.1)
	Pregabalin	1 (0.1)
	Topiramate	1 (0.1)
	Valproate semisodium	1 (0.1)
Antifungals for dermatological use		1 (0.1)
	Terbinafine hydrochloride	1 (0.1)
Antigout preparations		12 (1.2)
	Febuxostat	12 (1.2)
Antihistamines for systemic use		2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
	Ebastine	1 (0.1)
	Levocetirizine dihydrochloride	1 (0.1)
Antiobesity preparations, excluding diet products		1 (0.1)
	Orlistat	1 (0.1)
Antithrombotic agents		131 (12.7)
	Acenocoumarol	1 (0.1)
	Acetylsalicylic acid	91 (8.8)
	Acetylsalicylic acid, Clopidogrel bisulfate	11 (1.1)
	Cilostazol	2 (0.2)
	Clopidogrel	42 (4.1)
	Nattokinase	1 (0.1)
Beta blocking agents		121 (11.8)
	Amlodipine besilate, Bisoprolol fumarate	1 (0.1)
	Amlodipine, Atenolol	1 (0.1)
	Amlodipine, Metoprolol	4 (0.4)
	Amlodipine, Nebivolol	1 (0.1)
	Atenolol	8 (0.8)
	Bisoprolol	4 (0.4)
	Carvedilol	7 (0.7)
	Chlortalidone, Metoprolol	3 (0.3)
	Cilnidipine, Nebivolol	2 (0.2)
	Hydrochlorothiazide, Nebivolol hydrochloride	2 (0.2)
	Metoprolol	65 (6.3)
	Nebivolol	21 (2.0)
	Propranolol	3 (0.3)
Bile and liver therapy		10 (1.0)
	Folic acid, Metadoxine, Ornithine aspartate, Pyridoxine hydrochloride, Silybum marianum	1 (0.1)
	Metadoxine, Ornithine aspartate, Silybum marianum	1 (0.1)
	Ursodeoxycholic acid	9 (0.9)
Calcium channel blockers		105 (10.2)
	Amlodipine	56 (5.4)
	Cilnidipine	42 (4.1)
	Diltiazem hydrochloride	4 (0.4)
	Levamlodipine besilate	1 (0.1)
	Nifedipine	2 (0.2)
Cardiac therapy		18 (1.7)
	Amiodarone hydrochloride	2 (0.2)
	Digoxin	1 (0.1)
	Glyceryl trinitrate	3 (0.3)
	Isosorbide mononitrate	6 (0.6)
	Ivabradine hydrochloride	1 (0.1)
	Levocarnitine	1 (0.1)
	Nicorandil	3 (0.3)
	Trimetazidine	3 (0.3)
	Ubidecarenone	1 (0.1)
Corticosteroids for systemic use		1 (0.1)
	Methylprednisolone	1 (0.1)
Cough and cold preparations		7 (0.7)
	Acetylcysteine, Taurine	6 (0.6)
	Chlorphenamine maleate, Dextromethorphan hydrobromide, Guaifenesin, Phenylephrine hydrochloride	1 (0.1)
Digestives, including enzymes		3 (0.3)
	Carum carvi oil, Cinnamomum verum oil, Diastase, Elettaria cardamomum oil	2 (0.2)
	Pancreatin	1 (0.1)
Diuretics		78 (7.6)
	Chlortalidone	30 (2.9)
	Eplerenone	1 (0.1)
	Furosemide	3 (0.3)
	Furosemide, Spironolactone	1 (0.1)
	Hydrochlorothiazide	21 (2.0)
	Indapamide	6 (0.6)
	Spironolactone	3 (0.3)
	Spironolactone, Torasemide	2 (0.2)
	Torasemide	17 (1.7)
Drugs for acid related disorders		61 (5.9)
	Aluminium hydroxide	1 (0.1)
	Domperidone, Omeprazole	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
	Domperidone, Pantoprazole	7 (0.7)
	Domperidone, Rabeprazole	6 (0.6)
	Esomeprazole	8 (0.8)
	Esomeprazole magnesium, Levosulpiride	1 (0.1)
	Ilaprazole	1 (0.1)
	Ilaprazole, Levosulpiride	1 (0.1)
	Omeprazole	1 (0.1)
	Pantoprazole	18 (1.7)
	Rabeprazole	19 (1.8)
	Ranitidine	2 (0.2)
Drugs for constipation		20 (1.9)
	Lactitol	2 (0.2)
	Macrogol 3350	1 (0.1)
	Magnesium citrate	2 (0.2)
	Magnesium hydroxide, Paraffin	1 (0.1)
	Plantago ovata	11 (1.1)
	Senna alexandrina	1 (0.1)
	Sodium picosulfate	2 (0.2)
Drugs for functional gastrointestinal disorders		24 (2.3)
	Domperidone	12 (1.2)
	Itopride hydrochloride	1 (0.1)
	Levosulpiride	6 (0.6)
	Mosapride	4 (0.4)
	Simeticone	1 (0.1)
Drugs for obstructive airway diseases		6 (0.6)
	Budesonide, Formoterol fumarate	2 (0.2)
	Doxofylline	2 (0.2)
	Etofylline, Theophylline	1 (0.1)
	Ipratropium bromide, Salbutamol	1 (0.1)
	Montelukast sodium	1 (0.1)
Drugs for treatment of bone diseases		1 (0.1)
	Risedronate sodium	1 (0.1)
Drugs for treatment of tuberculosis		1 (0.1)
	Ethambutol dihydrochloride, Isoniazid, Pyrazinamide, Rifampicin	1 (0.1)
General nutrients		2 (0.2)
	Calcium, Carbohydrates nos, Colecalciferol, Iron, Nicotinamide, Proteins nos, Retinol, Riboflavin, Vitamin b1 nos, Zinc	1 (0.1)
	Not Applicable	1 (0.1)
Homeopathic preparations		1 (0.1)
	Homeopathics nos	1 (0.1)
Lipid modifying agents		577 (56.1)
	Acetylsalicylic acid, Atorvastatin	30 (2.9)
	Acetylsalicylic acid, Atorvastatin calcium, Clopidogrel bisulfate	2 (0.2)
	Acetylsalicylic acid, Atorvastatin, Ramipril	8 (0.8)
	Acetylsalicylic acid, Rosuvastatin calcium	3 (0.3)
	Atorvastatin	228 (22.2)
	Atorvastatin, Clopidogrel	5 (0.5)
	Atorvastatin, Colecalciferol	13 (1.3)
	Atorvastatin, Fenofibrate	11 (1.1)
	Atorvastatin, Ramipril	1 (0.1)
	Clopidogrel, Rosuvastatin	1 (0.1)
	Colecalciferol, Rosuvastatin	5 (0.5)
	Docosahexaenoic acid	1 (0.1)
	Docosahexaenoic acid, Eicosapentaenoic acid, Folic acid, Mecobalamin, Pyridoxine hydrochloride, Selenium, Zinc sulfate	1 (0.1)
	Eicosapentaenoic acid	2 (0.2)
	Fenofibrate	5 (0.5)
	Fenofibrate, Rosuvastatin	12 (1.2)
	Omega-3-Acid Ethyl Ester	2 (0.2)
	Pitavastatin	9 (0.9)
	Rosuvastatin	238 (23.1)
	Simvastatin	14 (1.4)
Mineral supplements		63 (6.1)
	Calcitriol, Calcium	2 (0.2)
	Calcitriol, Calcium carbonate, Folic acid, Mecobalamin, Pyridoxine	4 (0.4)
	Calcitriol, Calcium carbonate, Zinc	14 (1.4)
	Calcium	6 (0.6)
	Calcium acetate	1 (0.1)
	Calcium carbonate	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
	Calcium glubionate	1 (0.1)
	Calcium, Colecalciferol	26 (2.5)
	Calcium, Vitamin d nos	7 (0.7)
	Magnesium	1 (0.1)
	Zinc sulfate	1 (0.1)
Other alimentary tract and metabolism products		16 (1.6)
	Acetylcysteine	2 (0.2)
	Amino acids nos	2 (0.2)
	Arginine	2 (0.2)
	Bacteria nos	1 (0.1)
	Levocarnitine	1 (0.1)
	Probiotics nos	2 (0.2)
	Sodium bicarbonate	2 (0.2)
	Thioctic acid	5 (0.5)
	Ubidecarenone	6 (0.6)
Other gynecologicals		16 (1.6)
	Ascorbic acid, Biotin, Boron, Calcium pantothenate, Chromium, Colecalciferol, Copper, Cyanocobalamin, Folic acid, Iodine, Ironpentacarbonyl, Magnesium, Manganese, Nicotinamide, Pyridoxine, Retinol, Riboflavin, Selenium, Soya Isoflavones, Thiamine, Tocopherol, Zinc	16 (1.6)
Other hematological agents		1 (0.1)
	Hyaluronidase	1 (0.1)
Other nervous system drugs		5 (0.5)
	Betahistine	1 (0.1)
	Gabapentin, Mecobalamin	4 (0.4)
Peripheral vasodilators		4 (0.4)
	Cilostazol	3 (0.3)
	Pentoxifylline	1 (0.1)
Psychoanaleptics		17 (1.7)
	Amitriptyline	6 (0.6)
	Clonazepam, Escitalopram	2 (0.2)
	Donepezil hydrochloride	1 (0.1)
	Dosulepin	1 (0.1)
	Fluoxetine hydrochloride	2 (0.2)
	Nortriptyline	4 (0.4)
	Rivastigmine	1 (0.1)
Psycholeptics		14 (1.4)
	Alprazolam	5 (0.5)
	Alprazolam, Melatonin	2 (0.2)
	Clonazepam	1 (0.1)
	Melatonin, Zolpidem	1 (0.1)
	Pregabalin	1 (0.1)
	Risperidone	2 (0.2)
	Trifluoperazine, Trihexyphenidyl	1 (0.1)
	Zolpidem	3 (0.3)
Sex hormones and modulators of the genital system		1 (0.1)
	Norethisterone	1 (0.1)
Thyroid therapy		115 (11.2)
	Levothyroxine	115 (11.2)
Topical products for joint and muscular pain		1 (0.1)
	Diclofenac diethylamine, Linolenic acid, Methyl salicylate	1 (0.1)
Unspecified herbal and traditional medicine		7 (0.7)
	D-mannose, Vaccinium macrocarpon	1 (0.1)
	Ginseng nos	5 (0.5)
	Herbal extract nos	1 (0.1)
Urologicals		8 (0.8)
	Dutasteride	1 (0.1)
	Dutasteride, Tamsulosin	3 (0.3)
	Tamsulosin hydrochloride	4 (0.4)
Vasoprotectives		3 (0.3)
	Bismuth subgallate, Matricaria recutita, Zinc oxide	1 (0.1)
	Diosmin, Hesperidin	2 (0.2)
Vitamins		347 (33.7)
	Alfacalcidol	2 (0.2)
	Amino acids nos, Mecobalamin, Minerals nos, Vitamins nos	1 (0.1)
	Aminobenzoic acid, Biotin, Calcium pantothenate, Choline bitartrate, Cyanocobalamin, Folic acid, Inositol, Nicotinamide, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
	Aminobenzoic acid, Biotin, Calcium pantothenate, Choline chloride, Cyanocobalamin, Folic acid, Nicotinic acid, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride	3 (0.3)
	Ascorbic acid	33 (3.2)
	Ascorbic acid, Calcium pantothenate, Ergocalciferol, Nicotinamide, Pyridoxine hydrochloride, Retinol, Riboflavin, Thiamine hydrochloride	4 (0.4)
	Ascorbic acid, Biotin, Calcium pantothenate, Calcium phosphate dibasic, Chromic chloride, Colecalciferol, Cupric oxide, Cyanocobalamin, Ferrous fumarate, Folic acid, Manganese chloride, Nicotinamidem, Pyridoxine hydrochloride, Retinol, Riboflavin, Sodium selenate, Thiamine mononitrate, Tocopherol, Zinc sulfate	30 (2.9)
	Ascorbic acid, Biotin, Calcium pantothenate, Calcium phosphate dibasic, Chromic chloride, Colecalciferol, Cupric oxide, Ferrous sulfate, Folic acid, Magnesium oxide, Manganese chloride, Mecobalamin, Nicotinamide, Pyridoxine hydrochloride, Retinol acetate, Riboflavin, Sodium molybdate, Thiamine mononitrate, Tocopherol, Zinc sulfate	6 (0.6)
	Ascorbic acid, Biotin, Calcium, Calcium pantothenate, Copper sulfate, Cyanocobalamin, Ergocalciferol, Folic acid, Iron, Magnesium, Manganese sulfate, Nicotinamide, Phosphorus, Pyridoxine hydrochloride, Retinol palmitate, Riboflavin sodium phosphate, Sodium molybdate, Thiamine mononitrate, Tocopheryl acetate, Zinc	4 (0.4)
	Ascorbic acid, Biotin, Calcium, Chromic chloride, Colecalciferol, Cupric oxide, Ferrous sulfate, Folic acid, Magnesiumoxide, Magnesium chloride, Mecobalamin, Nicotinamide, Pyridoxine, Retinol, Riboflavin, SodiumThiamine, Tocopherol, Zinc	10 (1.0)
	Ascorbic acid, Calcium pantothenate, Chromium picolinate, Colecalciferol, Copper sulfate, Folic acid, Magnesium oxide, Manganese sulfate monohydrate, Nicotinamide, Potassium iodide, Pyridoxine hydrochloride, Retinol acetate, Riboflavin, Selenium oxide, Silicon dioxide, Sodium borate, Sodium molybdate, Thiamine mononitrate, Tocopheryl acetate, Zinc sulfate	8 (0.8)
	Ascorbic acid, Calcium pantothenate, Cyanocobalamin, Folic acid, Nicotinamide, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride	26 (2.5)
	Ascorbic acid, Calcium pantothenate, Folic acid, Nicotinamide, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, vitamin b12 nos, Zinc sulfate monohydrate	5 (0.5)
	Ascorbic acid, Calcium phosphate dibasic, Colecalciferol, Copper sulfate, Dexpanthenol, Folic acid, Magnesium oxide, Manganese sulfate monohydrate, Nicotinamide, Potassium iodide, Pyridoxine hydrochloride, Retinol, Riboflavin, Thiamine hydrochloride, Tocopherol, Vitamin b12 nos, Zinc sulfate monohydrate	1 (0.1)
	Ascorbic acid, Cod-liver oil, Colecalciferol, Nicotinamide, Pyridoxine, Retinol, Riboflavin, sodium phosphate, Thiamine	6 (0.6)
	Ascorbic acid, Cyanocobalamin, Folic acid, Nicotinic acid, Pantothenic acid, Pyridoxine, Riboflavin, Thiamine, Zinc	1 (0.1)
	Ascorbic acid, Dexpanthenol, Nicotinamide, Pyridoxine, Riboflavin, Thiamine	1 (0.1)
	Ascorbic acid, Folic acid, Vitamin b nos, Vitamin e nos, Zinc	1 (0.1)
	Ascorbic acid, Lycopene, Omega-3 fatty acids, Tocopherol	3 (0.3)
	Benfotiamine, Chromium picolinate, Inositol, Mecobalamin, Thioctic acid	1 (0.1)
	Benfotiamine, Mecobalamin, Pyridoxine	2 (0.2)
	Betacarotene, Biotin, Chromic chloride, Colecalciferol, Inositol, Lysine hydrochloride, Manganese chloride tetrahydrate, Nicotinamide, Potassium iodide, Pyridoxine, hydrochloride, Sodium molybdate dihydrate, Sodium selenate, Zinc gluconate	42 (4.1)
	Calcium pantothenate, Chromium picolinate, Folic acid, Mecobalamin, Nicotinamide, Pyridoxine hydrochloride, Thiamine hydrochloride, Zinc sulfate	8 (0.8)
	Calcium pantothenate, Ergocalciferol, Nicotinamide, Pyridoxine hydrochloride, Retinol palmitate, Riboflavin, Thiamine hydrochloride	7 (0.7)
	Chromium picolinate, Cyanocobalamin, Folic acid, Lycopene, Nicotinamide, Pyridoxine hydrochloride, Selenium, Zinc sulfate	1 (0.1)
	Chromium picolinate, Cyanocobalamin, Folic acid, Nicotinamide, Pyridoxine hydrochlorid, Selenium, Zinc sulfate	9 (0.9)
	Chromium picolinate, Docosahexaenoic acid, Eicosapentaenoic acid, Folic acid, Lycopene, Mecobalamin, Policosanol, Pyridoxine hydrochloride, Selenium oxide, Thioctic acid, Tocopherol, Zinc Ascorbate	2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [2]	Overall (N = 1029)
	Colecalciferol	124 (12.1)
	Colecalciferol, Folic acid, Mecobalamin, Pyridoxine, Thioctic acid	30 (2.9)
	Cyanocobalamin, Pyridoxine hydrochloride, Thiamine disulfide	6 (0.6)
	Folic acid, Lycopene, Minerals nos, Vitamins nos, Xantofyl	2 (0.2)
	Folic acid, Nicotinamide	2 (0.2)
	Herbal nos, Vitamins nos	1 (0.1)
	Minerals nos, Vitamins nos	43 (4.2)
	Pyridoxine	1 (0.1)
	Vitamin b complex	3 (0.3)
	Vitamin d nos	1 (0.1)
	Vitamins nos	46 (4.5)

Source Data: Listing 16.4.2; Table: 14.3.3.1
Note:
[1] Percentages was calculated using corresponding column header as denominator.
General Note:
[1] Medications was coded using WHO Drug Dictionary version of 1st March 2017 or later. Patients may have taken more than one medication within a drug class or preferred name. Patients are only counted once for each drug class or preferred name summary.

12.6 Safety Conclusions

Overall, Ryzodeg™ was well tolerated. A total of 30 AEs in 23 patients were observed during the study. Majority of AEs were mild and unlikely related to study drug. There were only 2 SAEs reported in this study. Both SAEs were unlikely related to the study drug as study drug was not given to patients prior to onset of the study of SAE. Both SAEs had fatal outcomes. Majority of AEs were recovered/resolved during the study period. No episode of severe hypoglycaemia was observed during the study after baseline also there is reduction in BG confirmed hypoglycaemic events.

13 DISCUSSION AND OVERALL CONCLUSIONS

This multicentre, prospective, open-label, single-arm, non-interventional PMS/PASS study demonstrates the efficacy and tolerability of insulin co-formulation IDeg/IAsp (RyzodegTM) in real world. The study was conducted in accordance to the regulatory authority's requirement. Patients with DM requiring insulin therapy and qualified for starting RyzodegTM were included in this study. In this real-world clinical practice, the safety and efficacy was assessed in patients who started or switched to IDeg/IAsp, mostly from another conventional anti-diabetic medication including OADs and different insulins.

The efficacy of IDeg/IAsp was previously explored in several phases II and III studies. The studies demonstrated that our study drug have comparable glycaemic control with reduction in events hypoglycaemia with conventional basal insulins (11, 12). In a study of Niskanen the IDeg/IAsp has provided comparable overall glycaemic control with lower risk of hypoglycaemia (13). In another 26 weeks phase III study on Japanese population of T2DM patients once daily IDeg/IAsp was found to be superior in lowering glycaemic index and was associated with lowering of hypoglycaemic events in comparison to conventional basal insulin (insulin glargine) (14). A study of 26-week, treat-to-target, open-label involving 394 T2DM patients reported that twice-daily IDeg/IAsp provided effective reduction in HbA1c comparable with basal insulin, with reductions in FPG levels. Hypoglycaemia is the most commonly observed adverse reaction in patients using insulin. Rates of confirmed hypoglycaemia and nocturnal-confirmed hypoglycaemia rates were significantly reduced ($p<0.0001$) (15). In line with previously studies, in this study HbA1c was reduced by -1.7 mmol/mol from baseline in a year. The reduction in patients previously treated with OAD and Insulin was comparable. There was a significant decline at Visit 4 ($p < 0.0001$) in FPG was observed in this study by 50.3 ± 67.90 from basline, in conjunction with significant reduction ($P<0.0001$) in Post breakfast and Post lunch glucose by 81.6 ± 85.31 and 63.1 ± 73.13 mg/dL from baseline.

Analysing reasons for switching patients to IDeg/IAsp demonstrate that majority patients had unsatisfactory HbA1c, FBG, and PPG at baseline. In some cases, patients were switched due to side-effect from previous therapies and risk of hypoglycaemia. Previous studies suggest that patients switched to IDeg/IAsp from multiple daily injection of basal insulin to reduce the drug burden (16).

The safety of IDeg/IAsp in patients with type 1 or type 2 diabetes was evaluated in 5 treat-to-target clinical studies lasting 6 to 12 months. Adverse reactions occurring in ≥5% of patients with type 1 diabetes included nasopharyngitis (24.6%), headache (9.7%), upper respiratory tract infection (9.1%), and influenza (6.9%). Adverse reactions occurring in ≥5% of patients with type 2 diabetes included nasopharyngitis (11.1%), upper respiratory tract infection (5.7%), and headache (5.6%) (17). In our study, AEs were associated with General disorders and administration site conditions, Metabolism and nutrition disorders, Infections and infestations, Nervous system disorders, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Eye disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders and vascular disorder. In this study 2 SAEs were reported in two patients and had fatal outcome however both SAEs were found to be unrelated to study Drug.

In conclusion, IDeg/IAsp was shown to be a promising treatment option for initiating insulin therapy in subjects with DM inadequately controlled with OADs and other Insulin. In this study IDeg/IAsp demonstrate the long-term safety profile for 1 year in routine clinical practice. IDeg/IAsp was safe and well tolerated and provided overall glycaemic control at a lower rate of confirmed hypoglycaemia. It is possible that these

advantages with IDeg/IAsp, in-particular, efficacious lowering of HbA1c, FPG and PPG values together with lower rates of hypoglycaemic events could encourage physicians and patients to titrate insulin regimens more rigorously to reach glycaemic target values.

14 TABLES, FIGURES, AND GRAPHS REFERRED BUT NOT INCLUDED IN THE TEXT

The following Tables were referred but not included in the text.

14.1 Demographic Data

Not applicable

14.1.1 Patient Disposition

Not applicable

14.2 Efficacy Data

Not applicable

14.3 Safety Data

Table 34 Summary of adverse events by System Organ Class and Preferred Term by relation to a technical complaint - SAS Population (N = 1029)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Technical complaint	Overall (N = 1029)
Total number of patients with at least one adverse 1029event		23 (2.2)
Total number of adverse events, n		30
Cardiac disorders		1 (0.1) [1]
Cardiogenic shock		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Gastrointestinal disorders		2 (0.2) [2]
Constipation		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Diarrhoea		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
General disorders and administration site conditions		8 (0.8) [9]
Death		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Fatigue		2 (0.2) [2] (0.0006)
	Yes	-
	No	1 (0.1) [2]
Gait disturbance		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Pyrexia		5 (0.5) [5] (0.0014)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Technical complaint	Overall (N = 1029)
	Yes	-
	No	1 (0.1) [5]
Infections and infestations		3 (0.3) [3]
Skin bacterial infection		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Upper respiratory tract infection		2 (0.2) [2] (0.0006)
	Yes	-
	No	1 (0.1) [2]
Injury, poisoning and procedural complications		1 (0.1) [1]
Road traffic accident		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Investigations		1 (0.1) [1]
Weight increased		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Metabolism and nutrition disorders		3 (0.3) [4]
Hyperglycaemia		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Hypoglycaemia		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Increased appetite		1 (0.1) [2] (0.0006)
	Yes	-
	No	1 (0.1) [2]
Musculoskeletal and connective tissue disorders		2 (0.2) [2]
Muscle spasms		2 (0.2) [2] (0.0006)
	Yes	-
	No	1 (0.1) [2]
Nervous system disorders		2 (0.2) [2]
Dizziness		2 (0.2) [2] (0.0006)
	Yes	-
	No	1 (0.1) [2]
Renal and urinary disorders		1 (0.1) [1]
Urinary incontinence		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Respiratory, thoracic and mediastinal disorders		1 (0.1) [1]
Dyspnoea exertional		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Skin and subcutaneous tissue disorders		1 (0.1) [1]
Swelling face		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]
Vascular disorders		2 (0.2) [2]
Accelerated hypertension		1 (0.1) [1] (0.0003)

System Organ Class (SOC)/ Preferred Term, n (%)) [1]	Technical complaint	Overall (N = 1029)
	Yes	-
	No	1 (0.1) [1]
Hypertension		1 (0.1) [1] (0.0003)
	Yes	-
	No	1 (0.1) [1]

Source Data: Listing 16.2.7; Table 14.3.1.7
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Adverse events were coded using MedDRA version 20.0 or later.
[2] All Adverse events except preferred terms were presented as: number of patients (percent of patients) (number of events). Preferred Terms were presented as number of patients (percent of patients) (number of events) (rate per 100 PYE).
[3] Patients may have reported more than one event per system organ class or preferred term. Patients were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "- ".

Table 35 Visit Wise Summary of change from Baseline of lab parameters - SAS Population (N = 1029)

Visit/Parameter	Statistic	Overall (N = 1029)
Visit 2		
Total Cholesterol	N	232
	Missing	763
	Mean	-9.5
	SD	37.57
	Median	-6.9
	Range (Min.: Max..)	(-144:188)
High Density Lipoprotein-Cholesterol	N	225
	Missing	770
	Mean	0.2
	SD	10.45
	Median	-1.0
	Range (Min.: Max..)	(-22:55.0)
Low Density Lipoprotein-Cholesterol	N	225
	Missing	770
	Mean	-7.5
	SD	32.43
	Median	-4.2
	Range (Min.: Max..)	(-110:101)
Triglyceride	N	226
	Missing	769
	Mean	-17.2
	SD	62.31
	Median	-7.0
	Range (Min.: Max..)	(-509:152)
Free Fatty Acid	N	0
	Missing	995
	Mean	.
	SD	.

Visit/Parameter	Statistic	Overall (N = 1029)
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	N	210
	Missing	785
	Mean	0.0
	SD	0.71
	Median	0.0
	Range (Min.: Max..)	(-1.9:7.1)
Urine albumin	N	10
	Missing	985
	Mean	0.3
	SD	10.75
	Median	-1.7
	Range (Min.: Max..)	(-6.0:30.0)
Visit 3		
Total Cholesterol	N	270
	Missing	716
	Mean	-20.0
	SD	36.64
	Median	-10
	Range (Min.: Max..)	(-156:64.0)
High Density Lipoprotein-Cholesterol	N	266
	Missing	720
	Mean	-0.5
	SD	10.56
	Median	-2.0
	Range (Min.: Max..)	(-25:50.0)
Low Density Lipoprotein-Cholesterol	N	265
	Missing	721
	Mean	-14.9
	SD	33.67
	Median	-5.6
	Range (Min.: Max..)	(-130:72.0)
Triglyceride	N	266
	Missing	720
	Mean	-22.6
	SD	56.19
	Median	-8.7
	Range (Min.: Max..)	(-267:143)
Free Fatty Acid	N	0
	Missing	986
	Mean	.
	SD	.
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	N	239
	Missing	747
	Mean	-0.5

Visit/Parameter	Statistic	Overall (N = 1029)
	SD	4.63
	Median	0.0
	Range (Min.: Max..)	(-69:8.0)
Urine albumin	N	7
	Missing	979
	Mean	-4.1
	SD	1.86
	Median	-3.0
	Range (Min.: Max..)	(-7.0: -2.0)
Visit 4		
Total Cholesterol	N	319
	Missing	652
	Mean	-28.4
	SD	39.36
	Median	-20
	Range (Min.: Max..)	(-151:77.0)
High Density Lipoprotein-Cholesterol	N	303
	Missing	668
	Mean	-0.4
	SD	14.45
	Median	-1.0
	Range (Min.: Max..)	(-50:55.0)
Low Density Lipoprotein-Cholesterol	N	303
	Missing	668
	Mean	-18.1
	SD	37.48
	Median	-7.3
	Range (Min.: Max..)	(-147:102)
Triglyceride	N	309
	Missing	662
	Mean	-35.1
	SD	69.41
	Median	-21
	Range (Min.: Max..)	(-601:113)
Free Fatty Acid	N	0
	Missing	971
	Mean	.
	SD	.
	Median	.
	Range (Min.: Max..)	(.:.)
Serum creatinine	N	258
	Missing	713
	Mean	0.1
	SD	1.56
	Median	-0.1
	Range (Min.: Max..)	(-7.1:8.3)
Urine albumin	N	3
	Missing	968
	Mean	-54.9

Visit/Parameter	Statistic	Overall (N = 1029)
	SD	85.97
	Median	-11
	Range (Min.: Max..)	(-154:0.2)

Source Data: Listing 16.2.8; Table 14.3.6.2.1
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator

Table 36 Visit wise Summary of change in Body Measurements and Vital Signs- SAS Population (N = 1029)

Visit	Parameter	Statistic/Category, n (%)) [1]	Overall (N = 1029)
Visit 2			
	Weight(kg)		
		N	1005
		Missing	3
		Mean	0.1
		SD	2.53
		Median	0
		Range (Min.: Max.)	(-20.8:37.8)
	Waist(cm)		
		N	411
		Missing	597
		Mean	-0.2
		SD	2.65
		Median	0
		Range (Min.: Max.)	(-20.0:12.0)
	Hip(cm)		
		N	374
		Missing	634
		Mean	0.2
		SD	5.15
		Median	0
		Range (Min.: Max.)	(-15.0:61.0)
	Systolic Blood Pressure(sitting)(mmHg)		
		N	989
		Missing	19
		Mean	-2.1
		SD	12.22
		Median	0
		Range (Min.: Max.)	(-60.0:64.0)
	Diastolic Blood Pressure(sitting)(mmHg)		
		N	989
		Missing	19
		Mean	0.3
		SD	8.39
		Median	0
		Range (Min.: Max.)	(-30.0:48.0)

Visit	Parameter	Statistic/Category, n (%)) [1]	Overall (N = 1029)
Visit 3			
	Weight(kg)		
		N	982
		Missing	8
		Mean	0.2
		SD	2.78
		Median	0.2
		Range (Min.: Max.)	(-19.5:29.7)
	Waist(cm)		
		N	398
		Missing	592
		Mean	-0.3
		SD	6.54
		Median	0
		Range (Min.: Max.)	(-67.0:65.0)
	Hip(cm)		
		N	359
		Missing	631
		Mean	-0.5
		SD	8.11
		Median	0
		Range (Min.: Max.)	(-79.1:51.0)
	Systolic Blood Pressure(sitting)(mmHg)		
		N	966
		Missing	24
		Mean	-2.6
		SD	14.21
		Median	0
		Range (Min.: Max.)	(-64.0:52.0)
	Diastolic Blood Pressure(sitting)(mmHg)		
		N	966
		Missing	24
		Mean	0.4
		SD	9.15
		Median	0
		Range (Min.: Max.)	(-31.0:38.0)

Visit	Parameter	Statistic/Category, n (%)) [1]	Overall (N = 1029)
Visit 4			
	Weight(kg)		
		N	935
		Missing	41
		Mean	0.3
		SD	4.91
		Median	0.1
		Range (Min.: Max.)	(-63.3:88.0)
	Waist(cm)		
		N	386
		Missing	590
		Mean	-0.7
		SD	5.28
		Median	0
		Range (Min.: Max.)	(-71.0:17.0)
	Hip(cm)		
		N	354
		Missing	622
		Mean	-0.7
		SD	6.78
		Median	0
		Range (Min.: Max.)	(-76.0:53.0)
	Systolic Blood Pressure(sitting)(mmHg)		
		N	916
		Missing	60
		Mean	-5.5
		SD	14.34
		Median	-6
		Range (Min.: Max.)	(-66.0:50.0)
	Diastolic Blood Pressure(sitting)(mmHg)		
		N	915
		Missing	61
		Mean	0.2
		SD	9.33
		Median	0
		Range (Min.: Max.)	(-70.0:32.0)
(**Source Data:** Listing 16.4.4; Table 14.3.4.2			

Table 37 Summary of Diabetes Mellitus Treatment at each visit -SAS population (N = 1029)

Visit	Medication	Overall (N = 1029)
Visit 1 Baseline Visit		
	Metformin	766(74.4)
	Sulphonylureas	599(58.2)
	Alpha-Glucosidaseinhibitors	203(19.7)
	Metiglinides	2(0.2)
	Thiazolidinediones	86(8.4)
	DDP-IV	363(35.3)
	Premix Insulin	135(13.1)
	Basal Insulin	124(12.1)
	Bolus Insulin	95(9.2)
	GLP-1	5(0.5)
	Others	21(2.0)
Visit 2 Follow Up Visit		
	Metformin	722(70.2)
	Sulphonylureas	472(45.9)
	Alpha-Glucosidaseinhibitors	157(15.3)
	Metiglinides	6(0.6)
	Thiazolidinediones	62(6.0)
	DDP-IV	314(30.5)
	Premix Insulin	531(51.6)
	Bolus Insulin	158(15.4)
	GLP-1	10(1.0)
	Others	37(3.6)
Visit 3 Follow Up Visit		
	Metformin	708(68.8)
	Sulphonylureas	462(44.9)
	Alpha-Glucosidaseinhibitors	161(15.6)
	Metiglinides	6(0.6)
	Thiazolidinediones	57(5.5)
	DDP-IV	294(28.6)
	Premix Insulin	537(52.2)
	Bolus Insulin	160(15.5)
	GLP-1	11(1.1)
	Others	40(3.9)

Visit	Medication	Overall (N = 1029)
Visit 4 Final Visit		
	Metformin	684(66.5)
	Sulphonylureas	456(44.3)
	Alpha-Glucosidaseinhibitors	159(15.5)
	Metiglinides	6(0.6)
	Thiazolidinediones	58(5.6)
	DDP-IV	283(27.5)
	Premix Insulin	536(52.1)
	Bolus Insulin	162(15.7)
	GLP-1	5(0.5)
	Others	63(6.1)

Source Data: Listing 16.4.2.1; Table 14.3.3.2
[1] Percentages were calculated by taking respective column header count as denominator.

Table 38 Visit wise Summary of Antihypertensive Medications - SAS Population (N = 1029)

VISIT	Parameter	Category, n (%)) [1]	Overall (N = 1029)
Visit 1 Baseline Visit	Antihypertensive medications are being taken by the patient	Yes	583 (56.7)
		No	446 (43.3)
	Antihypertensive medications	ACE inhibitors	147 (14.3)
		Angiotensin 2 receptor antagonists	341 (33.1)
		Beta blockers	134 (13.0)
		Diuretics	122 (11.9)
		Calcium channel blockers	130 (12.6)
		Other	24 (2.3)
Visit 2 Follow Up Visit	Antihypertensive medications are being taken by the patient	Yes	405 (39.4)
		No	602 (58.5)
	Antihypertensive medications	ACE inhibitors	113 (11.0)
		Angiotensin 2 receptor antagonists	210 (20.4)
		Beta blockers	92 (8.9)
		Diuretics	91 (8.8)
		Calcium channel blockers	79 (7.7)
		Other	18 (1.7)
Visit 3 Follow Up Visit	Antihypertensive medications are being taken by the patient	Yes	392 (38.1)
		No	593 (57.6)
	Antihypertensive medications	ACE inhibitors	118 (11.5)
		Angiotensin 2 receptor antagonists	197 (19.1)
		Beta blockers	87 (8.5)
		Diuretics	83 (8.1)
		Calcium channel blockers	72 (7.0)
		Other	16 (1.6)

VISIT	Parameter	Category, n (%)) [1]	Overall (N = 1029)
Visit 4 Final Visit	Antihypertensive medications are being taken by the patient	Yes	323 (31.4)
		No	648 (63.0)
	Antihypertensive medications	ACE inhibitors	99 (9.6)
		Angiotensin 2 receptor antagonists	164 (15.9)
		Beta blockers	62 (6.0)
		Diuretics	76 (7.4)
		Calcium channel blockers	51 (5.0)
		Other	14 (1.4)

Source Data: Listing 16.4.3; Table 14.3.3.3
Note:
[1] Percentages were calculated by taking count of corresponding column header group as denominator.

Table 39 Visit wise Summary of lipid-lowering Medications - SAS Population (N = 1029)

Visit	Drug Class, n (%)) [1]	Category	Overall (N = 1029)
Visit 1 Baseline Visit	Lipid-lowering medications are being taken by the patient	Yes	648 (63.0)
		No	381 (37.0)
	Lipid-lowering medications	Statins	634 (61.6)
		Fibrates	25 (2.4)
		Other	15 (1.5)
Visit 2 Follow Up Visit	Lipid-lowering medications are being taken by the patient	Yes	426 (41.4)
		No	582 (56.6)
	Lipid-lowering medications	Statins	416 (40.4)
		Fibrates	17 (1.7)
		Other	10 (1.0)
Visit 3 Follow Up Visit	Lipid-lowering medications are being taken by the patient	Yes	418 (40.6)
		No	571 (55.5)
	Lipid-lowering medications	Statins	409 (39.7)
		Fibrates	17 (1.7)
		Other	14 (1.4)
Visit 4 Final Visit	Lipid-lowering medications are being taken by the patient	Yes	360 (35.0)
		No	615 (59.8)
	Lipid-lowering medications	Statins	353 (34.3)
		Fibrates	16 (1.6)
		Other	11 (1.1)

Source Data: Listing 16.4.3; Table 14.3.3.4
Note:
[1] Percentage was calculated by taking count of corresponding column header group as denominator.

Table 40 Shift Table to show changes in different visits in Antihypertensive medications - SAS Population (N = 1029)

			Visit 2		Visit 3		Visit 4	
	Medication		**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
	ACE inhibitors	Yes	108(73.5)	30(20.4)	15(10.2)	107(72.8)	10(6.8)	106(72.1)
		No	5(0.6)	865(98.0)	104(11.8)	763(86.4)	89(10.1)	770(87.2)
	Angiotensin 2 receptor antagonists	Yes	198(58.1)	137(40.2)	23(6.7)	99(29.0)	18(5.3)	98(28.7)
		No	13(1.9)	660(95.8)	174(25.3)	693(100.6)	146(21.2)	713(103.5)
Baseline	Beta blockers	Yes	84(62.7)	45(33.6)	27(20.1)	95(70.9)	14(10.4)	102(76.1)
		No	8(0.9)	871(97.2)	60(6.7)	807(90.1)	49(5.5)	810(90.4)
	Diuretics	Yes	86(70.5)	34(27.9)	18(14.8)	104(85.2)	13(10.7)	103(84.4)
		No	5(0.6)	883(97.2)	66(7.3)	801(88.2)	63(6.9)	796(87.7)
	Calcium channel blockers	Yes	75(57.7)	50(38.5)	71(54.6)	51(39.2)	45(34.6)	71(54.6)
		No	5(0.6)	878(97.6)	3(0.3)	864(96.0)	6(0.7)	853(94.8)
Source: Table 14.3.3.3.1								

Table 41 Shift Table to show changes in different visits in lipid-lowering medications - SAS Population (N = 1029)

n (%)			**Visit 2**		**Visit 3**		**Visit**	
	Medication		**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
	Statins	Yes	407 (64.2)	211 (33.3)	10 (1.6)	14 (2.2)	9 (1.4)	14 (2.2)
Baseline		No	9 (2.3)	381 (96.5)	399 (101.0)	566 (143.3)	344 (87.1)	608 (153.9)
	Fibrates	Yes	17 (68.0)	8 (32.0)	16 (64.0)	8 (32.0)	13 (52.0)	10 (40.0)
		No	-	983 (97.9)	1 (0.1)	964 (96.0)	3 (0.3)	949 (94.5)
Source: Table 14.3.3.4.1								

15 REFERENCE LIST

1. IDF. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: 2017 [cited 2018 11 January 2018]. Available from: http://www.diabetesatlas.org.
2. da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, Guariguata L, Seuring T, Zhang P, et al. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. Diabetes research and clinical practice. 2016;117:48-54.
3. Petznick A. Insulin management of type 2 diabetes mellitus. American family physician. 2011;84(2):183-90.
4. Devries JH, Nattrass M, Pieber TR. Refining basal insulin therapy: what have we learned in the age of analogues? Diabetes/metabolism research and reviews. 2007;23(6):441-54.
5. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes, obesity & metabolism. 2007;9(5):648-59.
6. Tibaldi JM. Evolution of insulin: from human to analog. The American journal of medicine. 2014;127(10 Suppl):S25-38.
7. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, et al. Insulin Degludec Versus Insulin Glargine in Insulin-Naive Patients With Type 2 Diabetes. A 1-year, randomized, treat-to-target trial (BEGIN Once Long). 2012;35(12):2464-71.
8. Garber M, Yosef N, Goren A, Raychowdhury R, Thielke A, Guttman M, et al. A high throughput Chromatin ImmunoPrecipitation approach reveals principles of dynamic gene regulation in mammals. Molecular cell. 2012;47(5).
9. Vora J, Christensen T, Rana A, Bain SC. Insulin Degludec Versus Insulin Glargine in Type 1 and Type 2 Diabetes Mellitus: A Meta-Analysis of Endpoints in Phase 3a Trials. Diabetes Therapy. 2014;5(2):435-46.
10. o Nordisk (2013) Ryzodeg (70% Insulin Degludec/30% Insulin Aspart) Summary of Product Characteristics EPAR. 2013 [Available from: http://www.ema.europa.eu/ema/.
11. Heise T, Nosek L, Roepstorff C, Chenji S, Klein O, Haahr H. Distinct Prandial and Basal Glucose-Lowering Effects of Insulin Degludec/Insulin Aspart (IDegAsp) at Steady State in Subjects with Type 1 Diabetes Mellitus. Diabetes Therapy. 2014;5(1):255-65.
12. Hirsch IB, Bode B, Courreges JP, Dykiel P, Franek E, Hermansen K, et al. Insulin Degludec/Insulin Aspart Administered Once Daily at Any Meal, With Insulin Aspart at Other Meals Versus a Standard Basal-Bolus Regimen in Patients With Type 1 Diabetes: A 26-week, phase 3, randomized, open-label, treat-to-target trial. Diabetes Care. 2012;35(11):2174-81.
13. Niskanen L, Leiter LA, Franek E, Weng J, Damci T, Muñoz-Torres M, et al. Comparison of a soluble co-formulation of insulin degludec/insulin aspart vs biphasic insulin aspart 30 in type 2 diabetes: a randomised trial. European Journal of Endocrinology. 2012;167(2):287-94.
14. Onishi Y, Ono Y, Rabol R, Endahl L, Nakamura S. Superior glycaemic control with once-daily insulin degludec/insulin aspart versus insulin glargine in Japanese adults with type 2 diabetes inadequately controlled with oral drugs: a randomized, controlled phase 3 trial. Diabetes, obesity & metabolism. 2013;15(9):826-32.
15. Franek E, Haluzik M, Canecki-Varzic S, Sargin M, Macura S, Zacho J, et al. PO231 IDEGASP PROVIDES SUPERIOR FPG CONTROL AND REDUCED HYPOGLYCEMIA VS BIASP 30 IN INSULIN-NAIVE ADULTS WITH TYPE 2 DIABETES: A RANDOMIZED PHASE 3 TRIAL. Diabetes research and clinical practice.106:S166-S7.

16. Raedler LA. Tresiba (Insulin Degludec Injection) and Ryzodeg 70/30 (Insulin Degludec and Insulin Aspart Injection): Two New Insulin Analogs for Glycemic Control in Diabetes Mellitus. American Health & Drug Benefits. 2016;9(Spec Feature):144-8.
17. Kelly FJ, Fussell JC. Air pollution and public health: emerging hazards and improved understanding of risk. Environmental Geochemistry and Health. 2015;37(4):631-49.

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form(s)

16.1.3 List of IEC's or IRB's (plus the name of committee chair if required by the regulatory authority) and representative written information for patient and sample consent forms

16.1.4 List of description if investigators and other Important Participants in the study (including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5 Signature of Principal or Coordinating Investigator(s) or Sponsor's responsible medical officer, depending on the regulatory authority's requirement

16.1.6 Listing of patients receiving test drug(s) / investigational product(s) from specific batches, where more than one batch was used

16.1.7 Randomization Schemes and Codes (Patient Identification and treatment assigned)

16.1.8 Audit certificates (if available)

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardization methods and

16.1.11 Quality Assurance Procedures If Used

16.1.12 Important publications referenced in the report

16.2 Patient Data Listings

16.2.1 Discontinued Patients

16.2.2 Patient Data Listings

16.2.3 Patients Excluded from the Efficacy Analysis

16.2.4 Demographic Data

16.2.5 Compliance and/or drug concentration data (if available)

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each patient)

16.2.8 Listing of individual laboratory measurements by patient, when required by Regulatory authorities

16.3 Case Report Form

16.3.1 CRFs for CRF's for deaths, other serious adverse events, and withdrawals for Adverse events

16.3.2 Other CRF's Submitted

16.4 Individual Patient Data Listings (US Archival Listing)