CLINICAL STUDY REPORT

1 TITLE PAGE

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

Protocol NN1250-4129

Investigational Product:	Tresiba® (Insulin degludec)
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:	NN 1250-4129
Phase of Development:	Post Marketing Surveillance (PMS)/ Post Authorization Safety Study (PASS)
Study Initiation Date:	24 JULY 2015.
Study Completion Date:	05 APR 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

CLINICAL STUDY REPORT PREPARED AND APPROVED BY

I have prepared or read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.	
Clinical study report prepared by:	
Medical Writing Responsible Person:	**Name:** [redacted] **Address**: [redacted] **Date and signature:**
Clinical study report approved by:	
Novo Nordisk India Private Ltd.	**Name**: Dr. [redacted] **Address:** Novo Nordisk India Private Ltd. Plot No.32, 47 - 50, EPIP Area, Whitefield, Bangalore - 560 066 India **Date and signature:**
Biostatistician:	**Name**: [redacted] **Address:** [redacted] **Date and signature**:

2 SYNOPSIS

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

Title and Number of Study:

A multi-centre, prospective, open-label, single-arm, non-interventional, post marketing surveillance (PMS) study of Tresiba® (insulin degludec) to evaluate long term safety and efficacy in patients with diabetes mellitus in routine clinical practice in India (Study Number: NN 1250-4129).

Investigators:

The list of investigators is presented in Section 6.1 and Appendix 16.1.4.

Study Sites:

The Study was conducted at 42 sites in India.

Publications:

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

Phase of Development:

Post Marketing Study (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 (Tresiba®) in insulin requiring patients with diabetes mellitus, initiating treatment with Tresiba® 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 Tresiba®

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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 Tresiba® in patients with diabetes mellitus (DM) requiring insulin therapy under normal clinical practice conditions in India. A total of 1057 patients were enrolled to investigate safety of Tresiba®.

Based on the clinical judgement of treating physician, Patients were started with Tresiba® in their routine clinical practice. The assignment of the patients to Tresiba® was decided in advance in the protocol. The patients were decided to be prescribed with Tresiba®, by physicians before the enrollment in the Study, based on requirement and clinical judgment in diabetes management.

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

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 and PASS was initiated), most recent glycated hemoglobin (HbA1c) (if available), most recent fasting plasma glucose/fasting blood sugar (FPG/FBG) value (if available) and Study treatment was initiated
- *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),

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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:

A total of 1057 patients who met the eligibility criteria were recruited at 42 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 activity 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, severe hypoglycaemia before the start of Tresiba® therapy) can be used for baseline data.
2. Patients with insulin requiring diabetes mellitus and who is scheduled to start treatment with Tresiba® based on the clinical judgment of their treating physician.

Exclusion Criteria:

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

1. Known or suspected allergy to Tresiba®, 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 are or have previously been on Tresiba® therapy
5. Patients who are participating in other studies or clinical trials
6. Patients who are pregnant, breast feeding or have the intention of becoming pregnant within the following 12 months

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Duration of Treatment:

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 Tresiba® based on clinical judgment by their treating physician were treated with Tresiba® (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:

- SAEs by preferred term
- SADRs by preferred term
- ADRs by preferred term
- Severe hypoglycaemia

Secondary Efficacy Endpoints:

The secondary efficacy endpoints of the Study was:

- Change from baseline in HbAlc after 1 year of treatment
- Change from baseline in FPG after 1 year of treatment

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- Incidence of confirmed hypoglycaemia during 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 subjects who had receive at least one dose of Tresiba® during the PMS/PASS Study. The descriptive analysis of AEs and demographic data was based on the SAS
- **Efficacy Analysis Set (EAS) population**: The EAS population was defined as all subjects 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 Tresiba®. A Sample size of 1000 patients, assuming 20% dropouts who had been exposed to insulin degludec (IDeg) 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:

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 trial values and change from baseline values were presented. Missing values were subject to last observation carried forward (LOCF).

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.

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Efficacy Endpoint Analysis:

Descriptive statistics was used to evaluate the efficacy aspect of Tresiba® for HbA1c, FPG and confirmed hypoglycaemic events. Baseline, end of trial 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. Missing values were subject LOCF. Also, paired-t test was used to evaluate the changes in HbA1c, FPG and confirmed hypoglycaemic events by visit wise within the treatment. Test was carried out as two-sided on a 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 subjects 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 subjects with event, number of events, incidence rate and rate per 100PYE and subject 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 more males (60.1%), compared to females (39.9%)
- Majority of the patients (99.5%) had T2DM as compared to T1DM (0.5%)
- The mean ± SD (years) of DM duration was higher in patients with T1DM (22.2 ± 21.90) than T2DM (10.1 ± 7.37)
- The prevalence of Peripheral Neuropathy was 19.2% and Coronary Heart Disease was 8.5% in the Study Cohort
- Metformin was the most commonly prescribed medication at each visit, followed by sulphonylureas
- At baseline 15.5%, 14.3% and 11.2% patients were on basal, bolus and premix insulin, respectively
- Bolus insulin was maintained in more than 15% of patients throughout the Study

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period (18.7% patients at visit 2 & 3; 17.4% patients at visit 4)

- Premix insulin was prescribed to 5.5%, 5.1% and 4.7% patients at visit 2, visit 3 and visit 4, respectively
- Out of total patients, improvement of HbA1c was the most common reason in majority (83.8%) of patients to start insulin degludec (IDeg)
- Improvement in FBG (mg/dL) and PPG (mg/dL) was the reason in 63.7% and 59.4% patients
- Approximately one-fourth (25.8%) of patients were shifted to IDeg due to risk of hypoglycaemia with their current treatment strategy
- Out of total reasons, improvement in HbA_{1c} (29.1%) was the most common reasons to start IDeg, followed by improvement in FPG (mg/dL) (22.1%) and PPG (mg/dL) (20.6%)
- Amongst the population with OAD (either 1, 2 or more than 2) at baseline, improvement in HbA1c was the most common reason to start IDeg in more than two-third patients
- A decline in HbA1c was observed in at different time points. The mean ± SD value of HbA1c (%) was reduced from 9.6 ± 1.92 at baseline to 7.8 ± 1.18 at visit 4
- A decline in HbA1c was also noted in patients receiving OAD at baseline. In those patients, mean ± SD HbA1c was reduced from 9.5 ± 1.83 at baseline to 7.5 ± 0.99 at visit 4
- A decline in HbA1c was also noted in patients receiving insulin previously. In those patients, mean ± SD HbA1c was reduced from 9.8 ± 2.08 at baseline to 8.2 ± 1.39 at visit 4
- A decline in FPG (mg/dL) was observed in at different time points. The mean ± SD FPG (mg/dL) in was reduced from 190.7 ± 69.02 at baseline to 125.4 ± 31.86 at visit 4
- A decline in FPG (mg/dL) was also noted in patients receiving OAD at baseline. In those patients, mean ± SD FPG (mg/dL) was reduced from 185.3 ± 62.21 at baseline to 123.0 ± 27.16 at visit 4

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- A decline in FPG (mg/dL) was also noted in patients receiving insulin previously. In those patients, mean ± SD FPG (mg/dL) was reduced from 202.9 ± 81.17 at baseline to 130.2 ± 39.26 at visit 4
- A decline in PPG (mg/dL) levels were observed at corresponding timepoints during each visit
  - The mean ± SD of Post breakfast PPG (mg/dL) levels were reduced from 277.4 ± 81.69 at baseline to 187.1 ± 48.33 at visit 4
  - The mean ± SD of Post lunch PPG (mg/dL) levels were reduced from 273.3 ± 109.4 at baseline to 174.3 ± 34.63 at visit 4
  - The mean ± SD of Post dinner PPG (mg/dL) levels were reduced from 242.0 ± 103.4 at baseline to 168.0 ± 29.18 at visit 4
- A decline in mean PPG (mg/dL) levels was also noted in patients, previously on OAD and insulin, at different time points
  - The mean ± SD Post breakfast PPG (mg/dL) values was reduced from 276.5 ± 75.70 at baseline to 181.2 ± 39.66 at visit 4 in patients on OAD at baseline
  - The mean ± SD Post breakfast PPG (mg/dL) values was reduced from 279.1 ± 93.23 at baseline to 196.8 ± 58.78 at visit 4 in patients previously on insulin
  - The mean ± SD Post lunch PPG (mg/dL) values was reduced from 267.8 ± 95.70 at baseline to 171.2 ± 33.91 at visit 4 in patients on OAD at baseline
  - The mean ± SD Post lunch PPG (mg/dL) values was reduced from 286.0 ± 135.6 at baseline to 179.2 ± 35.59 at visit 4 in patients previously on insulin
  - The mean ± SD Post dinner PPG (mg/dL) values was reduced from 256.7 ± 115.7 at baseline to 170.3 ± 37.98 at visit 4 in patients on OAD at baseline
  - The mean ± SD Post dinner PPG (mg/dL) values was reduced from 224.8 ± 94.54 at baseline to 164.5 ± 21.92 at visit 4 in patients previously on insulin
- A significant reduction ($p<0.001$) was noted in HbA1c (%) and FPG (mg/dL) from baseline to each subsequent visit in overall population
- A significant reduction in HbA1c (%) and FPG (mg/dL) was noted from baseline to each subsequent visit in patients receiving either OAD ($p<0.001$) or

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insulin (p<0.001) previously

- A significant reduction (p<0.001) was noted in PPG (mg/dL) values, at corresponding timepoints, from baseline to each subsequent visit in overall population
- A significant reduction was noted in PPG (mg/dL) values, at corresponding time points, from baseline to each subsequent visit in patients receiving either OAD (p<0.001) or insulin (p<0.001) at baseline
- A significant reduction was noted in HbA1c (%) (p<0.0001), FPG (mg/dL) (p<0.0001) and PPG (mg/dL) [Post breakfast (p<0.0001) and Post lunch (p<0.0001)] levels from baseline to visit 4 in EAS population
- The mean ± SD reduction in HbA1c (%) and FPG (mg/dL) was 1.8 ± 1.68 and 64.7 ± 72.84 from baseline to visit 4, respectively
- The reduction in Post breakfast and Post lunch PPG (mg/dL) was 86.1 ± 94.80 and 87.8 ± 100.2 from baseline to visit 4, respectively
- A decrease in confirmed hypoglycaemic events were noted from baseline to subsequent follow up visits with respect to both number of subjects and number of events
- A total of 44 AEs have been reported during the Study period
- Among total AEs, there were 2 serious and 42 non-serious AEs which was presented in 2 (0.2%) and 28 (2.6%) patients, respectively.
- Both SAEs were not life threatening
- Both SAEs were moderate and were resolved/recovered during Study
- Majority of AEs were mild [36 AEs in 24 (2.3%) patients] in nature
- No AE was severe in nature
- Except 2 AEs in 2 (0.2%) patients, 41 AEs in 27 (2.6%) patients got recovered/resolved during Study period
- Causality assessment showed 38 events, encountered in 23 (2.2%) patients, to be unlikely associated with Study drug. Additionally, 5 and 1 events were in Probable and possible category, respectively.

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- No dose was changed in 12 (1.1%) patients, while dose was reduced and increased in 3 (0.3%) and 2 (0.2%) patients, respectively.
- A total of 8 (0.8%) patients were encountered with 9 events in the class of General disorders and administration site conditions. This was followed by Metabolism and nutrition disorders [6 (0.6%)], Infections and infestations [5 (0.5%)], Nervous system disorders [5 (0.5%)], Musculoskeletal and connective tissue disorders [4 (0.4%)], Gastrointestinal disorders [3 (0.3%)], Skin and subcutaneous tissue disorders [3 (0.3%)], Ear and labyrinth disorders [1 (0.1%)], Eye disorders [1 (0.1%)], Renal and urinary disorders [1 (0.1%)], Respiratory, thoracic and mediastinal disorders [1 (0.1%)] and vascular disorder [1 (0.1%)].
- A total of 6 ADRs were reported in 5 (0.5%) Subjects during the Study.
- No ADRs were serious in nature
- 5 ADRs, in 4 (0.4%) patients, were mild and 1 was moderate
- All the ADRs were Recovered/resolved during the course of Study
- In 2 (0.2%) patients, the dose of Study drug was reduced, while in 1 (0.1%) patient it was increased
- No dose was changed in 2 (0.2%) patients
- Of the total ADR reported, 3 (0.3%) patients had Metabolism and nutrition disorders and 2 (0.2%) had Infections and infestations.
    - Among Metabolism and nutrition disorders, 2 (0.2%) and 1 (0.1%) patients had Hypoglycaemia and Hyperglycaemia, respectively.
- A total of 3 events of Severe Hypoglycaemic Episodes were observed in 2 (0.2%) patients at Baseline Visit
- No further Severe Hypoglycaemic Episodes were noted at any follow Up Visit during the Study period

Conclusion:

In conclusion, this study demonstrates the long-term safety profile of IDeg for 1 year in routine clinical practice in Indian patients. Starting or switching to IDeg has the potential to improve glycaemic control with a reduced risk of hypoglycaemia. It is possible that these advantages with IDeg, in particular, efficacious lowering of HbA1c

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(%), FPG (mg/dL) and PPG (mg/dL) values together could encourage physicians and patients to titrate insulin regimens more rigorously to reach glycaemic target values.		
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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 Hemoglobin
ICF	Informed Consent Form
ICH-GCP	International Council of Harmonization- Good Clinical Practices
IDeg	Insulin Degludec
IEC	Institutional Ethics Committee
IGlar	Insulin Glargine
IRB	Institutional Review Board
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
OAD	Oral Antidiabetic Drug
OD	Once a Day

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 29 July 2013, was reviewed and approved by competent authorities and the local independent ethics committee (IEC)/institutional review board (IRB) of the respective sites according to local regulations. The Study was carried out in conformity with the protocol and International Council on Harmonization Guideline for Good Clinical Practice (ICH-GCP). The original protocol (version 1.0, dated 29 July 2013) 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
- 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 51 sites in India where 09 sites (site#[redacted], site#[redacted], site#[redacted], site#[redacted], site#[redacted], site#[redacted], site#[redacted], site#[redacted], and site#[redacted]) participated in the Study but did not enroll any patient. 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, International Conference on Harmonization-Good Clinical Practices (ICH-GCP) guidelines, Indian Council of Medical Research, Indian GCP guidelines, and as per the protocol version 1.0 dated 29 July 2013, submitted to IEC/IRB. All patient related documents like 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 trial.

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 less than 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 EC approved ICF (English) is provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators

The Study was initiated at 51 sites in India where 9 sites (Site Nos [redacted] and [redacted]) participated in the Study but did not enroll any patient. The following investigators participated in the Study:

S. No	Site No.	Name of Principal Investigator	Address of Study Site
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]

S. No	Site No.	Name of Principal Investigator	Address of Study Site
			[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]
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]

S. No	Site No.	Name of Principal Investigator	Address of Study Site
			[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]
40	[redacted]	Dr. [redacted]	[redacted]
41	[redacted]	Dr. [redacted]	[redacted]
42	[redacted]	Dr. [redacted]	[redacted]
43	[redacted]	Dr. [redacted]	[redacted]
44	[redacted]	Dr. [redacted]	[redacted]
45	[redacted]	Dr. [redacted]	[redacted]
46	[redacted]	Dr. [redacted]	[redacted]
47	[redacted]	Dr. [redacted]	[redacted]
48	[redacted]	Dr. [redacted]	[redacted]
49	[redacted]	Dr. [redacted]	[redacted]
50	[redacted]	Dr [redacted]	[redacted]

S. No	Site No.	Name of Principal Investigator	Address of Study Site
51	[redacted]	Dr. [redacted]	[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 trial 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.[1] The number of people with diabetes is predicted to rise to 629 million by 2045. In 2017 India has approximately72.9 million patients living with diabetes, which will reach up to 134.3 million by 2045.[2] 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.[4]

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.[5] 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.[6, 7]

New basal insulin analogues with improved pharmacodynamic and pharmacokinetic profiles, which confer a lower risk of hypoglycaemia and more flexible dosing schedules, have been developed with the aim of improving long-term glycaemic control and the patient's experience with basal insulin therapy. Insulin degludec (IDeg) is a new-generation, ultra-long-acting insulin developed for once-daily administration with a distinct mechanism of protraction. On subcutaneous (SC) injection, IDeg forms multi-hexamers. These form a soluble depot in the SC tissue, from which monomers gradually separate at a consistent rate and are absorbed into the circulation.[8, 9] This mechanism of absorption leads to flat, consistent, and long pharmacokinetic and pharmacodynamic profiles.[8] In addition, IDeg has a lower within-day variability and 4-fold lower pharmacodynamic day-to-day variability in glucose-lowering effect compared with insulin glargine (IGlar) under steady state conditions.[10] These findings, coupled with the duration of action of IDeg, which extends beyond 42h, suggests that a delayed or missed injection might not compromise glycaemic control to the same extent as currently available basal insulins.[8, 11]

Furthermore, throughout the clinical development program, IDeg was associated with significantly lower rates of nocturnal hypoglycaemia at similar levels of glycaemic control in T1DM and T2DM patients compared with IGlar.[12] In addition, studies in adults have shown that the IDeg injection time may be varied from day to day with a window of 8 to 40 hours without compromising efficacy or safety in T1DM and T2DM patients, hence offering greater convenience and flexibility.[11, 13]

7.2 Clinical Studies

The efficacy and safety of IDeg once daily was assessed in a large clinical trial program, BEGIN, which included nine 26- or 52-week trials.[11, 13-19] Three trials have explored the relationship of IDeg versus IGlar in basal-bolus therapy in patients with T1DM and T2DM.[11, 14, 15] In BEGIN Basal-Bolus Type 1 trial, reduction in HbA1c was observed by 0·40% points (SE 0·03) and 0·39% points (0·07) in IDeg and IGlar group at 1 year, respectively (estimated treatment difference -0·01% points [95% CI -0·14 to 0·11]; p<0·0001 for non-inferiority testing). Moreover, 188 (40%) and 67 (43%) participants achieved a target HbA1c of less than 7% (<53 mmol/mol) during the Study.[14] In BEGIN: Flex T1 trial, mean HbA1c was reduced with IDeg Forced- Flex (-0.40%), IDeg (-0.41%), and IGlar (-0.58%). The Study further reported that IDeg can be administered OD at any time of day, without compromising glycemic control or safety vs same-time-daily IDeg or IGlar.[11] The other 6 trials evaluated the combination of IDeg and mealtime insulin or as an adjunct to common background oral antidiabetic drugs in patients with T2DM.[20] These trials showed that IDeg improved glycemic control, achieving similar reductions in HbA1c levels compared with FDA-approved comparators viz. IGlar or IDet.[21]

In another Study, IDeg was administered at the same time each day or at any time in combination with a rapid-acting insulin analog at mealtimes. This 26-week randomized, open-label, multicenter clinical trial showed 0.17% (95% confidence interval [CI], 0.04%-0.30%) HbA1c reduction from baseline in 493 patients with T1DM, which met the prespecified non-inferiority margin of 0.4%.[21]

Overall, 6 studies in more than 2700 patients investigated the efficacy and safety of IDeg combined with mealtime insulin or common background oral antidiabetic drugs in patients with T2DM who had inadequate blood glucose control. In this treat-to-target trials, IDeg showed reduction in HbA1c levels when compared to the previously approved long-acting insulins.[21] In a trial comparing IDeg OD with sitagliptin OD with all the patients also receiving 1 or 2 oral antidiabetic drugs, at the end of 26 weeks, IDeg demonstrated superior reduction in HbA1c levels compared with sitagliptin (p <.001).[19] Different trials of IDeg in T1DM and T2DM patients are presented in Table 1 and Table 2.

Table 1 Type 1 Diabetes Trials

	Change in HbA1c from baseline (%)	HbA1c at end of trial (%)	Mean basal daily insulin dose at end of trial (units/kg)	Mean weight gain (kg)
BEGIN Basal-Bolus Type 1 (52 weeks)[14]				
Degludec	(–0.40)	(7.3)	0.35	1.8
Glargine	(–0.39)	(7.3)	0.39	1.6
BEGIN: Flex T1 (26 week fixed-flexible period)[11]				
Degludec	(–0.41)	(7.3)	0.38	0.8
Degludec-flexible	(–0.40)	(7.3)	0.42	1.2
Glargine	(–0.58)	(7.1)	0.42	1.6
*p value for treatment ratio <0.0001.				

Table 2 Type 2 Diabetes Trial

	Change in HbA1c from baseline (%)	HbA1c at end of trial (%)	Mean total daily insulin dose at end of trial (units/kg)	Mean weight gain (kg)
BEGIN Once Long (52 weeks, insulin-naive patients)[18]				
Degludec	(–1.06)	(7.1)	0.59	2.4
Glargine	(–1.19)	(7.0)	0.60	2.1
BEGIN Low Volume (26 weeks, insulin-naive patients, higher strength)[16]				
Degludec	(–1.30)	(6.99)	0.53*	1.9
Glargine	(–1.32)	(6.93)	0.60	1.5
BEGIN Basal-Bolus Type 2 (52 weeks, insulin-experienced patients)[15]				
Degludec	(–1.1)	(7.2)	1.46	3.6
Glargine	(–1.2)	(7.2)	1.42	4.0
BEGIN Flex (26 weeks, insulin-naive and experienced patients)[13]				
Degludec	(–1.07)	(7.2)	0.5 (naive) 0.6 (experienced)	1.6
Degludec-Flexible	(–1.28)	(7.3)	0.5 (naive) 0.6 (experienced)	1.5
Glargine	(–1.26)	(7.1)	0.5 (naive) 0.6 (experienced)	1.3
*p value for treatment ratio <0.05				

7.3 Rationale

Phase III studies of IDeg showed non-inferior HbA1c reductions with it compared to the comparators..[14, 15] However, these phase III studies tested a specific group of patients who were selected according to strict criteria regarding baseline HbA1c, body mass index (BMI) and prior medication period, based on the regulatory authority's guidelines.

The rationale for conduct of this Study in India was that it is a primary regulatory requirement by the Indian health authority to assess the safety of all medicinal products approved for clinical use. In addition, although marketing approval for Tresiba® had been granted in India, there was a continuous need to monitor the safety of medicinal products as post-approval surveillance while they were 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 in some instances, identify unexpected ADRs.

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 (Tresiba®) in insulin requiring patients with diabetes mellitus, initiating treatment with Tresiba® 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 Tresiba®

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:

- SAEs by preferred term
- SADRs by preferred term
- ADRs by preferred term
- Severe hypoglycaemia

8.3.3 Secondary Efficacy Endpoints:

- Change from baseline in HbAlc after 1 year of treatment
- Change from baseline in FPG after 1 year of treatment
- Incidence of confirmed hypoglycaemia during 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, PMS/PASS Study to evaluate safety and efficacy during long-term treatment (1-year) with Tresiba® in patients with DM requiring insulin therapy under normal clinical practice conditions in India. A total of 1057 patients were enrolled to investigate safety of Tresiba®. Data were collected at baseline (Visit 1), 3 months (Visit 2), 6 months (Visit 3) and finally at 1-year (Visit 4). The protocol, including amendments, and a case report form (CRF) are included as Appendices 16.1.1 and 16.1.2, respectively. The assignment of the patient to Tresiba® was decided in advance of this the protocol and as part of current practice. Hence, the prescription of Tresiba® was clearly separated from the decision to include the patient in the Study.

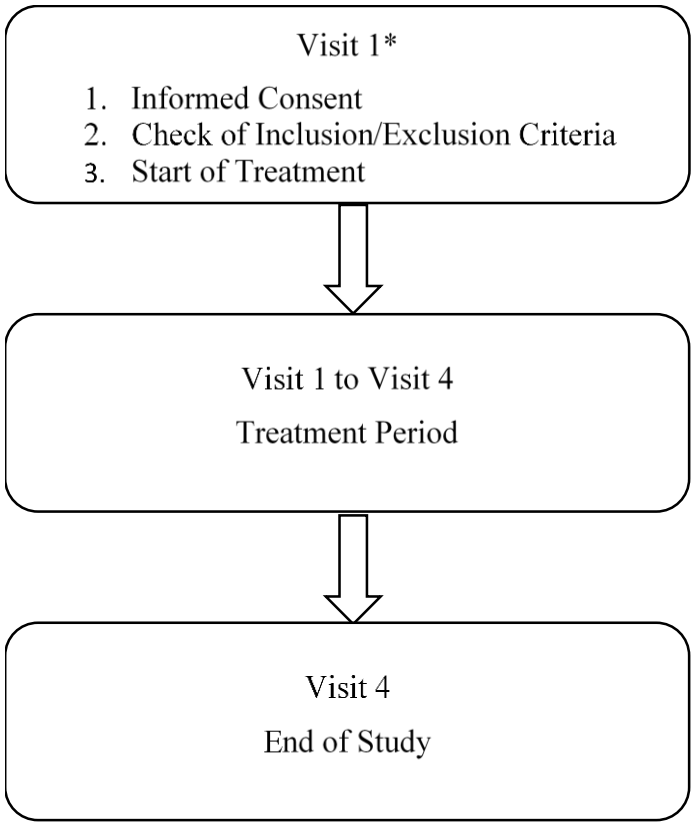
9.1.2 Description of Study Visits

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 can be recorded and analyzed for measuring safety and efficacy of Tresiba®.

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 into 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 (over past 4 weeks before starting on insulin degludec) so the last contact?"

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 address(es) and telephone number(s) of the physician and/or site staff. The Flow chart of Study visit is depicted in Figure 1.

Figure 1 Layout of Study visits



* The assignment of the patient to Tresiba® is not decided in advance by the protocol but falls within current practice and the prescription of Tresiba® is clearly separated from the decision to include the patient in the Study.

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 date
- 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 IDeg treatment (if available)
- DM treatment prescribed during PMS/PASS Study
- Reasons why decision was taken to start therapy with IDeg (increased HbAlc, increased FPG/FBG, increased PPBG/PPPG, side effects from previous therapy, hypoglycaemia, patient dissatisfaction with previous therapy, flexibility need, once-daily treatment need)
- Starting date of Tresiba® 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 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 hypoglycaemia experienced since last visit
- Date and value of most recent HbAlc since last visit
- Most recent FPG/FBG value and date of measurement since last visit
- DM treatment prescribed since the last visit
- Change in Tresiba® 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

9.2 Discussion of Study Design, including Choice of Control Groups

The Study was assessing the safety profile of Tresiba® used in patients under normal clinical practice conditions without any intervention, in India and without a comparator as it is not considered needed. The 1-year observation period was expected to be sufficient to capture untoward medical occurrences that were likely to be associated with long-term use of Tresiba®. Frequency and timing of visit were based on normal clinical practice for patients with DM requiring insulin therapy in India.

Based on the clinical judgement, patients were started on Tresiba® in routine clinical practice. The assignment of the patient to Tresiba® was not decided in advance by the protocol but falls within current practice and the prescription of the medicine was clearly separated from the decision to include the patient in the Study. Tresiba® was 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. Tresiba® was used in accordance with the Indian package insert.

9.3 Selection of Study Population

Patients with DM requiring insulin therapy and qualified for starting treatment with Tresiba® were enrolled in this Study. Patients were excluded if they had known or suspected allergy to Tresiba® or any of the excipients or in case of previous participation in this Study. Patients can be withdrawn at their will at any time. Also, a patient may be withdrawn from this PMS/PASS at the discretion of the physician due to a safety concern.

9.3.1 Inclusion Criteria

Patients were included in the Study if they met all the following criteria:

1. Informed consent obtained before any Study-related activities (Study related activity 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, severe hypoglycaemia before the start of Tresiba® therapy) can be used for baseline data.
2. Patients with insulin requiring diabetes mellitus and who is scheduled to start treatment with Tresiba® based on the clinical judgment of their treating physician.

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 Tresiba®, 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 are or have previously been on Tresiba® therapy
5. Patients who are participating in other studies or clinical trials
6. Patients who are 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 may withdraw at will at any time
2. The patient may be withdrawn from this PMS/PASS Study at the discretion of the physician due to a safety concern

9.4 Treatments

9.4.1 Treatments Administered

Following treatments were administered in patients:

- **Test:** Tresiba® (100 u/mL**)**
- **References:** Due to the non-interventional nature of this trial and the Study conducted in a real-life setting there was no comparator/control arm

9.4.2 Identity of Investigational Products

9.4.2.1 Description of Investigational Product

The marketed product of Tresiba® FlexTouch™ prefilled pen injector (100 u/mL) was used in this PMS/PASS, and was not provided by Novo Nordisk India Private Ltd.

9.4.2.2 Study Medication Packaging, Labeling, and Storage

All Study medication was available in the market by prescription and purchase/supply as in routine practice and according to local regulations.

9.4.3 Method of Assigning Patients to Treatment Groups

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

9.4.4 Selection of Doses in the Study

Tresiba® 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 Tresiba® and other anti-diabetic medications that were taken during the Study. Details of all concomitant medications were recorded at trial entry (i.e. at the first visit [Visit 1]). The information collected for each concomitant medication includes 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 3.

Table 3 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			
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 FPG/PBG value and date of measurement (if available)[3]	X	X	X	X
Diabetes treatment before the PMS/PASS Study 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

[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 1 mmol/L (56 mg/dL). Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point (1 mmol/L) in the
definition of confirmed hypoglycaemia.
Confirmed hypoglycaemic episodes are defined as episodes that are severe (i.e, an episode requiring assistance of another person to

	Visit 1 (0 Week)	Visit 2 (3 months ± 2 weeks)	Visit 3 (6 months ± 2 weeks)	Visit 4 (1 year ± 2 weeks)
actively administer carbohydrate, glucagon, or other resuscitative actions) and/or 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 I, the term recent means "over the past 4 weeks before starting on insulin degludec". [4] Each AE/SAE was recorded on a separate AE form according to existing reporting procedures. If the AE is serious then a Safety Information Form was also completed and the sponsor or their designee were notified within the specified period. Severe hypoglycacmic episodes (according to definition in footnote #2) always qualify for AE/SAE reporting				

9.5.1.1 Efficacy Parameters

HbAlc, FPG and confirmed hypoglycaemic events were evaluated for efficacy aspect of Tresiba®.

9.5.1.2 Safety Parameters

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

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Adverse drug reactions (ADRs)
- Serious adverse drug reactions (SADRs)
- Pregnancies in female patients and adverse events in the foetus or newborn infant
- AEs in infants exposed via breastfeeding, overdose, drug abuse or misuse, medication errors, lack of efficacy and technical complaints

9.5.1.2.1 Adverse Drug Reaction

An adverse drug reaction 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 adverse drug reaction 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 adverse drug reaction 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[a] experience
- In-patient hospitalization or prolongation of existing hospitalization[b]
- A persistent or significant disability/incapacity[c]
- A congenital anomaly/birth defect
- Important medical events that did not result in death, were life-threatening[a] or require hospitalization[b] were considered a serious adverse event - when based upon appropriate medical judgement - they may jeopardised 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, eg 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 (eg 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, EPJP 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 (ie 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 (ie 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 newborn 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 newborn infant were collected and reported regardless of causality assessment.

Reporting of ADRs or AEs in foetus, newborn 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 newborn 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 Primary efficacy variable(s)

AEs/SAEs/ADRs/SADRs were collected for safety evaluation and HbAlc, FPG and confirmed hypoglycaemic events were evaluated for efficacy aspect of Tresiba®

9.5.4 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 trial. 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

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 trial values and change from baseline values were presented. Missing values were subject to last observation carried forward (LOCF).

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 2 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 is defined as all subjects who had received at least one dose of Tresiba® 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 is defined as all subjects 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.

9.7.1.2 Demographics and Other Baseline Characteristics

9.7.1.2.1 Demographics

Demographic variables include age, gender, race, body measurements and vital signs (weight, height, waist circumference, hip circumference and blood pressure) and diabetes mellitus history. All efficacy and safety parameters which were collected at baseline was 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 and confirmed hypoglycaemic events were evaluated for efficacy aspect of Tresiba® by means of descriptive statistics. Baseline, end of trial 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. Missing values were subject to LOCF. Also, paired-t test was used to evaluate the changes in HbA1c, FPG 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

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 subjects 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 subjects with event, number of events, incidence rate and rate per 100PYE and subject 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 newborn 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 Tresiba®. A sample size of 1000 patients, assuming 20% dropout rate who had been exposed to the IDeg 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.

For an unobserved event, with the above sample size the upper limit of 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.

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

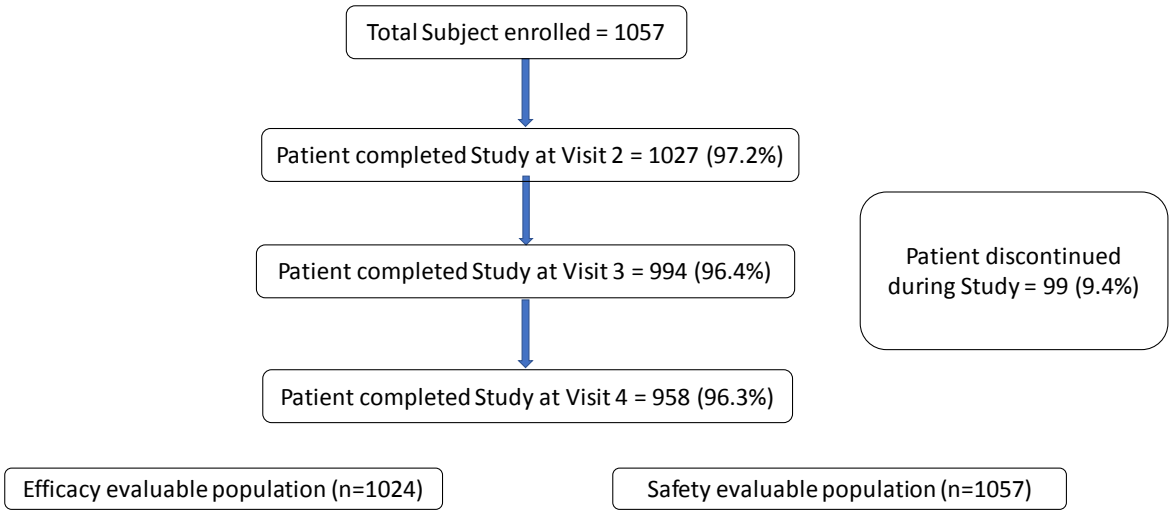
9.8.2 Changes in Planned Analysis

No changes were made in the planned analysis

10 STUDY SUBJECTS

10.1 Disposition of Subjects

Figure 2 Patient Disposition



10.2 Protocol Deviations

There were no protocol deviations observed during the Study.

11 EFFICACY EVALUATION

11.1 Data Sets Analyzed

Safety Analysis Set (SAS) Population: All patients who had received at least one dose of Tresiba® during the PS/PASS Study.

Efficacy Analysis Set (EAS) Population: All patients in the SAS who had at least one post baseline measurement concerning HbA1c, FPG or confirmed hyperglycaemic event(s).

11.2 Demographic and Other Baseline Characteristics

In this Study, there were more males [635 (60.1%)], compared to females [422 (39.9%)]. The mean ± SD age of Study patients were 55.0 ± 11.35 years. The mean ± SD Height (cm), Weight (kg), Waist Circumference (cm) and Hip Circumference (cm) of patients were 162.2 ± 8.70, 71.7 ± 13.43, 94.2 ± 11.57 and 97.5 ± 11.68, respectively (Table 4).

Table 4 Summary of Subject Demographics at Screening visit-SAS Population (N = 1057)

Parameters	Statistic/Category, n (%) [1]	Overall (N = 1057)
Gender		
	Male	635 (60.1)
	Female	422 (39.9
Age	n	1057
	Missing	0
	Mean	55.0
	SD	11.35
	Median	55.0
	Range (Min.:Max.)	(16.0:86.0)
Height (cm)	n	1043
	Missing	14
	Mean	162.2
	SD	8.70
	Median	162.0
	Range (Min.:Max.)	(107.0:187.9)
Weight (kg)	n	1052
	Missing	5
	Mean	71.7
	SD	13.43
	Median	70.2
	Range (Min.:Max.)	(40.2:134.0)
Waist Circumference (cm)	n	609
	Missing	448
	Mean	94.2
	SD	11.57
	Median	93.0
	Range (Min.:Max.)	(56.0:160.0)
Hip Circumference (cm)		
	n	516
	Missing	541
	Mean	97.5
	SD	11.68
	Median	97.0
	Range (Min.:Max.)	(58.0:155.0)

Source Data: Table 14.1.2.1, Listing 16.2.4.1
Note:
[1] Respective column header count were used as denominator for percentage calculation.
General Note:
[1] Zero frequencies are presented by "- ".
[2] The unavailable data were shown in 'Missing' category.

11.2.1 Other Baseline Medical History

Summary of Diabetes Mellitus History

Majority of the patients, [1052 (99.5%)] had T2DM as compared to T1DM [5 (0.5%)]. The mean ± SD duration (years) of DM was higher in T1DM (22.2 ± 21.90) than T2DM patients (10.1 ± 7.37) (Table 5).

Table 5 Summary of Diabetes Mellitus History type - SAS population (N = 1057)

Parameter	Statistic/Category n (%) [1]	Overall(N = 1057)
Type of Diabetes		
	Type1	5(0.5)
	Type2	1052(99.5)
Duration (completed years)		
Type1		
	n	5
	Missing	0
	Mean	22.2
	SD	21.90
	Median	18.0
	Range(Min.:Max.)	(0.0:57.0)
Type2		
	n	1008
	Missing	44
	Mean	10.1
	SD	7.37
	Median	9.0
	Range(Min.:Max.)	(0.0:58.0)

Source Listing: Table 14.1.2.3.1, Listing 16.2.4.2
Note:[1] Percentage was calculated by taking respective column header count as denominator.

Complications due to Diabetes Mellitus

Among the microvascular complications, majority of patients [203 (19.2%)] had Peripheral Neuropathy. This was followed by Nephropathy [92 (8.7%)], Retinopathy [76 (7.2%)], and Autonomic Neuropathy [66 (6.2%)]. Among the macrovascular complications, Coronary Heart Disease [90 (8.5%)] was relatively higher, followed by Macroangiopathy (including Peripheral Vascular Disease) [19 (1.8%)] and Stroke [10 (0.9%)] (Table 6).

Table 6 Summary of complications due to Diabetes Mellitus-SAS population (N = 1057)

Parameter	Statistic/Category, n (%) [1]	Overall (N = 1057)
Micro-vascular complications		
Autonomic Neuropathy	Yes	66 (6.2)
	No	991 (93.8)
Peripheral Neuropathy	Yes	203 (19.2)
	No	854 (80.8)
Nephropathy	Yes	92 (8.7)

	No	965 (91.3)
Retinopathy	Yes	76 (7.2)
	No	981 (92.8)
Macro-vascular complications		
Macroangiopathy (including Peripheral Vascular Disease)	Yes	19 (1.8)
	No	1038 (98.2)
Coronary Heart Disease	Yes	90 (8.5)
	No	967 (91.5)
Stroke	Yes	10 (0.9)
	No	1047 (99.1)

Source Data: Listing 16.2.4.2:
Note:
[1] Percentages were calculated by taking respective column header count as denominator.

11.3 Treatment Compliance

Diabetes Mellitus Treatment at each visit

Most of the patients in each visit [visit 1: 778 (73.6%), visit 2: 837 (79.2%), visit 3: 806 (76.3%) and visit 4 (799 (75.6%)] were on metformin, followed by sulphonylureas [visit 1: 602 (57.0%), visit 2: 628 (59.4%), visit 3: 603 (57.0%) and visit 4: 592 (56.0%)]. At baseline, 164 (15.5%), 151 (14.3%) and 118 (11.2%) patients were on basal, bolus and premix insulin, respectively. The proportion of patients on bolus insulin remained same at follow up visits [198 (18.7%)] (visit 2 and 3). 184 (17.4%) patients were on bolus insulin at the final visit. Premix insulin was prescribed to 58 (5.5%), 54 (5.1%) and 50 (4.7%) patients at visit 2, visit 3 and visit 4, respectively. The details of patients with their treatments are presented in Table 7.

Table 7 Summary of Diabetes Mellitus Treatment at each visit -SAS population (N = 1057)

Visit	Medication	Overall (N = 1057)
Visit 1 Baseline Visit	Alpha-Glucosidase inhibitors in mg	166 (15.7)
	Basal Insulin	164 (15.5)
	Bolus Insulin	151 (14.3)
	DDP-IV –inhibitor	345 (32.6)
	GLP-1 analogs	7 (0.7)
	Metformin	778 (73.6)
	Metiglinides	7 (0.7)
	Others	54 (5.1)
	Premix Insulin	118 (11.2)
	Sulphonylureas	602 (57.0)
	Thiazolidinediones	78 (7.4)
Visit 2 Follow Up Visit	Alpha-Glucosidase inhibitors	170 (16.1)
	Bolus Insulin	198 (18.7)
	DDP-IV –inhibitor	399 (37.7)
	GLP-1 analogs	15 (1.4)
	Metformin	837 (79.2)
	Metiglinides	6 (0.6)
	Others	52 (4.9)
	Premix Insulin	58 (5.5)
	Sulphonylureas	628 (59.4)
	Thiazolidinediones	74 (7.0)

Visit	Medication	Overall (N = 1057)
Visit 3 Follow Up Visit	Alpha-Glucosidase inhibitors	181 (17.1)
	Bolus Insulin	198 (18.7)
	DDP-IV –inhibitor	371 (35.1)
	GLP-1 analogs	15 (1.4)
	Metformin	806 (76.3)
	Metiglinides	8 (0.8)
	Others	56 (5.3)
	Premix Insulin	54 (5.1)
	Sulphonylureas	603 (57.0)
	Thiazolidinediones	70 (6.6)
Visit 4 Final Visit	Alpha-Glucosidase inhibitors	175 (16.6)
	Bolus Insulin	184 (17.4)
	DDP-IV –inhibitor	368 (34.8)
	GLP-1 analogs	17 (1.6)
	Metformin	799 (75.6)
	Metiglinides	6 (0.6)
	Others	85 (8.0)
	Premix Insulin	50 (4.7)
	Sulphonylureas	592 (56.0)
	Thiazolidinediones	65 (6.1)

Reason(s) to Start Therapy with Insulin degludec

In our Study, improvement of HbA1c was the most common reason in majority of patients [886 (83.8%)] to start IDeg. Improvement of HbA1c contributes 29.1% of total reasons reported. This was followed by improvement in FBG [673 (63.7%)] and PPG [628 (59.4%)], which contributes 22.1% and 20.9% of total reasons reported, respectively. In addition to this, approximately one-fourth [273 (25.8%)] of patients were shifted on IDeg due to risk of hypoglycaemia with other treatment strategy which contributes 9.0% of total reasons reported. The summary of reasons to start therapy with IDeg by patients and reason was mentioned in Table 8 and Table 9

Table 8 Summary of reason(s) to Start Therapy with Insulin degludec by patients - SAS population (N = 1057)

Reasons /Category, n (%) [1]	Overall (N = 1057)[2]
Improve HbA1c	886 (83.8)
Improve FBG	673 (63.7)
Improve PPG	628 (59.4)
Side effects from previous therapy	35 (3.3)
Reduce risk of hypoglycaemia	273 (25.8)
Patients dissatisfaction with previous therapy	91 (8.6)
Improve beta cell function	124 (11.7)
Improve weight control	164 (15.5)
Need for flexibility in timing of injection	137 (13.0)

Reasons /Category, n (%) [1]	Overall (N = 1057)[2]
Other	32 (3.0)

Source Data: Table: 14.1.2.3.4, Listing 14.1.2.3.4
Note:
[1] Percentage was calculated by taking respective column header count as denominator.
[2] One person may have more than one reason to start Insulin Degludec.

Table 9 Summary of reason(s) to Start Therapy with Insulin degludec – By reasons

Reasons /Category, n (%) [1]	Overall (N = 3043)[2][3]
Improve HbA1c	886 (29.1)
Improve FBG	673 (22.1)
Improve PPG	628 (20.6)
Side effects from previous therapy	35 (1.1)
Reduce risk of hypoglycaemia	273 (9.0)
Patients dissatisfaction with previous therapy	91 (3.0)
Improve beta cell function	124 (4.1)
Improve weight control	164 (5.4)
Need for flexibility in timing of injection	137 (4.5)
Other	32 (1.0)

Note:
[1] Percentage was calculated by taking respective column header count as denominator.
[2] One person may have more than one reason to start Insulin Degludec.
[3] 'N' denotes the total number of reasons to start Insulin Degludec for all patients

Further exploring the patients with existing therapy, it was found that unsatisfactory HbA1c was most common reason to start IDeg in more than two-third patients, who were on OAD (either 1, 2 or more than 2) at Baseline. For the same reason, 122 (74.4%) and 20 (71.4%) patients were switched on IDeg from Basal insulin ± OAD and Bolus/Premix insulin, respectively. In addition, 103 (88.0%) patients with unsatisfactory HbA1c were not receiving any treatment and shifted to IDeg. Similarly, a substantial proportion of patients administered on OADs and insulin (Basal insulin ± OAD and Bolus/Premix insulin) were switched to IDeg for improving their FBG (mg/dL) and PPG (mg/dL). 5 (4.3%) and 23 (19.7%) patients with no treatment at Baseline were switched on IDeg due to side effects from previous therapy and increased risk of hypoglycaemia, respectively. The summary of reasons to start IDeg were summarized in Table 10.

Table 10 Summary of reason(s) to Start Therapy with Insulin degludec - SAS population by Previous Medication (N = 1057)

	Insulin Use					
Reasons /Category, n (%) [1]	**No Treatment (N = 117)**	**1 OAD (N = 155)**	**2 OADs (N = 305)**	**>2 OADs (N = 288)**	**Basal insulin ± OAD (N = 164)**	**Bolus/Premix (N = 28)**
Improve HbA1c	103 (88.0)	134 (86.5)	268 (87.9)	239 (83.0)	122 (74.4)	20 (71.4)
Improve FBG	57 (48.7)	123 (79.4)	205 (67.2)	182 (63.2)	87 (53.0)	19 (67.9)
Improve PPG	56 (47.9)	104 (67.1)	204 (66.9)	173 (60.1)	74 (45.1)	17 (60.7)
Side effects from previous therapy	5 (4.3)	3 (1.9)	11 (3.6)	10 (3.5)	5 (3.0)	1 (3.6)
Reduce risk of hypoglycaemia	23 (19.7)	65 (41.9)	93 (30.5)	59 (20.5)	29 (17.7)	4 (14.3)

	Insulin Use					
Reasons /Category, n (%) [1]	**No Treatment (N = 117)**	**1 OAD (N = 155)**	**2 OADs (N = 305)**	**>2 OADs (N = 288)**	**Basal insulin ± OAD (N = 164)**	**Bolus/Premix (N = 28)**
Patients dissatisfaction with previous therapy	4 (3.4)	8 (5.2)	13 (4.3)	35 (12.2)	25 (15.2)	6 (21.4)
Improve beta cell function	15 (12.8)	23 (14.8)	35 (11.5)	34 (11.8)	14 (8.5)	3 (10.7)
Improve weight control	12 (10.3)	32 (20.6)	52 (17.0)	41 (14.2)	26 (15.9)	1 (3.6)
Need for flexibility in timing of injection	12 (10.3)	36 (23.2)	47 (15.4)	29 (10.1)	12 (7.3)	1 (3.6)
Other	2 (1.7)	1 (0.6)	4 (1.3)	14 (4.9)	10 (6.1)	1 (3.6)

Source Data: Table: 14.1.2.3.4.1, Listing 16.2.4.3
Note:
[1] Percentage were calculated by taking respective column header count as denominator.
[2] one person may have more than one reason to start Insulin Degludec**.**

11.4 Efficacy Results and Tabulation of Individual Subject Data

11.4.1 Analysis of Efficacy

A decline in HbA1c was observed in overall patients at different time points during their visit. The mean ± SD HbA1c in patients was 9.6 ± 1.92, 8.3 ± 1.61, 8.1 ± 1.39 and 7.8 ± 1.18 at visit 1, visit 2, visit 3 and visit 4, respectively (Table 11 and Figure 3).

A decline in HbA1c was also noted in patients, on OAD and insulin at baseline, at different time points. The mean ± SD HbA1c value was changed from 9.5 ± 1.83 (baseline) to 7.5 ± 0.99 (visit 4) in patients on OAD at baseline. Similarly, mean ± SD HbA1c was changed from 9.8 ± 2.08 (baseline) to 8.2 ± 1.39 (visit 4) in patients receiving insulin previously (Table 12).

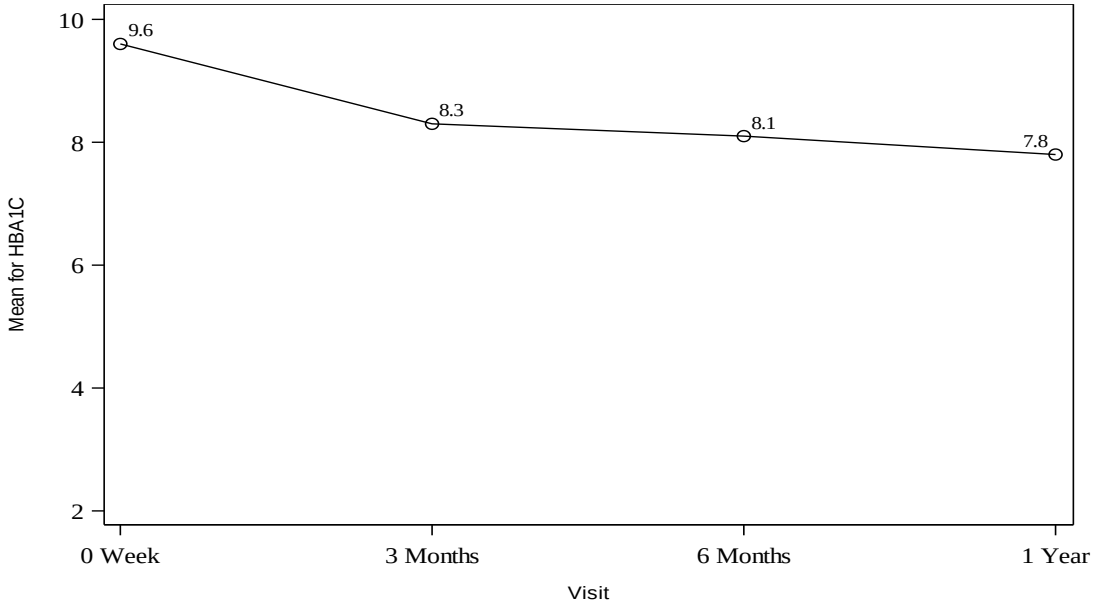
Table 11 Visit wise Summary of HbA1c-EAS population (N = 1024)

Visit	Statistic	Overall (N = 1024)
Visit 1	n	887
	Missing	137
	Mean	9.6
	SD	1.92
	Median	9.3
	Range (Min.:Max.)	(5.4 :18.2)
Visit 2	n	559
	Missing	461
	Mean	8.3
	SD	1.61
	Median	8.1
	Range (Min.:Max.)	(4.6 :13.9)
Visit 3	n	726
	Missing	264
	Mean	8.1
	SD	1.39
	Median	7.6
	Range (Min.:Max.)	(5.7 :14.9)
Visit 4	n	900
	Missing	57
	Mean	7.8
	SD	1.18
	Median	7.5
	Range (Min.:Max.)	(5.0 :14.2)
Source Data: Table 14.2.1.1, Listing 16.2.4.4		

Table 12 Visit wise Summary of HbA1c-EAS population by Previous Medication (N = 1024)

Visit	Statistic	Previous Medication	
Visit 1		OAD	Insulin
	n	600	287
	Missing	81	56
	Mean	9.5	9.8
	SD	1.83	2.08
	Median	9.2	9.6
	Range (Min.:Max.)	(5.4 :17.7)	(5.8 :18.2)
Visit 2	n	390	169
	Missing	291	170
	Mean	8.2	8.8
	SD	1.52	1.73
	Median	7.9	8.4
	Range (Min.:Max.)	(4.6 :13.9)	(6.2 :13.9)
Visit 3	n	507	219
	Missing	149	115
	Mean	7.9	8.5
	SD	1.26	1.60
	Median	7.6	8.0
	Range (Min.:Max.)	(5.7 :12.9)	(6.2 :14.9)
Visit 4	n	608	292
	Missing	26	31
	Mean	7.5	8.2
	SD	0.99	1.39
	Median	7.4	7.9
	Range (Min.:Max.)	(5.0 :12.5)	(5.6 :14.2)
Source Data: Table 14.2.1.1.1, Listing16.2.4.4			

Figure 3 Line Diagram for mean for HbA1c at each visit



Source: Figure 14.2.1.1

FPG-EAS population

A decline in FPG (mg/dL) was observed in overall patients at different time points during their visits. The mean ± SD value of FPG (mg/dL) in patients was 190.7 ± 69.02, 145.0 ± 49.77, 132.5 ± 37.85 and 125.4 ± 31.86 at visit 1, visit 2, visit 3 and visit 4, respectively (Table 13 and Figure 4)

A decline in FPG (mg/dL) was also noted in patients, on OAD and insulin at baseline at different time points. The mean ± SD FPG (mg/dL) was reduced from 185.3 ± 62.21 (baseline) to 123.0 ± 27.16 (visit 4) in patients receiving OAD at baseline. Similarly, mean ± SD FPG (mg/dL) was reduced from 202.9 ± 81.17 (baseline) to 130.2 ± 39.26 (visit 4) in patients previously on insulin (Table 14).

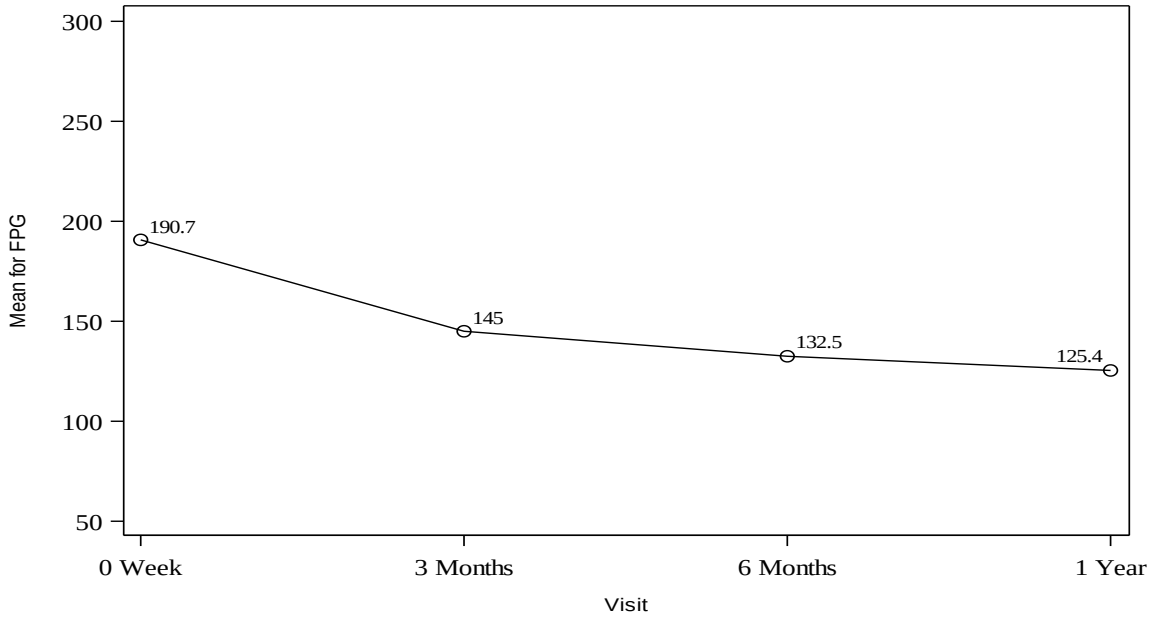
Table 13 Visit wise Summary of FPG-EAS population (N = 1024).

Visit	Statistic	Overall (N = 1024)
Visit 1	n	864
	Missing	160
	Mean	190.7
	SD	69.02
	Median	180.0
	Range (Min.:Max.)	(68.0 :720.0)
Visit 2	n	834
	Missing	186
	Mean	145.0
	SD	49.77
	Median	131.0
	Range (Min.:Max.)	(61.0 :510.0)
Visit 3	n	806
	Missing	184
	Mean	132.5
	SD	37.58
	Median	123.0
	Range (Min.:Max.)	(60.0 :365.0)
Visit 4	n	895
	Missing	62
	Mean	125.4
	SD	31.86
	Median	119.0
	Range (Min.:Max.)	(66.0 :372.0)
Source Data: Table 14.2.1.2, Listing 16.2.4.4		

Table 14 Visit wise Summary of FPG-EAS population by Previous Medication (N = 1024)

Visit	Statistic	Previous Medication	
Visit 1		**OAD**	**Insulin**
	n	599	265
	Missing	82	78
	Mean	185.3	202.9
	SD	62.21	81.17
	Median	174.0	191.0
	Range (Min.:Max.)	(68.0 :611.0)	(70.0 :720.0)
Visit 2	n	589	245
	Missing	92	94
	Mean	143.0	149.8
	SD	45.64	58.36
	Median	131.0	130.0
	Range (Min.:Max.)	(66.0 :431.0)	(61.0 :510.0)
Visit 3	n	561	245
	Missing	95	89
	Mean	131.7	134.4
	SD	36.17	40.63
	Median	122.0	125.0
	Range (Min.:Max.)	(78.0 :360.0)	(60.0 :365.0)
Visit 4	n	597	298
	Missing	37	25
	Mean	123.0	130.2
	SD	27.16	39.26
	Median	118.0	123.0
	Range (Min.:Max.)	(66.0 :333.0)	(67.0 :372.0)
Source Data: Table 14.2.1.2.1, Listing16.2.4.4			

Figure 4 Line Diagram for mean for FPG at each visit



Source: Figure 14.2.1.2

PPG - EAS population

A decline in mean PPG (mg/dL) were observed at corresponding timepoints during each visit in overall population. The mean ± SD of Post breakfast PPG (mg/dL) were reduced from 277.4 ± 81.69 at baseline to 212.0 ± 60.14, 199.8 ± 52.33 and 187.1 ± 48.33 at visit 2, visit 3 and visit 4, respectively. Similarly, mean ± SD of Post lunch PPG (mg/dL) were reduced from 273.3 ± 109.4 at baseline to 201.6 ± 58.33, 191.2 ± 49.19 and 174.3 ± 34.63 at visit 2, visit 3 and visit 4, respectively. The mean ± SD of Post dinner PPG (mg/dL) were reduced from 242.0 ± 103.4 at baseline to 154.0 ± 76.02, 170.0 ± 14.14 and 168.0 ± 29.18 at visit 2, visit 3 and visit 4, respectively (Table 15 and Figure 5).

A decline in mean PPG (mg/dL) was also noted in patients, on OAD and insulin at baseline, at different time points. The mean ± SD Post breakfast PPG (mg/dL) was changed from 276.5 ± 75.70 (baseline) to 212.0 ± 58.91, 198.1 ± 49.63 and 181.2 ± 39.66 at visit 2, visit 3 and visit 4, respectively in patients on OAD at baseline. Similarly, the mean ± SD Post breakfast PPG (mg/dL) was changed from 279.1 ± 93.23 (baseline) to 211.9 ± 62.73, 202.9 ± 56.84 and 196.8 ± 58.78 at visit 2, visit 3 and visit 4, respectively in patients previously on insulin.

The mean ± SD Post lunch PPG (mg/dL) was changed from 267.8 ± 95.70 (baseline) to 192.9 ± 51.33, 186.1 ± 41.42 and 171.2 ± 33.91 at visit 2, visit 3 and visit 4, respectively in patients on OAD at baseline. Similarly, the mean ± SD Post lunch PPG (mg/dL) was changed from 286.0 ± 135.6 (baseline) to 220.3 ± 67.78, 203.7 ± 63.15 and 179.2 ± 35.59 at visit 2, visit 3 and visit 4, respectively in patients previously on insulin.

The mean ± SD Post dinner PPG (mg/dL) was changed from 256.7 ± 115.7 (baseline) to 93.0 ± 1.41, 170.0 ± 14.14 and 170.3 ± 37.98 at visit 2, visit 3 and visit 4, respectively in patients on OAD at baseline. Similarly, the mean ± SD Post dinner PPG (mg/dL) was

changed from 224.8 ± 94.54 (baseline) to 215.0 ± 49.50 and 164.5 ± 21.92 at visit 2, and visit 4, respectively in patients previously on insulin (Table 16).

Table 15 Visit wise Summary of PPG - EAS population (N = 1024)

Parameter/Time point	Statistic	Overall (N = 1024)
Visit 1		
Post breakfast	n	520
	Missing	504
	Mean	277.4
	SD	81.69
	Median	267.0
	Range (Min.:Max.)	(80.0 :540.0)
Post lunch	n	253
	Missing	771
	Mean	273.3
	SD	109.4
	Median	253.0
	Range (Min.:Max.)	(80.7 :1006)
Post dinner	n	13
	Missing	1011
	Mean	242.0
	SD	103.4
	Median	220.0
	Range (Min.:Max.)	(110.0 :455.0)
Visit 2		
Post breakfast	n	512
	Missing	508
	Mean	212.0
	SD	60.14
	Median	200.0
	Range (Min.:Max.)	(62.0 :537.0)
Post lunch	n	246
	Missing	774
	Mean	201.6
	SD	58.33
	Median	192.0
	Range (Min.:Max.)	(102.0 :451.0)
Post dinner	n	4
	Missing	1016
	Mean	154.0
	SD	76.02
	Median	137.0
	Range (Min.:Max.)	(92.0 :250.0)
Visit 3		
Post breakfast	n	522
	Missing	468
	Mean	199.8
	SD	52.33
	Median	190.0
	Range (Min.:Max.)	(81.0 :532.0)
Post lunch	n	229
	Missing	761

Parameter/Time point	Statistic	Overall (N = 1024)
	Mean	191.2
	SD	49.19
	Median	183.0
	Range (Min.:Max.)	(105.0 :400.0)
Post dinner	n	2
	Missing	988
	Mean	170.0
	SD	14.14
	Median	170.0
	Range (Min.:Max.)	(160.0 :180.0)
Visit 4		
Post breakfast	n	564
	Missing	393
	Mean	187.1
	SD	48.33
	Median	180.0
	Range (Min.:Max.)	(87.0 :435.0)
Post lunch	n	284
	Missing	673
	Mean	174.3
	SD	34.63
	Median	170.0
	Range (Min.:Max.)	(111.0 :308.0)
Post dinner	n	5
	Missing	952
	Mean	168.0
	SD	29.18
	Median	152.0
	Range (Min.:Max.)	(145.0 :214.0)
Source Data: Table 14.2.1.3, Listing16.2.4.4		

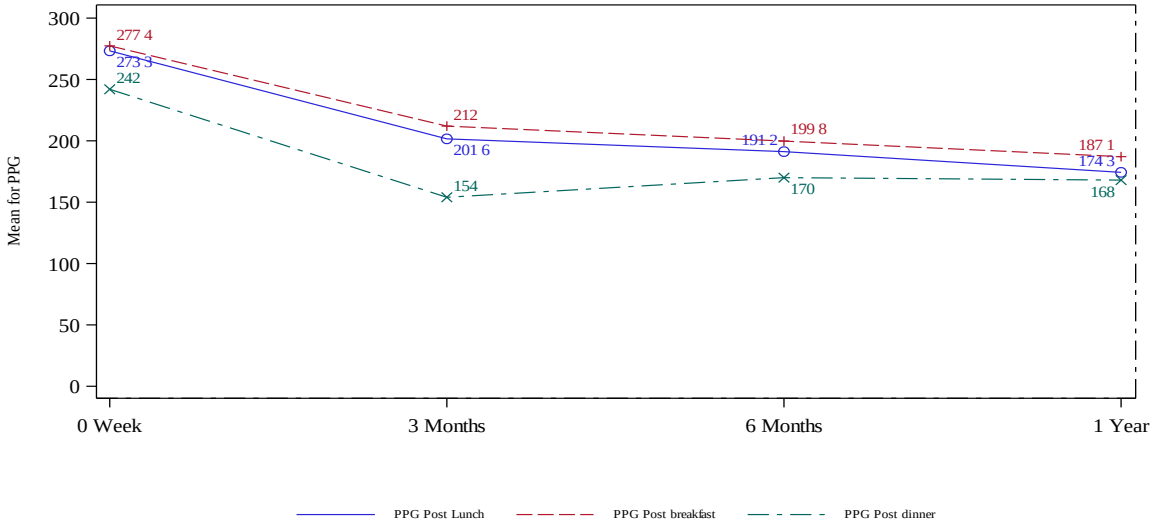
Table 16 Visit wise Summary of PPG-EAS population by Previous Medication (N = 1024)

Parameter/Time point	Statistic	Previous Medication	
Visit 1		**OAD**	**Insulin**
Post breakfast	n	352	168
	Missing	329	175
	Mean	276.5	279.1
	SD	75.70	93.23
	Median	267.0	267.0
	Range (Min.:Max.)	(100.0 :540.0)	(80.0 :538.0)
Post lunch	n	176	77
	Missing	505	266
	Mean	267.8	286.0
	SD	95.70	135.6
	Median	249.4	271.0
	Range (Min.:Max.)	(80.7 :646.0)	(96.0 :1006)
Post dinner	n	7	6
	Missing	674	337
	Mean	256.7	224.8
	SD	115.7	94.54

Parameter/Time point	Statistic	Previous Medication	
	Median	201.0	235.5
	Range (Min.:Max.)	(158.0 :455.0)	(110.0 :340.0)
Visit 2			
Post breakfast	n	342	170
	Missing	339	169
	Mean	212.0	211.9
	SD	58.91	62.73
	Median	197.0	201.0
	Range (Min.:Max.)	(90.0 :480.0)	(62.0 :537.0)
Post lunch	n	168	78
	Missing	513	261
	Mean	192.9	220.3
	SD	51.33	67.78
	Median	189.3	205.5
	Range (Min.:Max.)	(102.0 :451.0)	(124.0 :440.0)
Post dinner	n	2	2
	Missing	679	337
	Mean	93.0	215.0
	SD	1.41	49.50
	Median	93.0	215.0
	Range (Min.:Max.)	(92.0 :94.0)	(180.0 :250.0)
Visit 3			
Post breakfast	n	335	187
	Missing	321	147
	Mean	198.1	202.9
	SD	49.63	56.84
	Median	188.0	198.0
	Range (Min.:Max.)	(81.0 :445.0)	(120.0 :532.0)
Post lunch	n	163	66
	Missing	493	268
	Mean	186.1	203.7
	SD	41.42	63.15
	Median	181.0	190.5
	Range (Min.:Max.)	(105.0 :352.0)	(110.0 :400.0)
Post dinner	n	2	0
	Missing	654	334
	Mean	170.0	-
	SD	14.14	-
	Median	170.0	-
	Range (Min.:Max.)	(160.0 :180.0)	-
Visit 4			
Post breakfast	n	351	213
	Missing	283	110
	Mean	181.2	196.8
	SD	39.66	58.78
	Median	178.0	188.0
	Range (Min.:Max.)	(98.0 :345.0)	(87.0 :435.0)
Post lunch	n	185	99
	Missing	449	224
	Mean	171.6	179.2
	SD	33.91	35.59
	Median	169.0	175.0

Parameter/Time point	Statistic	Previous Medication	
	Range (Min.:Max.)	(111.0 :306.0)	(120.0 :308.0)
Post dinner			
	n	3	2
	Missing	631	321
	Mean	170.3	164.5
	SD	37.98	21.92
	Median	152.0	164.5
	Range (Min.:Max.)	(145.0 :214.0)	(149.0 :180.0)
Source Data: Table 14.2.1.3.1, Listing16.2.4.4			

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



Source: Figure 14.2.1.3

Visit wise summary of change in Glycaemic Control for - EAS population (N = 1024)

Visit wise analysis has shown a significant reduction (p<0.001) in HbA1c from baseline to each subsequent visit in overall population. The mean ± SD reduction in HbA1c from baseline to visit 2, visit 3 and visit 4 was 0.8 ± 1.23, 1.4 ± 1.50 and 1.8 ± 1.68, respectively (Table 17 and Figure 6).

Further results revealed a significant reduction in HbA1c values from baseline to each subsequent visit in patients receiving either OAD (p<0.001) or insulin (p<0.001) at baseline. The mean ± SD reduction in HbA1c from baseline to visit 2, visit 3 and visit 4 was 0.9 ± 1.16, 1.4 ± 1.43 and 1.9 ± 1.59, respectively in patients receiving OAD at baseline. Similarly, mean ± SD reduction in HbA1c from baseline to visit 2, visit 3 and visit 4 was 0.5 ± 1.32, 1.3 ± 1.66 and 1.6 ± 1.87, respectively in patients receiving insulin previously (Table 18).

Table 17 Summary of change in HbA1c for EAS population from Visit 1(Baseline) - EAS population (N = 1024)

Visit	Statistic	Overall (N = 1024)
Visit 4	n	784
	Missing	173

Visit	Statistic	Overall (N = 1024)
	Mean	-1.8
	SD	1.68
	Median	-1.5
	Range (Min.:Max.)	(-11.5 :3.3)
	p-value [1]	<.0001
Visit 3	n	659
	Missing	331
	Mean	-1.4
	SD	1.50
	Median	-1.1
	Range (Min.:Max.)	(-11.7 :4.8)
	p-value [1]	<.0001
Visit 2	n	520
	Missing	500
	Mean	-0.8
	SD	1.23
	Median	-0.5
	Range (Min.:Max.)	(-6.5 :3.3)
	p-value [1]	<.0001

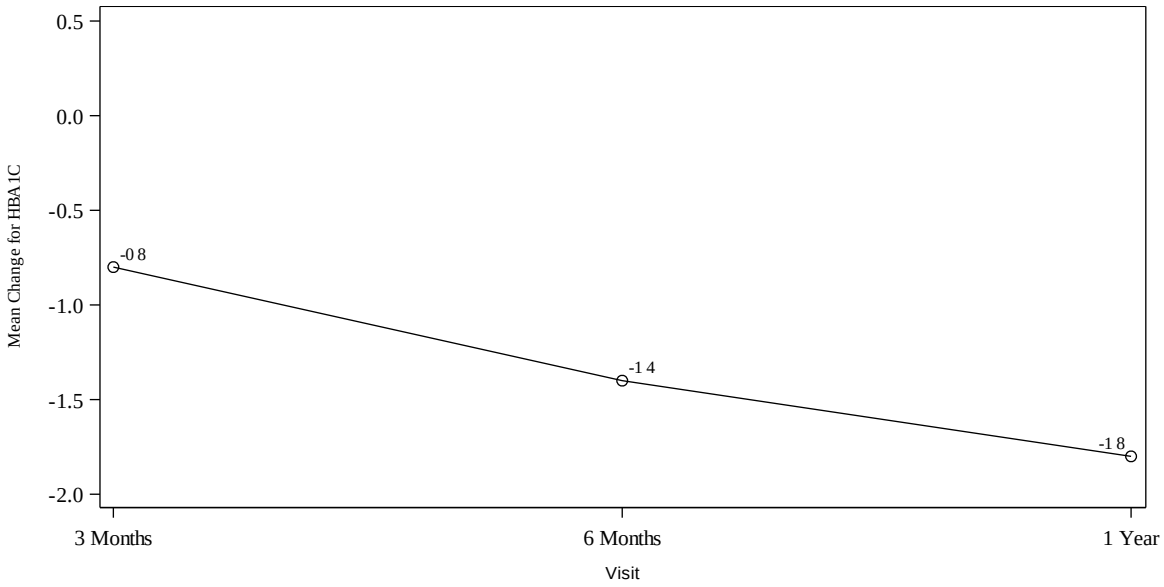
Source Data: Table 14.2.2.1, Listing16.2.4.4
Note:
[1] p-value were calculated by using one sample t- test.

Table 18 Summary of change in HbA1c for EAS population from Visit 1(Baseline) - EAS population by Previous Medication (N = 1024)

Visit	Statistic	Previous Medication	
Visit 4		OAD	Insulin
	n	534	250
	Missing	100	73
	Mean	-1.9	-1.6
	SD	1.59	1.87
	Median	-1.6	-1.3
	Range (Min.:Max.)	(-11.5 :2.1)	(-7.4 :3.3)
	p-value [1]	<.0001	<.0001
Visit 3	n	455	204
	Missing	201	130
	Mean	-1.4	-1.3
	SD	1.43	1.66
	Median	-1.1	-0.9
	Range (Min.:Max.)	(-11.7 :2.9)	(-7.7 :4.8)
	p-value [1]	<.0001	<.0001
Visit 2	n	362	158
	Missing	319	181
	Mean	-0.9	-0.5
	SD	1.16	1.32
	Median	-0.7	-0.3
	Range (Min.:Max.)	(-6.5 :3.3)	(-5.5 :3.3)
	p-value [1]	<.0001	<.0001

Source Data: Table: 14.2.2.1.1, Listing16.2.4.4
Note:
[1] p-value were calculated by using one sample t- test.

Figure 6 Line Diagram for mean change for HbA1c from baseline to each follow-up visit



Source: Figure 14.2.2.1

Change in FPG for EAS population from Visit 1 (Baseline) - EAS population (N = 1024)

Visit wise analysis has shown a significant reduction ($p<0.001$) in FPG (mg/dL) from baseline to each subsequent visit in overall population. The mean ± SD reduction in FPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 45.1 ± 62.97, 57.2 ± 69.84 and 64.7 ± 72.84, respectively (Table 19 and Figure 7).

Further results revealed a significant reduction in FPG (mg/dL) from baseline to each subsequent visit in patients receiving either OAD ($p<0.001$) or insulin ($p<0.001$) at baseline. The mean ± SD reduction in FPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 43.3 ± 51.85, 52.2 ± 59.83 and 62.3 ± 63.96, respectively in patients receiving OAD at baseline. Similarly, mean ± SD reduction in FPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 49.6 ± 85.09, 69.6 ± 89.27 and 70.4 ± 90.41, respectively in patients receiving insulin previously (Table 20).

Table 19 Summary of change in FPG for EAS population from Visit 1(Baseline) - EAS population (N = 1024)

Visit	Statistic	Overall (N = 1024)
Visit 4	n	766
	Missing	191
	Mean	-64.7
	SD	72.84
	Median	-54.0
	Range (Min.:Max.)	(-578 :180.0)
	p-value [1]	<.0001
Visit 3	n	729
	Missing	261
	Mean	-57.2
	SD	69.84
	Median	-48.0
	Range (Min.:Max.)	(-626 :236.0)
	p-value [1]	<.0001
Visit 2	n	770
	Missing	250
	Mean	-45.1
	SD	62.97
	Median	-35.0
	Range (Min.:Max.)	(-358 :433.0)
	p-value [1]	<.0001

Source Data: Table 14.2.2.2, Listing16.2.4.4
Note:
[1] p-value were calculated by using one sample t- test.

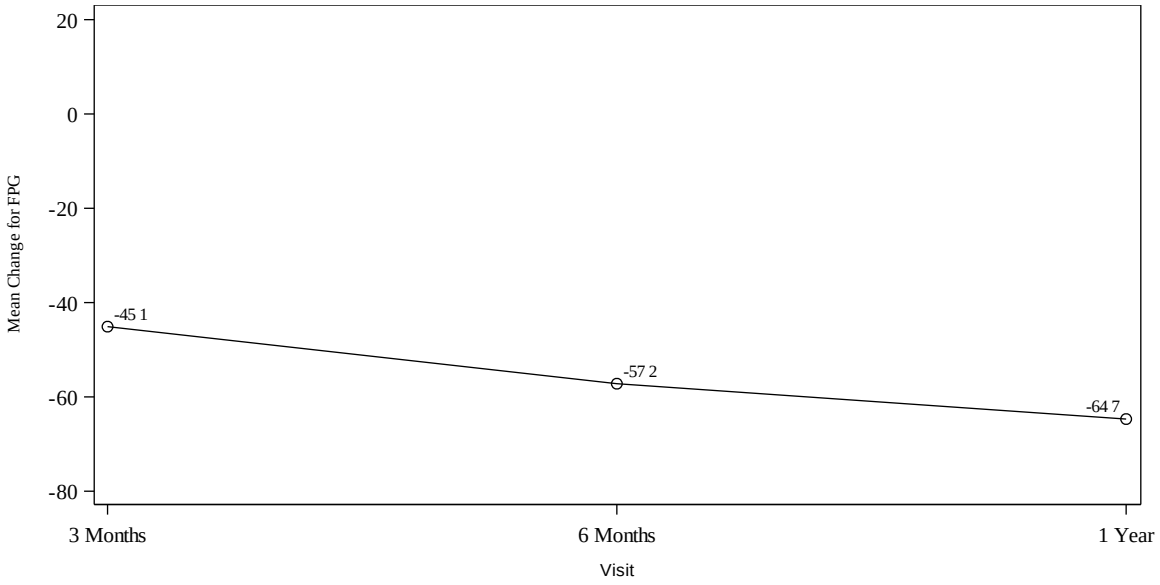
Table 20 Summary of change in FPG for EAS population from Visit 1(Baseline) - EAS population by Previous Medication (N = 1024)

Visit	Statistic	Previous Medication	
Visit 4	n	539	227
	Missing	95	96
	Mean	-62.3	-70.4
	SD	63.96	90.41
	Median	-52.0	-62.0
	Range (Min.:Max.)	(-433 :134.0)	(-578 :180.0)
	p-value [1]	<.0001	<.0001
Visit 3	n	522	207
	Missing	134	127
	Mean	-52.2	-69.6
	SD	59.83	89.27
	Median	-45.0	-56.0
	Range (Min.:Max.)	(-431 :236.0)	(-626 :142.0)
	p-value [1]	<.0001	<.0001
Visit 2	n	554	216
	Missing	127	123
	Mean	-43.3	-49.6
	SD	51.85	85.09
	Median	-34.0	-39.5
	Range (Min.:Max.)	(-320 :157.0)	(-358 :433.0)

Visit	Statistic	Previous Medication	
	p-value [1]	<.0001	<.0001

Source Data: Table: 14.2.2.2.1, Listing16.2.4.4
Note:
[1] p-value were calculated by using one sample t- test.

Figure 7 Line Diagram for mean change for FPG from baseline to each follow-up visit



Source: Figure 14.2.2.2

Change in PPG for EAS population from Visit 1(Baseline) EAS population

(N = 1024)

Visit wise analysis has shown a significant reduction (p<0.001) in PPG (mg/dL), at corresponding timepoints, from baseline to each subsequent visit in overall population. The mean ± SD reduction in Post breakfast PPG (mg/dL) from Baseline to visit 2, visit 3 and visit 4 was 60.3 ± 79.30, 72.1 ± 87.10 and 86.1 ± 94.80, respectively. Similarly, mean ± SD reduction in Post lunch PPG (mg/dL) values from Baseline to visit 2, visit 3 and visit 4 was 55.0 ± 74.46, 69.3 ± 86.70 and 87.8 ± 100.2, respectively. (Table 21 and Figure 8).

Further results revealed a significant reduction in PPG (mg/dL), at corresponding time points, from baseline to each subsequent visit in patients receiving either OAD (p<0.001) or insulin (p<0.001) at baseline. Amongst the patients receiving OAD at baseline, mean ± SD reduction in Post breakfast PPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 62.7 ± 70.76, 77.9 ± 82.76 and 94.1 ± 83.65, respectively. Similarly, in the same patients, mean ± SD reduction in Post lunch PPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 58.5 ± 72.90, 70.4 ± 84.62 and 85.7 ± 97.62, respectively (Table 22).

Amongst the patients receiving insulin previously, mean ± SD reduction in Post breakfast PPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 55.0 ± 95.57, 60.6 ± 94.53 and 70.2 ± 112.4, respectively. Similarly, in the same patients, mean ± SD reduction in

Post lunch PPG (mg/dL) from baseline to visit 2, visit 3 and visit 4 was 45.9 ± 78.32, 66.5 ± 93.15 and 94.8 ± 109.1, respectively (Table 22).

Table 21 Summary of change in PPG for EAS population from Visit 1(Baseline) EAS population (N = 1024)

Visit/Timepoint	Statistic	Overall (N = 1024)
Visit 4		
Post breakfast	n	451
	Missing	506
	Mean	-86.1
	SD	94.80
	Median	-79.0
	Range (Min.:Max.)	(-425 :242.0)
	p-value [1]	<.0001
Post lunch	n	165
	Missing	792
	Mean	-87.8
	SD	100.2
	Median	-73.0
	Range (Min.:Max.)	(-362 :149.0)
	p-value [1]	<.0001
Post dinner	n	0
	Missing	957
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
	p-value [1]	.
Visit 3		
Post breakfast	n	435
	Missing	555
	Mean	-72.1
	SD	87.10
	Median	-66.0
	Range (Min.:Max.)	(-391 :292.0)
	p-value [1]	<.0001
Post lunch	n	169
	Missing	821
	Mean	-69.3
	SD	86.70
	Median	-47.0
	Range (Min.:Max.)	(-294 :97.0)
	p-value [1]	<.0001
Post dinner	n	0
	Missing	990
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
	p-value [1]	.
Visit 2		
Post breakfast	n	436

Visit/Timepoint	Statistic	Overall (N = 1024)
	Missing	584
	Mean	-60.3
	SD	79.30
	Median	-48.5
	Range (Min.:Max.)	(-409 :182.0)
	p-value [1]	<.0001
Post lunch	n	185
	Missing	835
	Mean	-55.0
	SD	74.46
	Median	-38.0
	Range (Min.:Max.)	(-284 :175.0)
	p-value [1]	<.0001
Post dinner	n	0
	Missing	1020
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
	p-value [1]	.

Source Data: Table 14.2.2.3, Listing16.2.4.4
Note:
[1] p-value were calculated by using one sample t- test.

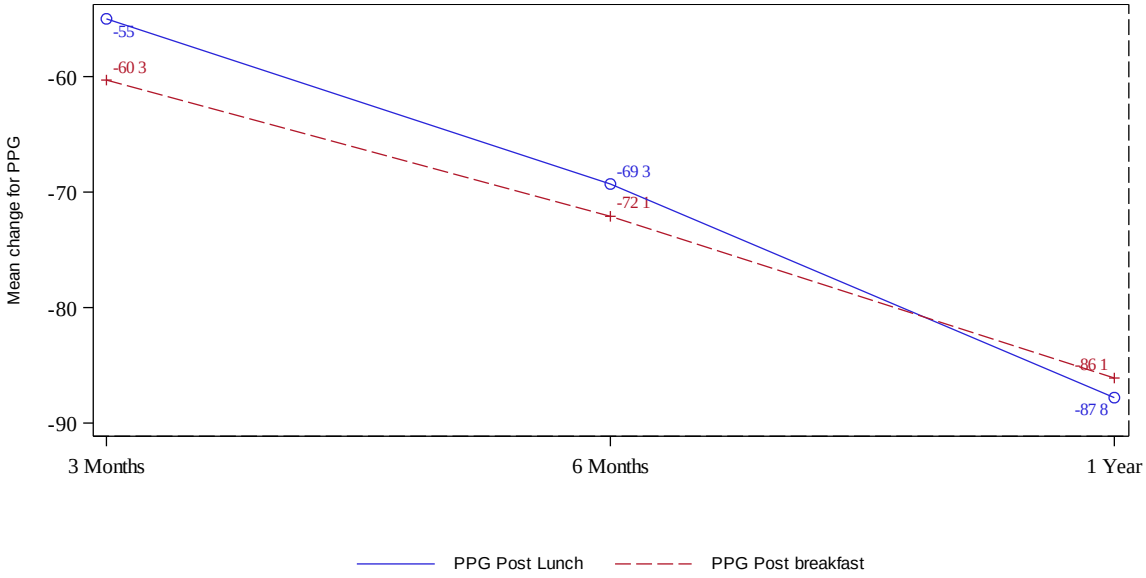
Table 22 Summary of change in PPG for EAS population from Visit 1(Baseline) - EAS population by Previous Medication (N = 1024)

Visit /Time point	Statistic	Previous Medication	
Visit 4		OAD	Insulin
Post breakfast	n	300	151
	Missing	334	172
	Mean	-94.1	-70.2
	SD	83.65	112.4
	Median	-86.4	-64.0
	Range (Min.:Max.)	(-375 :103.0)	(-425 :242.0)
	p-value [1]	<.0001	<.0001
Post lunch	n	126	39
	Missing	508	284
	Mean	-85.7	-94.8
	SD	97.62	109.1
	Median	-73.4	-71.0
	Range (Min.:Max.)	(-362 :129.0)	(-323 :149.0)
	p-value [1]	<.0001	<.0001
Post dinner	n	0	0
	Missing	634	323
	Mean	-	-
	SD	-	-
	Median	-	-
	Range (Min.:Max.)	-	-
	p-value [1]	.	.
Visit 3			
Post breakfast	n	290	145

Visit /Time point	Statistic	Previous Medication	
	Missing	366	189
	Mean	-77.9	-60.6
	SD	82.76	94.43
	Median	-71.0	-59.0
	Range (Min.:Max.)	(-391 :286.6)	(-326 :292.0)
	p-value [1]	<.0001	<.0001
Post lunch	n	124	45
	Missing	532	289
	Mean	-70.4	-66.5
	SD	84.62	93.15
	Median	-44.5	-56.0
	Range (Min.:Max.)	(-294 :88.9)	(-282 :97.0)
	p-value [1]	<.0001	<.0001
Post dinner	n	0	0
	Missing	656	334
	Mean	-	-
	SD	-	-
	Median	-	-
	Range (Min.:Max.)	-	-
	p-value [1]	.	.
Visit 2			
Post breakfast	n	300	136
	Missing	381	203
	Mean	-62.7	-55.0
	SD	70.76	95.57
	Median	-52.0	-36.5
	Range (Min.:Max.)	(-374 :132.0)	(-409 :182.0)
	p-value [1]	<.0001	<.0001
Post lunch	n	133	52
	Missing	548	287
	Mean	-58.5	-45.9
	SD	72.90	78.32
	Median	-40.0	-30.0
	Range (Min.:Max.)	(-284 :131.0)	(-261 :175.0)
	p-value [1]	<.0001	<.0001
Post dinner	n	0	0
	Missing	681	339
	Mean	-	-
	SD	-	-
	Median	-	-
	Range (Min.:Max.)	-	-
	p-value [1]	.	.

Source Data: Table: 14.2.2.3.2, Listing 16.2.4.4
Note:
[1] p-value were calculated by using one sample t- test.

Figure 8 Multiple Line Diagram for mean change for PPG from baseline to each follow-up visit



Source: Figure 14.2.2.3

Confirmed Hypoglycaemic Events - EAS Population

A decrease in confirmed hypoglycaemic events were noted from baseline to subsequent follow up visits with respect to both number of patients and number of events. At baseline, 50 (4.9%) patients were presented with 122 confirmed hypoglycaemic events. These events were reduced in 13 (1.3%), 18 (1.8%) and 27 (2.6%) patients (with 24, 23 and 37 number of events) at follow up visit 2, visit 3 and visit 4, respectively (Table 23).

Table 23 Summary of Confirmed Hypoglycaemic Events - EAS Population (N = 1024)

Visit/ Parameter	Overall (N = 1024)
Visit 1 Baseline Visit	
Confirmed hypoglycaemic events	50 (4.9) (122)
Visit 2 Follow Up Visit	
Confirmed hypoglycaemic events	13 (1.3) (24) [8.950]
Visit 3 Follow Up Visit	
Confirmed hypoglycaemic events	18 (1.8) (23) [9.186]
Visit 4 Final Visit	
Confirmed hypoglycaemic events	27 (2.6) (37) [7.815]

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 subjects (percent of subjects) (number of events) [rate per 100 PYE] in post baseline visits.
[2] Zero frequencies were presented by "- ".

Confirmed Hypoglycaemic Events - EAS Population by Previous Treatment

At baseline, patients on 2 OADs [16 (1.6%)] or more than 2 OADs [15 (1.5%)] were presented with 47 and 39 confirmed hypoglycaemic events, respectively. In addition, 9 (0.9%) and 2 (0.2%) patients with Basal insulin ± OAD and Bolus/Premix insulin had 18

and 4 confirmed hypoglycaemic events, respectively. Follow up visits showed decrease in confirmed hypoglycaemic events in all groups, irrespective of their previous treatment strategy (Table 24).

Table 24 Summary of Confirmed Hypoglycaemic Events - EAS Population by Previous Treatment (N = 1024)

	Previous Insulin Use					
Visit/ Parameter	**No Treatment (N = 113)**	**1 OAD (N = 152)**	**2 OADs (N = 294)**	**More than 2 OADs (N = 276)**	**Basal insulin ± OAD (N = 162)**	**Bolus / Premix (N = 27)**
Visit 1 Baseline Visit						
Confirmed hypoglycaemic events	3 (0.3) (5)	5 (0.5) (9)	16 (1.6) (47)	15 (1.5) (39)	9 (0.9) (18)	2 (0.2) (4)
Visit 2 Follow Up Visit						
Confirmed hypoglycaemic events	-	-	4 (0.4) (8) [10.301]	5 (0.5) (11) [15.203]	4 (0.4) (5) [11.772]	-
Visit 3 Follow Up Visit						
Confirmed hypoglycaemic events	5 (0.5) (7) [24.488]	2 (0.2) (2) [5.274]	4 (0.4) (5) [6.832]	4 (0.4) (4) [6.131]	3 (0.3) (5) [12.840]	-
Visit 4 Final Visit						
Confirmed hypoglycaemic events	6 (0.6) (8) [14.935]	2 (0.2) (2) [2.890]	5 (0.5) (8) [5.887]	7 (0.7) (8) [6.306]	6 (0.6) (10) [13.286]	1 (0.1) (1) [7.921]

Source Data: Table 14.2.3.1, Listing 16.2.6
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator.
General Notes:
[1] Confirmed hypoglycaemic events were presented as: number of subjects (percent of subjects) (number of events) [rate per 100 PYE].
[2] Zero frequencies were presented by "-".

The summary of confirmed hypoglycaemic events by previous medication were summarized in Table 25. Overall, 13 (1.3%), 18 (1.8%), and 27 (2.6%) patients were presented with 24, 23, and 27 confirmed hypoglycaemic events at visit 2, visit 3, and visit 4, respectively. Among patients on insulin, the confirmed hypoglycaemic events were noted in 7 (2.0%), 6 (1.7%) and 11 (3.2%) patients at visit 2 Follow Up, visit 3 Follow Up and visit 4 Final visit, respectively. Similarly, among patients on OAD, the confirmed hypoglycaemic events were noted in 6 (0.9%), 12 (1.8%) and 16 (2.3%) patients at visit 2 Follow Up, visit 3 Follow Up and visit 4 Final visit, respectively. In total, 51 (5.0%) patients have shown 84 confirmed hypoglycaemic events at post baseline visit. This includes 22 (6.4%) and 29 (4.3%) confirmed hypoglycaemic events from patients receiving insulin and OAD, respectively.

Table 25 Summary of Confirmed Hypoglycaemic Events - EAS Population by Previous Medication (N=1024)

Visit/ Parameter	Insulin (N=681)	OAD (N=343)	Overall (N=1024)
Visit 2 Follow Up Visit	7(2.0) (9) [9.947]	6(0.9) (15) [8.442]	13(1.3) (24) [8.950]
Visit 3 Follow Up Visit	6(1.7) (9) [11.003]	12(1.8) (14) [8.305]	18(1.8) (23) [9.186]
Visit 4 Final Visit	11(3.2) (17) [10.664]	16(2.3) (20) [6.369]	27(2.6) (37) [7.815]
Confirmed hypoglycaemic events at Post baseline visits	22(6.4) (35) [10.552]	29(4.3) (49) [7.421]	51(5.0) (84) [8.468]

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 subjects (percent of subjects) (number of events) [rate per 100 PYE] in post baseline visits.
[2] Zero frequencies were presented by "- ".

Glycemic Control from Baseline to Visit 4 EAS Population (N = 1024)

A significant reduction was noted in HbA1c (%) ($p<0.0001$), FPG (mg/dL) ($p<0.0001$) and PPG (mg/dL) [Post breakfast ($p<0.0001$) and Post lunch ($p<0.0001$)] levels from Baseline to visit 4 in EAS population. The mean ± SD reduction in HbA1c (%) and FPG (mg/dL) was 1.8 ± 1.68 and 64.7 ± 72.84 from Baseline to visit 4, respectively. The reduction in Post breakfast and Post lunch PPG (mg/dL) was 86.1 ± 94.80 and 87.8 ± 100.2 from Baseline to visit 4, respectively. Moreover, confirmed hypoglycaemic events at Visit 1 and Post Baseline visits were noted in 50 (4.9%) and 51 (5.0%) patients. The number of confirmed hypoglycaemic events were 122 and 85 at Visit 1 and Post Baseline visits, respectively. Additionally, 5(0.5%) patients were presented with 6 number of ADRs (Table 26).

Table 26 Summary of Glycaemic Control from Basline to Visit 4 EAS Population (N = 1024)

Visit	Statistic	Overall (N = 1024)
Change in HbA1c (%) from baseline to Visit 4		
	n	784
	Missing	173
	Mean	-1.8
	SD	1.68
	Median	-1.5
	Range (Min.:Max.)	(-11.5 :3.3)
	p-value [1]	<.0001
Change in FPG (mg/dl) from baseline to Visit 4		
	n	766
	Missing	191
	Mean	-64.7
	SD	72.84
	Median	-54.0
	Range (Min.:Max.)	(-578 :180.0)
	p-value [1]	<.0001
Change in PPG (mg/dl) from baseline to Visit 4		
Post breakfast	n	451
	Missing	506
	Mean	-86.1
	SD	94.80
	Median	-79.0
	Range (Min.:Max.)	(-425 :242.0)
	p-value [1]	<.0001
Post lunch	n	165
	Missing	792
	Mean	-87.8
	SD	100.2
	Median	-73.0
	Range (Min.:Max.)	(-362 :149.0)
	p-value [1]	<.0001
Post dinner	n	0
	Missing	957
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
	p-value [1]	.
Confirmed hypoglycaemic events at Visit 1		50 (4.9) (122)
Confirmed hypoglycaemic events at Post baseline visits		51 (5.0) (84) [8.5]
ADR		5(0.5) (6) [0.6]
Source Table: 14.2.4.		

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

For secondary efficacy data (i.e. for HbA1c and FBG), missing data points were dealt with using LOCF (Last Observation Carried Forward). There was no imputation for the repeated measure analysis. No other imputation was done for the missing data.

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 42 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 Subjects

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-Subject Displays

Not applicable.

11.4.7 Efficacy Conclusions

IDeg provides effective long-term improvements in glycaemic control. It significantly reduced HbA1c (%) (p<0.0001), FPG (mg/dL) (p<0.0001) and PPG (mg/dL) [Post breakfast (p<0.0001) and Post lunch (p<0.0001)] levels from baseline to end of Study. The reduction for pre- and post- breakfast, in particular, reflects the effect of greater basal control. Furthermore, majority of patients were started or switched to IDeg due to unsatisfactory HbA1c (%), FBG (mg/dL) and PPG (mg/dL) control. In some cases, patients were switched to IDeg due to side effect from previous therapies and risk of hypoglycaemia. It is possible that these advantages with IDeg, in particular, efficacious lowering of HbA1c (%), FPG (mg/dL) and PPG (mg/dL) values together 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 Tresiba®, based on clinical judgment by their treating physician, were treated with Tresiba®.

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

Adverse Events

AEs were collected and recorded from the time the patient signed the ICD until Study completion. A total of 44 AEs have been reported during the Study period. Among the cohort, a total of 28 (2.6%) patients reported at least 1 AE. Of 28 patients, 19 (1.8%) reported one and 9 (0.9%) reported more than 1 AEs. Among total AEs, there were 2 serious and 42 non-serious AEs which was presented in 2 (0.2%) and 28 (2.6%) patients, respectively. Both serious AEs were not life threatening. 36 AEs in 24 (2.3%) patients were mild in nature, while 8 AEs in 5(0.5%) patients were moderate in nature. No AE was severe in nature. Except 2 AEs in 2 (0.2%) patients, 41 AEs in 27 (2.6%) patient get recovered/resolved during Study period. Causality assessment showed 38 events, encountered in 23 (2.2%) patients, to be unlikely associated with Study drug. Additionally, 5 and 1 events were in Probable and possible category, respectively. No dose was changed in 12 (1.1%) patients, while dose was reduced and increased in 3 (0.3%) and 2 (0.2%) patients, respectively. An overall summary of treatment - emergent AEs (TEAEs) reported during the Study for the Safety population is presented in Table 27 and listed by patient in Listing.

Table 27 Summary of Adverse Event - SAS Population (N = 1057)

Category, n (%) [1]	Overall (N = 1057)
Total number of AEs reported	44
Subjects reporting any AEs	28(2.6)
Subjects reporting 1 AE	19(1.8)[19]

Category, n (%) [1]	Overall (N = 1057)
Subjects reporting >1 AEs	9(0.9)[25]
AE is serious	
Yes	2(0.2)[2]
No	28(2.6)[42]
If Yes, is it life threatening [2]	
Yes	-
No	2(100.0)[2]
Severity	
Mild	24(2.3)[36]
Moderate	5(0.5)[8]
Severe	-
Outcome of AE	
Recovered/resolved	27(2.6)[41]
Not recovered/not resolved	2(0.2)[2]
Recovering/resolving	-
Fatal	-
Recovered/resolved with sequelae	1(0.1)[1]
Unknown	-
Causality	
Probable	4(0.4)[5]
Possible	1(0.1)[1]
Unlikely	23(2.2)[38]
Action taken to Study product(s) due to AE	
Drug interrupted	-
Drug withdrawn	-
Dose reduced	3(0.3)[4]
Dose increased	2(0.2)[2]
Dose not changed	12(1.1)[19]
Unknown	-
Not applicable	14(1.3)[19]

Source Data: Table 14.3.1.1, Listing 16.2.7
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.
[3] All Adverse events were presented as: number of subjects (percent of subjects) (number of events).
[4] AE's were coded by using MedDRA version 20.0. Subjects were count once for each SOC or Preferred Term. One subject may had reported more than one event per SOC class or Preferred Term.

12.2.2 Display of adverse events

Adverse events by System Organ Class and Preferred Term - SAS Population (N = 1057)

AEs were coded using MedDRA. All AEs were categorized by System Organ Class (SOC) and summarized by Preferred Term. A total of 8 (0.8%) patients were encountered with 9 events in the class of General disorders and administration site conditions. This was followed by Metabolism and nutrition disorders [6 (0.6%)], Infections and infestations [5 (0.5%)], Nervous system disorders [5 (0.5%)], Musculoskeletal and connective tissue disorders [4 (0.4%)], Gastrointestinal disorders [3 (0.3%)], Skin and subcutaneous tissue disorders [3 (0.3%)], Ear and labyrinth disorders [1 (0.1%)], Eye disorders [1 (0.1%)], Renal and urinary disorders [1 (0.1%)], Respiratory, thoracic and mediastinal disorders [1 (0.1%)] and vascular disorder [1 (0.1%)].

Among General disorders and administration site conditions, Asthenia and Peripheral swelling were present in 3 (0.3%) patients each, followed by Pyrexia [2 (0.2%)] and Pain [1 (0.1%)]. The number of events of Asthenia, Peripheral swelling, Pyrexia and Pain were 3, 3, 2 and 1, respectively. The rates of overall Asthenia, Peripheral swelling, pyrexia and Pain were 0.303, 0.302, 0.202 and 0.101 episodes per 100 person-years'.

Among metabolism and nutrition disorder, Hypoglycaemia was reported in 5 (0.5%) patients, followed by Hyperglycaemia [1 (0.1%)], Hyperkalaemia [1 (0.1%)] and Hyponatraemia [1 (0.1%)]. The number of events of Hypoglycaemia, Hyperglycaemia, Hyperkalaemia and Hyponatraemia were 6, 1, 1 and 1, respectively. The rates of overall Hypoglycaemia, Hyperglycaemia, Hyperkalaemia and Hyponatraemia were 0.605, 0.101, 0.101 and 0.101 episodes per 100 person-years'.

Among Infections and infestations, Gastroenteritis was reported in 2 (0.2%) patients, followed by Common Cold [1 (0.1%)], Upper respiratory tract infection [1 (0.1%)] and Urinary tract infection [1 (0.1%)]. The number of events of Gastroenteritis, Common Cold, Upper respiratory tract infection and Urinary tract infection are 2, 1, 1 and 1, respectively. The rates of overall Gastroenteritis, Common Cold, Upper respiratory tract infection and Urinary tract infection were 0.202, 0.101, 0.101 and 0.101 episodes per 100 person-years'.

Among Nervous system disorders, Dizziness and Hypoaesthesia were present in 2 (0.2%) patients each, followed by lethargy [1 (0.1%)]. The number of events of Dizziness, Hypoaesthesia and Lethargy were 2 2 and 1, respectively. The rates of overall Dizziness, Hypoaesthesia and Lethargy were 0.202, 0.202 and 0.101 episodes per 100 person-years'.

Among Musculoskeletal and connective tissue disorders, Pain in extremity was reported in 2 (0.2%) patients, followed by Arthralgia [1 (0.1%)], Musculoskeletal pain [1 (0.1%)] and Musculoskeletal stiffness [1 (0.1%)]. The number of events of Gastroenteritis, Common Cold, Upper respiratory tract infection and Urinary tract infection are 2, 1, 1 and 1, respectively. The rates of overall Gastroenteritis, Common Cold, Upper respiratory tract infection and Urinary tract infection were 0.202, 0.101, 0.101 and 0.101 episodes per 100 person-years'.

Among Gastrointestinal disorders, Acid peptic disease, Gastritis and Nausea were reported in 1 (0.1%) patient each. One event was noted of Acid peptic disease, Gastritis and Nausea each. The rates of overall Acid peptic disease, Gastritis and Nausea were 0.101 episodes per 100 person-years'.

Among Skin and subcutaneous tissue disorders, Hyperkeratosis, Skin burning sensation and Swelling face were reported in 1 (0.1%) patient each. One event was noted in each class. The rates of overall Hyperkeratosis, Skin burning sensation and Swelling face were 0.101 episodes per 100 person-years'.

Other disorders, viz. Ear and labyrinth disorders, Eye disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders and Vascular disorders were present in 1 (0.1%) each. The rates of overall these diseases were 0.101 episodes per 100 person-years' (Table 28).

Table 28 Summary of adverse events by System Organ Class and Preferred Term - SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1057)
Total number of subjects with at least one adverse event	28 (2.6)
Total number of adverse events, n	44
General disorders and administration site conditions	8 (0.8) (9) [7.6]
Asthenia	3 (0.3) (3) [2.8] (0.303)
Peripheral swelling	3 (0.3) (3) [2.8] (0.302)
Pyrexia	2 (0.2) (2) [1.9] (0.202)
Pain	1 (0.1) (1) [0.9] (0.101)
Metabolism and nutrition disorders	6 (0.6) (9) [5.7]
Hypoglycaemia	5 (0.5) (6) [4.7] (0.605)
Hyperglycaemia	1 (0.1) (1) [0.9] (0.101)
Hyperkalaemia	1 (0.1) (1) [0.9] (0.101)
Hyponatraemia	1 (0.1) (1) [0.9] (0.101)
Infections and infestations	5 (0.5) (5) [4.7]
Gastroenteritis	2 (0.2) (2) [1.9] (0.202)
Common cold	1 (0.1) (1) [0.9] (0.101)
Upper respiratory tract infection	1 (0.1) (1) [0.9] (0.101)
Urinary tract infection	1 (0.1) (1) [0.9] (0.101)
Nervous system disorders	5 (0.5) (5) [4.7]
Dizziness	2 (0.2) (2) [1.9] (0.202)
Hypoaesthesia	2 (0.2) (2) [1.9] (0.202)
Lethargy	1 (0.1) (1) [0.9] (0.101)
Musculoskeletal and connective tissue disorders	4 (0.4) (5) [3.8]
Pain in extremity	2 (0.2) (2) [1.9] (0.202)
Arthralgia	1 (0.1) (1) [0.9] (0.101)
Musculoskeletal pain	1 (0.1) (1) [0.9] (0.101)
Musculoskeletal stiffness	1 (0.1) (1) [0.9] (0.101)
Gastrointestinal disorders	3 (0.3) (3) [2.8]
Acid peptic disease	1 (0.1) (1) [0.9] (0.101)
Gastritis	1 (0.1) (1) [0.9] (0.101)
Nausea	1 (0.1) (1) [0.9] (0.101)
Skin and subcutaneous tissue disorders	3 (0.3) (3) [2.8]
Hyperkeratosis	1 (0.1) (1) [0.9] (0.101)
Skin burning sensation	1 (0.1) (1) [0.9] (0.101)
Swelling face	1 (0.1) (1) [0.9] (0.101)
Ear and labyrinth disorders	1 (0.1) (1) [0.9]
Vertigo labyrinthine	1 (0.1) (1) [0.9] (0.101)
Eye disorders	1 (0.1) (1) [0.9]
Macular oedema	1 (0.1) (1) [0.9] (0.101)
Renal and urinary disorders	1 (0.1) (1) [0.9]
Nocturia	1 (0.1) (1) [0.9] (0.101)
Respiratory, thoracic and mediastinal disorders	1 (0.1) (1) [0.9]
Cough	1 (0.1) (1) [0.9] (0.101)
Vascular disorders	1 (0.1) (1) [0.9]
Hypertension	1 (0.1) (1) [0.9] (0.101)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1057)
Source Data: Table 14.3.1.2, Listing 16.2.7 **Note:** [1] Percentage 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 System Organ Class were presented as: number of subjects (percent of subjects) (number of events) [incidence rate] (rate per 100 PYE).System Organ Class were presented as: number of subjects (percent of subjects) (number of events) [incidence rate]. [3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 = 1057)

Majority of AEs in each SOC were mild in nature. Amongst the patients with General disorders and administration site conditions, one patient each with Pyrexia and Pain, had shown moderate AE.

Amongst the patients with Metabolism and nutrition disorders, Hypoglycaemia was mild in all the 5 (0.5%) patients. However, one patient with each Hyperglycaemia, Hyperkalaemia and Hyponatraemia had shown moderate AE.

Amongst the patients with Infections and infestations, Nervous system disorders, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, all patients had shown mild AE.

Amongst the patients with Skin and subcutaneous tissue disorders, one patient (0.1%) with Hyperkeratosis had shown moderate AE. Unlike to this, Skin burning sensation and Swelling face were mild in nature in all the patients.

Amongst the patients with Ear and labyrinth disorders, 1 (0.1%) patient with Vertigo labyrinthine had shown moderate AE.

Amongst the patients with Eye disorders, 1 (0.1%) patient with Macular oedema had shown moderate AE.

Other AEs viz. Renal and urinary disorders (Nocturia), Respiratory, thoracic and mediastinal disorders (Cough) and Vascular disorders (Hypertension) were mild in nature (Table 29).

Table 29 Summary of Adverse events by System Organ Class and Preferred Term by severity- SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Severity	Overall (N = 1057)
Total number of subjects with at least one adverse event		28 (2.6)
Total number of adverse events, n		44
General disorders and administration site conditions		8 (0.8) (9) [7.6]
Asthenia		3 (0.3) (3) [2.8]
	Mild	3 (0.3) [3] [2.8]
	Moderate	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Severity	Overall (N = 1057)
	Severe	-
Peripheral swelling		3 (0.3) (3) [2.8]
	Mild	3 (0.3) [3] [2.8]
	Moderate	-
	Severe	-
Pyrexia		2 (0.2) (2) [1.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
		1 (0.1) (1) [0.9]
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Metabolism and nutrition disorders		6 (0.6) (9) [5.7]
Hypoglycaemia		5 (0.5) (6) [4.7]
	Mild	5 (0.5) [6] [4.7]
	Moderate	-
	Severe	-
Hyperglycaemia		1 (0.1) (1) [0.9
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Hyperkalaemia		1 (0.1) (1) [0.9]
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Hyponatraemia		1 (0.1) (1) [0.9]
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Infections and infestations		5 (0.5) (5) [4.7]
Gastroenteritis		2 (0.2) (2) [1.9]
	Mild	2 (0.2) [2] [1.9]
	Moderate	-
	Severe	-
Common cold		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Upper respiratory tract infection		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Urinary tract infection		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Nervous system disorders		5 (0.5) (5) [4.7]
Dizziness		2 (0.2) (2) [1.9]
	Mild	2 (0.2) [2] [1.9]
	Moderate	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Severity	Overall (N = 1057)
	Severe	-
Hypoaesthesia		2 (0.2) (2) [1.9]
	Mild	2 (0.2) [2] [1.9]
	Moderate	-
	Severe	-
Lethargy		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Musculoskeletal and connective tissue disorders		4 (0.4) (5) [3.8]
Pain in extremity		2 (0.2) (2) [1.9]
	Mild	2 (0.2) [2] [1.9]
	Moderate	-
	Severe	-
Arthralgia		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Musculoskeletal pain		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Musculoskeletal stiffness		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Gastrointestinal disorders		3 (0.3) (3) [2.8]
Acid peptic disease		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Gastritis		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Nausea		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Skin and subcutaneous tissue disorders		3 (0.3) (3) [2.8]
Hyperkeratosis		1 (0.1) (1) [0.9]
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Skin burning sensation		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Swelling face		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Severity	Overall (N = 1057)
	Moderate	-
	Severe	-
Ear and labyrinth disorders		1 (0.1) (1) [0.9]
Vertigo labyrinthine		1 (0.1) (1) [0.9]
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Eye disorders		1 (0.1) (1) [0.9]
Macular oedema		1 (0.1) (1) [0.9]
	Mild	-
	Moderate	1 (0.1) [1] [0.9]
	Severe	-
Renal and urinary disorders		1 (0.1) (1) [0.9]
Nocturia		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Respiratory, thoracic and mediastinal disorders		1 (0.1) (1) [0.9]
Cough		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-
Vascular disorders		1 (0.1) (1) [0.9]
Hypertension		1 (0.1) (1) [0.9]
	Mild	1 (0.1) [1] [0.9]
	Moderate	-
	Severe	-

Source Data: Table: 14.3.1.3, Listing 16.2.7
Note:
[1] Percentage 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 were presented as: number of subjects (percent of subjects) (number of events) [incidence rate] .
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 Causality- SAS Population (N = 1057)

Majority of AEs in all SOC were Unlikely associated with Study drug. Amongst the General disorders and administration site conditions, all AEs were Unlikely associated with Study drug.

Amongst the events related to Metabolism and nutrition disorders, 3 hypoglycaemic events were Unlikely associated with Study drug. Moreover, 2 and 1 events had Probable and Possible relationship, respectively. In addition, 1 hyperglycaemic event in 1 (0.1%) patient had probable relationship with Study drug. One event of Hyperkalaemia and Hyponatraemia, in 1 (0.1) patient each, had Probable relationship with Study drug.

Amongst the events related with Infections and infestations, 1 event of each, Urinary tract infection and gastroentritis had probable relationship with Study drug. Other event in this class were Unlikely associated with Study drug.

All other event related to nervous system disorders, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Ear and labyrinth disorders, Eye disorders, Renal and urinary disorders and Respiratory, thoracic and mediastinal disorders were unlikely associated with the Study drug (Table 30).

Table 30 Summary of Adverse events by System Organ Class and Preferred Term by Causality- SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Causality	Overall (N = 1057)
Total number of subjects with at least one adverse event		28 (2.6)
Total number of adverse events, n		44
General disorders and administration site conditions		8 (0.8) (9) [7.6]
Asthenia		3 (0.3) (3) [2.8]
	Probable	-
	Possible	-
	Unlikely	3 (0.3) [3] [2.8]
Peripheral swelling		3 (0.3) (3) [2.8]
	Probable	-
	Possible	-
	Unlikely	3 (0.3) [3] [2.8]
Pyrexia		2 (0.2) (2) [1.9]
	Probable	-
	Possible	-
	Unlikely	2 (0.2) [2] [1.9]
Pain		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Metabolism and nutrition disorders		6 (0.6) (9) [5.7]
Hypoglycaemia		5 (0.5) (6) [4.7]
	Probable	1 (0.1) [2] [1.9]
	Possible	1 (0.1) [1] [0.9]
	Unlikely	3 (0.3) [3] [2.8]
Hyperglycaemia		1 (0.1) (1) [0.9]
	Probable	1 (0.1) [1] [0.9]
	Possible	-
	Unlikely	-
Hyperkalaemia		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Hyponatraemia		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Infections and infestations		5 (0.5) (5) [4.7]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Causality	Overall (N = 1057)
Gastroenteritis		2 (0.2) (2) [1.9]
	Probable	1 (0.1) [1] [0.9]
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Common cold		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Upper respiratory tract infection		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Urinary tract infection		1 (0.1) (1) [0.9]
	Probable	1 (0.1) [1] [0.9]
	Possible	-
	Unlikely	-
Nervous system disorders		5 (0.5) (5) [4.7]
Dizziness		2 (0.2) (2) [1.9]
	Probable	-
	Possible	-
	Unlikely	2 (0.2) [2] [1.9]
Hypoaesthesia		2 (0.2) (2) [1.9]
	Probable	-
	Possible	-
	Unlikely	2 (0.2) [2] [1.9]
Lethargy		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Musculoskeletal and connective tissue disorders		4 (0.4) (5) [3.8]
Pain in extremity		2 (0.2) (2) [1.9]
	Probable	-
	Possible	-
	Unlikely	2 (0.2) [2] [1.9]
Arthralgia		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Musculoskeletal pain		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Musculoskeletal stiffness		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Gastrointestinal disorders		3 (0.3) (3) [2.8]
Acid peptic disease		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Causality	Overall (N = 1057)
	Unlikely	1 (0.1) [1] [0.9]
Gastritis		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Nausea		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Skin and subcutaneous tissue disorders		3 (0.3) (3) [2.8]
Hyperkeratosis		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Skin burning sensation		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Swelling face		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Ear and labyrinth disorders		1 (0.1) (1) [0.9]
Vertigo labyrinthine		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Eye disorders		1 (0.1) (1) [0.9]
Macular oedema		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Renal and urinary disorders		1 (0.1) (1) [0.9]
Nocturia		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Respiratory, thoracic and mediastinal disorders		1 (0.1) (1) [0.9]
Cough		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]
Vascular disorders		1 (0.1) (1) [0.9]
Hypertension		1 (0.1) (1) [0.9]
	Probable	-
	Possible	-
	Unlikely	1 (0.1) [1] [0.9]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Causality	Overall (N = 1057)
Source Data: Table 14.3.1.4, Listing 16.2.7 **Note:** [1] Percentage 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 were presented as: number of subjects (percent of subjects) (number of events) [incidence rate] . [3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 Action taken- SAS Population (N = 1057)

Among the patients presented with General disorders and administration site conditions, majority of patients did not change the dose.

Amongst the patients with Metabolism and nutrition disorders, dose was reduced in 3 (0.3%) patients presented with Hypoglycaemia and increased in 1 (0.1%) patient with Hyperglycaemia. Doses were not changed in patients presented with Hyperkalaemia and Hyponatraemia.

Amongst the patients with eye disorder, dose was increased in 1 (0.1%) presented with Macular oedema.

For all other events, no dose of Study drug was changed during the course of Study (Table 31).

Table 31 Summary of adverse events by System Organ Class and Preferred Term by Action taken- SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Action Taken	Overall(N = 1057)
Total number of subjects with at least one adverse event		28 (2.6)
Total number of adverse events, n		44
General disorders and administration site conditions		8 (0.8) (9) [7.6]
Asthenia		3 (0.3) (3) [2.8]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	3 (0.3) [3] [2.8]
	Unknown	-
	Not applicable	-
Peripheral swelling		3 (0.3) (3) [2.8]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	2 (0.2) [2] [1.9]
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Pyrexia		2 (0.2) (2) [1.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	2 (0.2) [2] [1.9]
Pain		1 (0.1) (1) [0.9]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Action Taken	Overall(N = 1057)
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Metabolism and nutrition disorders		6 (0.6) (9) [5.7]
Hypoglycaemia		5 (0.5) (6) [4.7]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	3 (0.3) [4] [3.8]
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	2 (0.2) [2] [1.9]
Hyperglycaemia		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	1 (0.1) [1] [0.9]
	Dose not changed	-
	Unknown	-
	Not applicable	-
Hyperkalaemia		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Hyponatraemia		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Infections and infestations		5 (0.5) (5) [4.7]
Gastroenteritis		2 (0.2) (2) [1.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Action Taken	Overall(N = 1057)
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Common cold		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Upper respiratory tract infection		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Urinary tract infection		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Nervous system disorders		5 (0.5) (5) [4.7]
Dizziness		2 (0.2) (2) [1.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	2 (0.2) [2] [1.9]
Hypoaesthesia		2 (0.2) (2) [1.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	2 (0.2) [2] [1.9]
Lethargy		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Action Taken	Overall(N = 1057)
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Musculoskeletal and connective tissue disorders		4 (0.4) (5) [3.8]
Pain in extremity		2 (0.2) (2) [1.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	2 (0.2) [2] [1.9]
Arthralgia		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Musculoskeletal pain		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Musculoskeletal stiffness		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Gastrointestinal disorders		3 (0.3) (3) [2.8]
Acid peptic disease		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Action Taken	Overall(N = 1057)
Gastritis		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Nausea		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Skin and subcutaneous tissue disorders		3 (0.3) (3) [2.8]
Hyperkeratosis		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Skin burning sensation		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Swelling face		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-
Ear and labyrinth disorders		1 (0.1) (1) [0.9]
Vertigo labyrinthine		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Action Taken	Overall(N = 1057)
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Eye disorders		1 (0.1) (1) [0.9]
Macular oedema		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	1 (0.1) [1] [0.9]
	Dose not changed	-
	Unknown	-
	Not applicable	-
Renal and urinary disorders		1 (0.1) (1) [0.9]
Nocturia		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Respiratory, thoracic and mediastinal disorders		1 (0.1) (1) [0.9]
Cough		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	-
	Unknown	-
	Not applicable	1 (0.1) [1] [0.9]
Vascular disorders		1 (0.1) (1) [0.9]
Hypertension		1 (0.1) (1) [0.9]
	Drug interrupted	-
	Drug withdrawn	-
	Dose reduced	-
	Dose increased	-
	Dose not changed	1 (0.1) [1] [0.9]
	Unknown	-
	Not applicable	-

Source Data: Table: 14.3.1.5, Listing 16.2.7
Note:
[1] Percentage 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 were presented as: number of subjects (percent of subjects) (number of events) [incidence rate] .
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 Outcome- SAS Population (N = 1057)

Majority of events in this Study were recovered/resolved. Amongst the patients with General disorders and administration site conditions, all AEs were recovered/resolved, except 1 (0.1%) patient of Peripheral swelling who Recovered/resolved with sequelae.

Amongst the patients with Musculoskeletal and connective tissue disorders and Renal and urinary disorders, 1 event of Musculoskeletal pain and Nocturia each was not recovered/not resolved.

All other AEs from all SOC were recovered/resolved during the course of Study (Table 32).

Table 32 Summary of Adverse events by System Organ Class and Preferred Term by Outcome- SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Outcome	Overall (N = 1057)
Total number of subjects with at least one adverse event		28 (2.6)
Total number of adverse events, n		44
General disorders and administration site conditions		8 (0.8) (9) [7.6]
Asthenia		3 (0.3) (3) [2.8]
	Recovered/resolved	3 (0.3) [3] [2.8]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Peripheral swelling		3 (0.3) (3) [2.8]
	Recovered/resolved	2 (0.2) [2] [1.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	1 (0.1) [1] [0.9]
	Unknown	-
Pyrexia		2 (0.2) (2) [1.9]
	Recovered/resolved	2 (0.2) [2] [1.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Pain		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Outcome	Overall (N = 1057)
	Unknown	-
Metabolism and nutrition disorders		6 (0.6) (9) [5.7]
Hypoglycaemia		5 (0.5) (6) [4.7]
	Recovered/resolved	5 (0.5) [6] [5.7]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Hyperglycaemia		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Hyperkalaemia		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Hyponatraemia		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Infections and infestations		5 (0.5) (5) [4.7]
Gastroenteritis		2 (0.2) (2) [1.9]
	Recovered/resolved	2 (0.2) [2] [1.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Common cold		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Upper respiratory tract infection		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Outcome	Overall (N = 1057)
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Urinary tract infection		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Nervous system disorders		5 (0.5) (5) [4.7]
Dizziness		2 (0.2) (2) [1.9]
	Recovered/resolved	2 (0.2) [2] [1.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Hypoaesthesia		2 (0.2) (2) [1.9]
	Recovered/resolved	2 (0.2) [2] [1.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Lethargy		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Musculoskeletal and connective tissue disorders		4 (0.4) (5) [3.8]
Pain in extremity		2 (0.2) (2) [1.9]
	Recovered/resolved	2 (0.2) [2] [1.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Arthralgia		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Outcome	Overall (N = 1057)
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Musculoskeletal pain		1 (0.1) (1) [0.9]
	Recovered/resolved	-
	Not recovered/not resolved	1 (0.1) [1] [0.9]
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Musculoskeletal stiffness		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Gastrointestinal disorders		3 (0.3) (3) [2.8]
Acid peptic disease		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Gastritis		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Nausea		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Skin and subcutaneous tissue disorders		3 (0.3) (3) [2.8]
Hyperkeratosis		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Outcome	Overall (N = 1057)
Skin burning sensation		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Swelling face		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Ear and labyrinth disorders		1 (0.1) (1) [0.9]
Vertigo labyrinthine		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Eye disorders		1 (0.1) (1) [0.9]
Macular oedema		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Renal and urinary disorders		1 (0.1) (1) [0.9]
Nocturia		1 (0.1) (1) [0.9]
	Recovered/resolved	-
	Not recovered/not resolved	1 (0.1) [1] [0.9]
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Respiratory, thoracic and mediastinal disorders		1 (0.1) (1) [0.9]
Cough		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-
Vascular disorders		1 (0.1) (1) [0.9]

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Outcome	Overall (N = 1057)
Hypertension		1 (0.1) (1) [0.9]
	Recovered/resolved	1 (0.1) [1] [0.9]
	Not recovered/not resolved	-
	Recovering/resolving	-
	Fatal	-
	Recovered/resolved with sequelae	-
	Unknown	-

Source Data: Table 14.3.1.6, Listing 16.2.7
Note:
[1] Percentage 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 were presented as: number of subjects (percent of subjects) (number of events) [incidence rate] .
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects were only counted once for each system organ class or preferred term.
[4] 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 Patients were encountered with SAE during the Study. Both Patients reported 1 SAE each. Of these SAE, one led to In-patient hospitalization/prolongation of existing hospitalization and the other was an Important medical event. Both SAEs were moderate in nature. [redacted] The causality assessment showed Unlikely relationship between the SAEs and Study drug. No dose reduction of Study drug was done in any patients. Only 1 Patient received medication for the treatment of his/her SAE (Table 33).

Table 33 Summary of Serious Adverse Event - SAS Population (N = 1057)

Category, n (%) [1]	Overall (N = 1057)
Total number of SAEs reported	2
Subjects reporting any SAEs	2 (0.2)
Subjects reporting 1 SAE	2(0.2)[2]
Subjects reporting >1 SAEs	-
Severity	
Mild	-
Moderate	2(0.2)[2]
Severe	-
Outcome of SAE	
Recovered/resolved	[redacted]
Not recovered/not resolved	
Recovering/resolving	
Fatal	
Recovered/resolved with sequelae	

Category, n (%) [1]	**Overall (N = 1057)**
Unknown	-
Causality	
Probable	-
Possible	-
Unlikely	2(0.2)[2]
Action taken to Study product(s) due to SAE	
Drug interrupted	-
Drug withdrawn	-
Dose reduced	-
Dose increased	-
Dose not changed	1(0.1)[1]
Unknown	-
Not applicable	1(0.1)[1]
The SAE related to a Technical Complaint	
Yes	-
No	2(0.2)[2]
Was the condition recorded at baseline	
Yes	-
No	1(0.1)[1]
Unknown	1(0.1)[1]
If Yes did the symptoms increase or exacerbate	-
Did the patient receive any treatment for the event	
Yes	1(0.1)[1]
No	1(0.1)[1]
Seriousness category	
Death	-
In-patient hospitalization/prolongation of existing hospitalization	1(0.1)[1]
Congenital anomaly or birth defect	-
Life threatening	-
Persistent or significant disability or incapacity	-
Important medical event	1(0.1)[1]

Source Data: Table 14.3.1.1.1, Listing 16.2.7, 16.2.7.1:
Note:
[1] Percentage were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Serious adverse events was coded using MedDRA version 20.0 or later.
[2] All Serious adverse events were presented as: number of subjects (percent of subjects) (number of events).
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 at least one SAE during Study period. Additionally, only 2 SAEs were reported, 1 (0.1%) in each patient. Of these SAEs, 1 (0.1%) patient [redacted] (Table 34).

Table 34 Summary of Serious Adverse Events by System Organ Class and Preferred Term - SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1057)
Total number of subjects with at least one serious adverse event	2 (0.2)
Total number of serious adverse events, n	2
[redacted]	1 (0.1) (1) [0.9]
	1 (0.1) (1) [0.9] (0.101)
	1 (0.1) (1) [0.9]
	1 (0.1) (1) [0.9] (0.101)

Source Data: Table 14.3.2.1.2; Listing 16.2.7
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 except System Organ Class were presented as: number of subjects (percent of subjects) (number of events) [incidence rate] (rate per 100 PYE).System Organ Class were presented as: number of subjects (percent of subjects) (number of events) [incidence rate].
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects were only counted once for each system organ class or preferred term.
[4] Zero frequencies were presented by "-".

Adverse Drug Reaction

A total of 6 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 2 ADRs. No ADRs were serious in nature. On the severity scale, 5 ADRs, in 4 (0.4%) patients, were mild and 1 was moderate. All the ADRs were Recovered/resolved during the course of Study. In 2 (0.2%) patients, the dose of Study drug was reduced, while in 1 (0.1%) patient it was increased. No dose was changed in 2 (0.2%) patients (Table 35).

Table 35 Summary of Adverse Drug Reaction - SAS Population (N = 1057)

Category, n (%) [1]	Overall (N = 1057)
Total number of ADRs reported	6
Subjects reporting any ADRs	5(0.5)
Subjects reporting 1 ADR	4(0.4)[4]
Subjects reporting >1 ADRs	1(0.1)[2]
ADR is serious	
Yes	-
No	-
If Yes, is it life threatening [2]	
Yes	-
No	-
Severity	

Category, n (%) [1]	Overall (N = 1057)
Mild	4(0.4)[5]
Moderate	1(0.1)[1]
Severe	-
Outcome of ADR	
Recovered/resolved	5(0.5)[6]
Not recovered/not resolved	-
Recovering/resolving	-
Fatal	-
Recovered/resolved with sequelae	-
Unknown	-
Action taken to Study product(s) due to ADR	
Drug interrupted	-
Drug withdrawn	-
Dose reduced	2(0.2)[3]
Dose increased	1(0.1)[1]
Dose not changed	2(0.2)[2]
Unknown	-
Not applicable	-

Source Data: Table 14.3.2.2.1, Listing 16.2.7, 16.2.7.1
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 subjects (percent of subjects) (number of events).
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 = 1057)

Of the total ADR reported, 3 (0.3%) patient had Metabolism and nutrition disorders and 2 (0.2%) had Infections and infestations. Among Metabolism and nutrition disorders, 2 (0.2%) and 1 (0.1%) patients had Hypoglycaemia and Hyperglycaemia, respectively. The total event of Hypoglycaemia and Hyperglycaemia was 3 and 1, respectively. The rates of overall hypo-and hyperglycaemia were 0.302 and 0.101 per 100 person-years' in this Study (Table 36).

Among 2 (0.2%) patients with Infections and infestations, Gastroenteritis and Urinary tract infection was reported in 1 (0.1%) patient each. There was 1 event, each for both ADRs. The rates of overall event were 0.101 per 100 person-years' for both Gastroenteritis and Urinary tract infection (Table 36).

Table 36 Summary of Adverse drug reaction by Organ Class and Preferred Term - SAS Population (N = 1057)

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1057)
Total number of subjects with at least one Adverse Drug Reaction	5 (0.5)
Total number of Adverse Drug Reaction, n	6

System Organ Class (SOC)/ Preferred Term, n (%) [1]	Overall (N = 1057)
Metabolism and nutrition disorders	3 (0.3) (4) [2.8]
Hypoglycaemia	2 (0.2) (3) [1.9] (0.302)
Hyperglycaemia	1 (0.1) (1) [0.9] (0.101)
Infections and infestations	2 (0.2) (2) [1.9]
Gastroenteritis	1 (0.1) (1) [0.9] (0.101)
Urinary tract infection	1 (0.1) (1) [0.9] (0.101)

Source Data: Table 14.3.2.2.2, Listing 16.2.7
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 subjects (percent of subjects) (number of events) [incidence rate] (rate per 100 PYE).System Organ Class were presented as: number of subjects (percent of subjects) (number of events) [incidence rate].
[3] Subjects may had reported more than one event per system organ class or preferred term. Subjects 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 3 events of Severe Hypoglycaemic Episodes were observed in 2 (0.2%) patients at Baseline Visit. No further Severe Hypoglycaemic Episodes were noted at any follow Up Visit during the Study period (Table 37).

Table 37 Summary of Severe Hypoglycaemic Episodes - SAS Population (N = 1057)

Visit/ Parameter [1], n (%)	Overall (N = 1057)
Visit 1 Baseline Visit	
Severe hypoglycaemic episodes	2 (0.2)[3]
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: Table 14.3.2.4, Listing 16.2.6
Note:
[1] Percentage was calculated using respective column header count as denominator.
General Note:
> All Severe Hypoglycaemic Episodes are presented as: number of subjects (percent of subjects) (number of events) [incidence rate] (rate per 100 PYE) in post baseline visits.
> Zero frequencies are 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 subject

All AEs by patient are listed in Listing 16.2.7.

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

Not applicable.

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

Not applicable.

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 38. The mean ± SD (Min : Max) of Total Cholesterol (mg/dL) for each visit was within the Desirable range. The mean ± SD (Min : Max) of Total Cholesterol for visit 1, visit 2, visit 3 and visit 4 was 170.53 ± 44.991 (3.33 : 374), 162.66 ± 34.856 (87 : 266), 163.33 ± 32.137 (84:264) and 163.90 ± 37.942 (94 : 395.5), respectively.

The mean ± SD (Min : Max) of Triglyceride (mg/dL) for visit 1 was borderline high. At subsequent visits, the Triglyceride level was within the normal range. The mean ± SD (Min : Max) of Triglyceride for visit 1, visit 2, visit 3 and visit 4 was 161.48 ± 97.114 (39.95 : 1059),

143.09 ± 59.875 (42 : 535), 144.73 ± 55.964 (30:343) and 136.03 ± 55.400 (41 : 365.4), respectively.

The mean ± SD (Min : Max) of Free Fatty Acid (mg/dL) for each visit was within the normal range at baseline. No visit wise data on free fatty acid was available for other visits.

The mean ± SD of Serum Creatinine level was within the normal range at all visits. The mean ± SD of Urine albumin was higher at baseline visit (59.35 ± 124.429). A decline was observed at subsequent visits with normal range at visit 2 (25.30 ± 23.648) and visit 4 (18.42 ± 9.680).

Visit wise summary of change from Baseline of lab parameters in SAS Population (N = 1057) was presented in Table 14.3.6.1.2 (Not included in text).

Table 38 Visit Wise Summary of lab parameters- SAS Population (N = 1057)

Visit/Parameters	Statistic/Category, n (%) [1]	Overall (N = (1057)
Visit 1		
Total Cholesterol		
	N	525
	Missing	532
	Mean	170.53
	SD	44.991
	Median	167.00
	Range (Min.:Max.)	(3.33:374)
High Density Lipoprotein-Cholesterol		
	N	499
	Missing	558
	Mean	44.59
	SD	28.845
	Median	42.00
	Range (Min.:Max.)	(16:630)
Low Density Lipoprotein-Cholesterol		
	N	510
	Missing	547
	Mean	97.62
	SD	34.175
	Median	96.00
	Range (Min.:Max.)	(11:209)
Triglyceride		
	N	512
	Missing	545
	Mean	161.48
	SD	97.114
	Median	144.55
	Range (Min.:Max.)	(39.95:1059)
Free Fatty Acid		

Visit/Parameters	Statistic/Category, n (%) [1]	Overall (N = (1057)
	N	2
	Missing	1055
	Mean	13.25
	SD	9.263
	Median	13.25
	Range (Min.:Max.)	(6.7:19.8)
Serum Creatinine		
	N	504
	Missing	553
	Mean	1.00
	SD	0.548
	Median	0.90
	Range (Min.:Max.)	(0.08:7.88)
Urine albumin		
	N	49
	Missing	1008
	Mean	59.35
	SD	124.429
	Median	11.07
	Range (Min.:Max.)	(0.12:690)
Visit 2		
Total Cholesterol		
	N	188
	Missing	838
	Mean	162.66
	SD	34.856
	Median	159.00
	Range (Min.:Max.)	(87:266)
High Density Lipoprotein-Cholesterol		
	N	185
	Missing	841
	Mean	44.31
	SD	13.400
	Median	40.60
	Range (Min.:Max.)	(19:134)
Low Density Lipoprotein-Cholesterol		
	N	186
	Missing	840
	Mean	92.61
	SD	32.496
	Median	89.50
	Range (Min.:Max.)	(20:171)
Triglyceride		

Visit/Parameters	Statistic/Category, n (%) [1]	Overall (N = (1057)
	N	185
	Missing	841
	Mean	143.09
	SD	59.875
	Median	140.00
	Range (Min.:Max.)	(42:535)
Free Fatty Acid		
	N	0
	Missing	1026
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
Serum Creatinine		
	N	145
	Missing	881
	Mean	0.94
	SD	0.427
	Median	0.90
	Range (Min.:Max.)	(0.4:3.83)
Urine albumin		
	N	5
	Missing	1021
	Mean	25.30
	SD	23.648
	Median	23.90
	Range (Min.:Max.)	(1.1:50.8)
Visit 3		
Total Cholesterol		
	N	231
	Missing	763
	Mean	163.33
	SD	32.137
	Median	162.00
	Range (Min.:Max.)	(84:264)
High Density Lipoprotein-Cholesterol		
	N	223
	Missing	771
	Mean	46.62
	SD	60.816
	Median	40.00
	Range (Min.:Max.)	(13.1:936)
Low Density Lipoprotein-Cholesterol		

Visit/Parameters	Statistic/Category, n (%) [1]	Overall (N = (1057)
	N	227
	Missing	767
	Mean	94.56
	SD	31.585
	Median	97.00
	Range (Min.:Max.)	(14:187)
Triglyceride		
	N	227
	Missing	767
	Mean	144.73
	SD	55.964
	Median	140.30
	Range (Min.:Max.)	(30:343)
Free Fatty Acid		
	N	0
	Missing	994
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
Serum Creatinine		
	N	180
	Missing	814
	Mean	0.92
	SD	0.317
	Median	0.90
	Range (Min.:Max.)	(0.4:3.5)
Urine albumin		
	N	12
	Missing	982
	Mean	39.29
	SD	37.545
	Median	26.00
	Range (Min.:Max.)	(19:151.4)
Visit 4		
Total Cholesterol		
	N	233
	Missing	724
	Mean	163.90
	SD	37.942
	Median	162.00
	Range (Min.:Max.)	(94:395.5)
High Density Lipoprotein-Cholesterol		

Visit/Parameters	Statistic/Category, n (%) [1]	Overall (N = (1057)
	N	226
	Missing	731
	Mean	45.72
	SD	15.173
	Median	42.00
	Range (Min.:Max.)	(26:141)
Low Density Lipoprotein-Cholesterol		
	N	226
	Missing	731
	Mean	91.69
	SD	32.950
	Median	89.00
	Range (Min.:Max.)	(33:292)
Triglyceride		
	N	225
	Missing	732
	Mean	136.03
	SD	55.400
	Median	125.00
	Range (Min.:Max.)	(41:365.4)
Free Fatty Acid		
	N	0
	Missing	957
	Mean	-
	SD	-
	Median	-
	Range (Min.:Max.)	-
Serum Creatinine		
	N	239
	Missing	718
	Mean	0.86
	SD	0.232
	Median	0.89
	Range (Min.:Max.)	(0.1:2.2)
Urine albumin		
	N	10
	Missing	947
	Mean	18.42
	SD	9.680
	Median	22.50
	Range (Min.:Max.)	(1.3:28)
Source Data: Table 14.3.6.1.1, Listing 16.2.8		

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 39. The Body Measurements and vital signs of the subjects in the SAS population were comparable at baseline, 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 = 1057) was presented in Table 14.3.4.2 (Not included in text)

Table 39 Visit wise Summary of Body Measurements and Vital Signs at - SAS Population (N = 1057)

Visit	Parameter	Statistic/Category, n (%) [1]	Overall(N = 1057)
Visit 1			
	Weight (cm)		
		n	1052
		Missing	5
		Mean	71.68
		SD	13.434
		Median	70.20
		Range (Min.:Max.)	(40.2:134)
	Waist (cm)		
		n	609
		Missing	448
		Mean	94.24
		SD	11.569

Visit	Parameter	Statistic/Category, n (%) [1]	Overall(N = 1057)
		Median	93.00
		Range (Min.:Max.)	(56:160)
	Hip (cm)		
		n	516
		Missing	541
		Mean	97.52
		SD	11.681
		Median	97.00
		Range (Min.:Max.)	(58:155)
	Systolic(mmHg)		
		n	1044
		Missing	13
		Mean	129.4
		SD	14.06
		Median	130.0
		Range (Min.:Max.)	(90:200)
	Diastolic(mmHg)		
		n	1044
		Missing	13
		Mean	79.0
		SD	7.98
		Median	80.0
		Range (Min.:Max.)	(50:120)
Visit 2			
	Weight (cm)		
		n	992
		Missing	34
		Mean	71.96
		SD	13.137
		Median	70.75
		Range (Min.:Max.)	(41:130.1)
	Waist (cm)		
		n	311
		Missing	715
		Mean	91.81
		SD	10.583
		Median	91.00
		Range (Min.:Max.)	(56:129)
	Hip (cm)		
		n	302
		Missing	724
		Mean	95.48
		SD	10.410

Visit	Parameter	Statistic/Category, n (%) [1]	Overall(N = 1057)
		Median	95.00
		Range (Min.:Max.)	(60:123)
	Systolic(mmHg)		
		n	981
		Missing	45
		Mean	126.6
		SD	10.78
		Median	128.0
		Range (Min.:Max.)	(100:180)
	Diastolic(mmHg)		
		n	981
		Missing	45
		Mean	79.1
		SD	6.51
		Median	80.0
		Range (Min.:Max.)	(57:100)
Visit 3			
	Weight (cm)		
		n	967
		Missing	27
		Mean	72.10
		SD	13.097
		Median	71.00
		Range (Min.:Max.)	(40:128.6)
	Waist (cm)		
		n	315
		Missing	679
		Mean	92.09
		SD	11.552
		Median	91.00
		Range (Min.:Max.)	(55:158)
	Hip (cm)		
		n	305
		Missing	689
		Mean	96.18
		SD	11.665
		Median	96.00
		Range (Min.:Max.)	(59:158)
	Systolic(mmHg)		
		n	959
		Missing	35
		Mean	126.5
		SD	10.22

Visit	Parameter	Statistic/Category, n (%) [1]	Overall(N = 1057)
		Median	128.0
		Range (Min.:Max.)	(90:170)
	Diastolic(mmHg)		
		n	959
		Missing	35
		Mean	79.1
		SD	6.46
		Median	80.0
		Range (Min.:Max.)	(40:100)
Visit 4			
	Weight (cm)		
		n	933
		Missing	24
		Mean	72.24
		SD	12.877
		Median	71.00
		Range (Min.:Max.)	(40:129)
	Waist (cm)		
		n	403
		Missing	554
		Mean	92.89
		SD	11.293
		Median	92.00
		Range (Min.:Max.)	(61:159)
	Hip (cm)		
		n	396
		Missing	561
		Mean	95.94
		SD	11.323
		Median	95.00
		Range (Min.:Max.)	(60:155)
	Systolic(mmHg)		
		n	926
		Missing	31
		Mean	125.5
		SD	9.55
		Median	124.0
		Range (Min.:Max.)	(90:190)
	Diastolic(mmHg)		
		n	926
		Missing	31
		Mean	79.4
		SD	6.07

Visit	Parameter	Statistic/Category, n (%) [1]	Overall(N = 1057)
		Median	80.0
		Range (Min.:Max.)	(60:100)
Source Data: Table 14.3.4.1, Listing 16.4.4			

12.5.1 Dose Administration

The visit wise summary of dose administration is presented in Table 40.

The mean ± SD (Min : Max) of dose administration was the lowest at baseline visit (14.79 ± 7.997) and the highest at Visit 4 (18.01 ± 9.456) respectively. At visits 2 and 3, the mean ± SD (Min : Max) of dose administration was comparable.

Visit wise summary of change from Baseline of Dose Administration in SAS Population (N = 1057) was presented in Table 14.3.8.2. (Not included in text).

Table 40 Visit wise Summary of Dose Administration - SAS Population (N = 1057)

Visit	Statistics	Overall (N = (1057)
Visit 1		
	n	1057
	Missing	0
	Mean	14.79
	SD	7.997
	Median	14.00
	Range (Min.:Max.)	(3:80)
Visit 2		
	n	436
	Missing	590
	Mean	17.62
	SD	15.685
	Median	16.00
	Range (Min.:Max.)	(2:264)
Visit 3		
	n	353
	Missing	641
	Mean	17.46
	SD	9.286
	Median	16.00
	Range (Min.:Max.)	(3:78)
Visit 4		
	n	326
	Missing	631
	Mean	18.01
	SD	9.456
	Median	16.00
	Range (Min.:Max.)	(2:75)

12.5.2 Concomitant Medications

The concomitant medications are summarized in Table 41. Among the Study cohort, more than 10% of the patient population was on Agents Acting on the Renin-Angiotensin System (38.1%), Antithrombotic Agents (12.8%), Beta Blocking Agents (11.2%), Lipid Modifying Agents (50.2%), Thyroid Therapy (10.6%) and Vitamins (31.3%). Among Agents Acting On The Renin-Angiotensin System, 140 (13.2%) patients were on Telmisartan. Among Lipid Modifying Agents, 231 (21.9%) and 179 (16.9%) patients were on Atorvastatin and Rosuvastatin, respectively.

Visit wise Summary of Antihypertensive Medications and its change during different visits in SAS Population (N = 1057) was mentioned in Table 14.3.3.3 (Not included in text) and Table 14.3.3.3.1, respectively.

Visit wise Summary of lipid-lowering Medications and its change during different visits in SAS Population (N = 1057) was mentioned in Table 14.3.3.4 (Not included in text) and Table 14.3.3.4.1, respectively.

Table 41 Summary of Concomitant Medication - SAS Population (N = 1057)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
Agents Acting On The Renin-Angiotensin System		403 (38.1)
	Amlodipine Besilate, Hydrochlorothiazide, Telmisartan	1 (0.1)
	Amlodipine Besilate, Lisinopril	1 (0.1)
	Amlodipine Besilate, Olmesartan	6 (0.6)
	Amlodipine Besilate, Perindopril Erbumine	5 (0.5)
	Amlodipine Besilate, Ramipril	4 (0.4)
	Amlodipine, Chlortalidone, Olmesartan Medoxomil	1 (0.1)
	Amlodipine, Hydrochlorothiazide, Olmesartan	3 (0.3)
	Amlodipine, Losartan	2 (0.2)
	Amlodipine, Telmisartan	17 (1.6)
	Atorvastatin Calcium, Telmisartan	1 (0.1)
	Chlortalidone,olmesartan Medoxomil	3 (0.3)
	Chlortalidone, Cilnidipine, Telmisartan	1 (0.1)
	Chlortalidone, Telmisartan	6 (0.6)
	Cilnidipine, Olmesartan Medoxomil	1 (0.1)
	Cilnidipine, Telmisartan	4 (0.4)
	Enalapril	17 (1.6)
	Hydrochlorothiazide, Losartan	8 (0.8)
	Hydrochlorothiazide, Olmesartan Medoxomil	13 (1.2)
	Hydrochlorothiazide, Ramipril	2 (0.2)
	Hydrochlorothiazide, Telmisartan	21 (2.0)
	Indapamide, Perindopril	3 (0.3)
	Irbesartan	1 (0.1)
	Lisinopril	2 (0.2)
	Losartan	48 (4.5)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Metoprolol, Ramipril	1 (0.1)
	Metoprolol, Telmisartan	8 (0.8)
	Olmesartan	41 (3.9)
	Perindopril	2 (0.2)
	Ramipril	48 (4.5)
	Telmisartan	140 (13.2)
	Valsartan	8 (0.8)
All Other Therapeutic Products		2 (0.2)
	Acetylcysteine	1 (0.1)
	Sevelamer	1 (0.1)
Anabolic Agents For Systemic Use		3 (0.3)
	Nandrolone Decanoate	3 (0.3)
Analgesics		93 (8.8)
	Acetylsalicylic Acid	18 (1.7)
	Chlorphenamine Maleate,paracetamol,pseudoephedrine Hydrochloride	1 (0.1)
	Duloxetine	1 (0.1)
	Folic Acid, Mecobalamin, Pregabalin, Pyridoxine Hydrochloride, Thiamine Mononitrate, Thioctic Acid	5 (0.5)
	Gabapentin	9 (0.9)
	Gabapentin, Nortriptyline	8 (0.8)
	Mecobalamin, Pregabalin	17 (1.6)
	Paracetamol	10 (0.9)
	Paracetamol, Tramadol	6 (0.6)
	Pregabalin	27 (2.6)
Anesthetics		1 (0.1)
	Amitriptyline, Ketamine	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
Anthelmintics		1 (0.1)
	Albendazole	1 (0.1)
	Diethylcarbamazine Citrate	1 (0.1)
Anti-Inflammatory And Antirheumatic Products		13 (1.2)
	Aceclofenac	3 (0.3)
	Aceclofenac, Paracetamol	1 (0.1)
	Chondroitin Sulfate, Glucosamine Sulfate	2 (0.2)
	Diacerein, Glucosamine Hydrochloride	1 (0.1)
	Diclofenac	1 (0.1)
	Glucosamine	1 (0.1)
	Hydroxychloroquine Sulfate	1 (0.1)
	Ketoprofen	1 (0.1)
	Ketorolac Tromethamine	2 (0.2)
	Mefenamic Acid	1 (0.1)
Antianemic Preparations		81 (7.7)
	Ascorbic Acid, Cyanocobalamin, Docusate Sodium, Ferrous Fumarate, Folic Acid, Tocopheryl Acid Succinate	1 (0.1)
	Benfotiamine,chromium Nicotinate,folic Acid,inositol,mecobalamin,pyridoxine Hydrochloride, Thioctic Acid	2 (0.2)
	Benfotiamine, Cobamamide, Folic Acid, Mecobalamin, Pyridoxine Hydrochloride	1 (0.1)
	Benfotiamine, Folic Acid, Inositol, Mecobalamin, Pyridoxine, Thioctic Acid	2 (0.2)
	Benfotiamine, Folic Acid, Mecobalamin, Pyridoxine, Thioctic Acid	2 (0.2)
	Benfotiamine, Inositol, Mecobalamin, Pyridoxine Hydrochloride, Thioctic Acid	2 (0.2)
	Biotin, Folic Acid, Mecobalamin, Pyridoxine, Thioctic Acid	5 (0.5)
	Cyanocobalamin	2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Cyanocobalamin, Ferric Ammonium Citrate, Glycyrrhiza Glabra Liquid Extract, Liver Extract, Nicotinic Acid, Pyridoxine, Thiamine, Yeast	1 (0.1)
	Cyanocobalamin, Folic Acid	1 (0.1)
	Cyanocobalamin, Folic Acid, Pyridoxine	1 (0.1)
	Docosahexaenoic Acid, Folic Acid, Mecobalamin, Pyridoxine Hydrochloride	1 (0.1)
	Erythropoietin	2 (0.2)
	Ferrous	2 (0.2)
	Ferrous Ascorbate, Folic Acid	6 (0.6)
	Ferrous Ascorbate, Folic Acid, Zinc	1 (0.1)
	Ferrous Fumarate,folic Acid	1 (0.1)
	Folic Acid	4 (0.4)
	Folic Acid,iron,zinc Sulfate	1 (0.1)
	Folic Acid,levocarnitine Tartrate,mecobalamin	2 (0.2)
	Folic Acid, Iron	2 (0.2)
	Folic Acid, Mecobalamin	3 (0.3)
	Folic Acid, Mecobalamin, Pyridoxine Hydrochloride, Thioctic Acid	4 (0.4)
	Iron	3 (0.3)
	Levomefolic Acid, Mecobalamin, Pyridoxal	2 (0.2)
	Mecobalamin	25 (2.4)
	Mecobalamin, Nicotinamide, Pyridoxine	9 (0.9)
	Mecobalamin, Pregabalin	11 (1.0)
Antibacterials For Systemic Use		33 (3.1)
	Amikacin	1 (0.1)
	Amoxicillin, Clavulanic Acid	8 (0.8)
	Azithromycin	1 (0.1)
	Cefixime	3 (0.3)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Cefoperazone Sodium, Sulbactam Sodium	1 (0.1)
	Cefpodoxime Proxetil	1 (0.1)
	Cefpodoxime Proxetil, Clavulanate Potassium	1 (0.1)
	Cefuroxime	2 (0.2)
	Clindamycin	5 (0.5)
	Ertapenem	1 (0.1)
	Faropenem	1 (0.1)
	Levofloxacin	10 (0.9)
	Linezolid	1 (0.1)
	Metronidazole	1 (0.1)
	Nitrofurantoin	1 (0.1)
	Ofloxacin	2 (0.2)
	Piperacillin Sodium, Tazobactam Sodium	1 (0.1)
Antibiotics And Chemotherapeutics For Dermatological Use		1 (0.1)
	Bacitracin Zinc, Gramicidin, Polymyxin B Sulfate	1 (0.1)
Antidiarrheals, Intestinal Anti-Inflammatory/Anti-Infective Agents		3 (0.3)
	Atropine Sulfate, Diphenoxylate Hydrochloride	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)
	Bifidobacterium Longum,lactobacillus Acidophilus,lactobacillus Rhamnosus,saccharomyces Boulardii.	1 (0.1)
Antiepileptics		16 (1.5)
	Clonazepam	2 (0.2)
	Folic Acid,mecobalamin,pregabalin,pyridoxine Hydrochloride,thioctic Acid	2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Folic Acid, Mecobalamin, Pregabalin, Pyridoxine Hydrochloride, Thiamine Mononitrate, Thioctic Acid	1 (0.1)
	Gabapentin	2 (0.2)
	Gabapentin, Mecobalamin, Thioctic Acid	4 (0.4)
	Nortriptyline, Pregabalin	2 (0.2)
	Oxcarbazepine	2 (0.2)
	Valproate Sodium	1 (0.1)
Antifungals For Dermatological Use		1 (0.1)
	Clotrimazole	1 (0.1)
Antigout Preparations		5 (0.5)
	Allopurinol	1 (0.1)
	Febuxostat	4 (0.4)
Antihemorrhagics		1 (0.1)
	Tranexamic Acid	1 (0.1)
Antihistamines For Systemic Use		14 (1.3)
	Cetirizine	2 (0.2)
	Choline Citrate, Cyproheptadine Hydrochloride	1 (0.1)
	Fexofenadine	2 (0.2)
	Hydroxyzine	1 (0.1)
	Levocetirizine	9 (0.9)
Antimycobacterials		2 (0.2)
	Ethambutol	1 (0.1)
	Ethambutol Dihydrochloride, Isoniazid, Rifampicin	1 (0.1)
Antimycotics For Systemic Use		4 (0.4)
	Fluconazole	4 (0.4)
Antineoplastic Agents		2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Methotrexate	2 (0.2)
Antiobesity Preparations, Excluding Diet Products		1 (0.1)
	Orlistat	1 (0.1)
Antiseptics And Disinfectants		1 (0.1)
	Carbomer,propylene Glycol,silver Colloidal,trolamine	1 (0.1)
Antithrombotic Agents		135 (12.8)
	Acenocoumarol	1 (0.1)
	Acetylsalicylic Acid	74 (7.0)
	Acetylsalicylic Acid, Clopidogrel Bisulfate	20 (1.9)
	Cilostazol	1 (0.1)
	Clopidogrel	48 (4.5)
Antivirals For Systemic Use		1 (0.1)
	Valaciclovir Hydrochloride	1 (0.1)
Beta Blocking Agents		118 (11.2)
	Amlodipine,nebivolol	1 (0.1)
	Amlodipine, Atenolol	4 (0.4)
	Amlodipine, Metoprolol	5 (0.5)
	Atenolol	3 (0.3)
	Bisoprolol	5 (0.5)
	Carvedilol	13 (1.2)
	Chlortalidone, Metoprolol	1 (0.1)
	Hydrochlorothiazide, Olmesartan Medoxomil	2 (0.2)
	Metoprolol	67 (6.3)
	Nebivolol	11 (1.0)
	Propranolol Hydrochloride	6 (0.6)
Bile And Liver Therapy		3 (0.3)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Folic Acid, Metadoxine, Ornithine, Pyridoxine, Silybum Marianum	2 (0.2)
	Silybum Marianum	1 (0.1)
Blood Substitutes And Perfusion Solutions		1 (0.1)
	Albumin Human	1 (0.1)
Calcium Channel Blockers		82 (7.8)
	Amlodipine	52 (4.9)
	Cilnidipine	27 (2.6)
	Diltiazem	3 (0.3)
	Verapamil Hydrochloride	1 (0.1)
Cardiac Therapy		24 (2.3)
	Cordarone	1 (0.1)
	Digoxin	10 (0.9)
	Glyceryl Trinitrate	3 (0.3)
	Isosorbide Mononitrate	5 (0.5)
	Ivabradine Hydrochloride	1 (0.1)
	Levocarnitine	1 (0.1)
	Nicorandil	5 (0.5)
	Ranolazine	2 (0.2)
	Trimetazidine	5 (0.5)
Corticosteroids For Systemic Use		10 (0.9)
	Deflazacort	7 (0.7)
	Fludrocortisone Acetate	1 (0.1)
	Prednisolone	1 (0.1)
	Triamcinolone Acetonide	1 (0.1)
Corticosteroids, Dermatological Preparations		1 (0.1)
	Clobetasol Propionate,salicylic Acid	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
Cough And Cold Preparations		15 (1.4)
	Acetylcysteine, Taurine	9 (0.9)
	Ambroxol	2 (0.2)
	Bromhexine Hydrochloride, Guaifenesin, Salbutamol Sulfate	1 (0.1)
	Chlorphenamine Maleate, Dextromethorphan Hydrobromide, Guaifenesin, Phenylephrine Hydrochloride	1 (0.1)
	Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, Triprolidine Hydrochloride	2 (0.2)
Digestives, Including Enzymes		5 (0.5)
	Diastase,pepsin,simeticone	4 (0.4)
	Pancreatin, Sodium Tauroglycocholate	1 (0.1)
Diuretics		68 (6.4)
	Chlortalidone	20 (1.9)
	Eplerenone, Torasemide	2 (0.2)
	Furosemide	12 (1.1)
	Furosemide, Spironolactone	4 (0.4)
	Hydrochlorothiazide	14 (1.3)
	Indapamide	3 (0.3)
	Metolazone	1 (0.1)
	Spironolactone	6 (0.6)
	Tolvaptan	2 (0.2)
	Torasemide	13 (1.2)
Drugs For Acid Related Disorders		84 (7.9)
	Domperidone,pantoprazole	12 (1.1)
	Domperidone, Esomeprazole	4 (0.4)
	Domperidone, Omeprazole	1 (0.1)
	Domperidone, Rabeprazole	13 (1.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Esomeprazole	5 (0.5)
	Esomeprazole Magnesium, Levosulpiride	1 (0.1)
	Levosulpiride, Pantoprazole	2 (0.2)
	Levosulpiride, Rabeprazole	4 (0.4)
	Omeprazole	2 (0.2)
	Pantoprazole	23 (2.2)
	Rabeprazole	23 (2.2)
	Ranitidine	1 (0.1)
Drugs For Constipation		14 (1.3)
	Bisacodyl	1 (0.1)
	Cassia Fistula,foeniculum Vulgare,glycyrrhiza Glabra,plantago Ovata,senna Spp.,terminalia Chebula Extract	1 (0.1)
	Lactitol	1 (0.1)
	Lactitol, Plantago Ovata Husk	1 (0.1)
	Lactulose	5 (0.5)
	Magnesium Hydroxide, Paraffin, Liquid	3 (0.3)
	Plantago Ovata	1 (0.1)
	Sodium Picosulfate	1 (0.1)
Drugs For Functional Gastrointestinal Disorders		12 (1.1)
	Choline Citrate,sorbitol	1 (0.1)
	Domperidone	7 (0.7)
	Levosulpiride	4 (0.4)
Drugs For Obstructive Airway Diseases		9 (0.9)
	Budesonide, Formoterol Fumarate	1 (0.1)
	Doxofylline	2 (0.2)
	Etofylline, Theophylline	2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Fexofenadine, Montelukast	1 (0.1)
	Fluticasone Propionate, Salmeterol Xinafoate	1 (0.1)
	Levocetirizine Dihydrochloride, Montelukast Sodium	1 (0.1)
	Montelukast	2 (0.2)
	Tiotropium Bromide	1 (0.1)
Drugs For Treatment Of Bone Diseases		1 (0.1)
	Ibandronate Sodium	1 (0.1)
Emollients And Protectives		2 (0.2)
	Allantoin, Dimeticone, Glycerol, Paraffin, Liquid, Propylene Glycol, Urea	2 (0.2)
General Nutrients		5 (0.5)
	Calcium Caseinate, Fructooligosaccharides, Fructose, Glycine Max Fibre, Glycine Max Oil, Helianthus Annuus Oil, Inositol, Levocarnitine, Maltodextrin, Minerals Nos, Taurine, Vitamins Nos	1 (0.1)
	Casein Hydrolysate	2 (0.2)
	Nutrients Nos	2 (0.2)
Immunosuppressants		1 (0.1)
	Pirfenidone	1 (0.1)
Lipid Modifying Agents		531 (50.2)
	Acetylsalicylic Acid, Atorvastatin	43 (4.1)
	Acetylsalicylic Acid, Atorvastatin Calcium, Clopidogrel	2 (0.2)
	Acetylsalicylic Acid, Atorvastatin, Ramipril	8 (0.8)
	Acetylsalicylic Acid, Rosuvastatin	6 (0.6)
	Atorvastatin	231 (21.9)
	Atorvastatin Calcium, Ezetimibe	2 (0.2)
	Atorvastatin, Clopidogrel	7 (0.7)
	Atorvastatin, Colecalciferol	10 (0.9)
	Atorvastatin, Fenofibrate	25 (2.4)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Atorvastatin, Ramipril	1 (0.1)
	Clopidogrel, Rosuvastatin	4 (0.4)
	Colecalciferol, Rosuvastatin	1 (0.1)
	Docosahexaenoic Acid, Eicosapentaenoic Acid, Folic Acid, Mecobalamin, Pyridoxine Hydrochloride, Selenium, Zinc Sulfate	1 (0.1)
	Fenofibrate	20 (1.9)
	Fenofibrate,rosuvastatin	6 (0.6)
	Omega-3 Fatty Acids	1 (0.1)
	Omega-3-Acid Ethyl Ester	1 (0.1)
	Pitavastatin	6 (0.6)
	Rosuvastatin	179 (16.9)
	Rosuvastatin Calcium, Telmisartan	3 (0.3)
	Rosuvastatin, Telmisartan	3 (0.3)
	Simvastatin	10 (0.9)
Mineral Supplements		89 (8.4)
	Alfacalcidol, Calcium Carbonate	1 (0.1)
	Calcitriol, Calcium	3 (0.3)
	Calcitriol, Calcium Carbonate, Zinc	6 (0.6)
	Calcitriol, Calcium, Folic Acid, Mecobalamin, Pyridoxine Hydrochloride	1 (0.1)
	Calcium	12 (1.1)
	Calcium Carbonate	4 (0.4)
	Calcium Citrate Malate, Colecalciferol, Folic Acid	1 (0.1)
	Calcium,colecalciferol,menaquinone	1 (0.1)
	Calcium, Colecalciferol	33 (3.1)
	Calcium, Magnesium Citrate	3 (0.3)
	Chromium	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Chromium Picolinate	1 (0.1)
	Magnesium Citrate	20 (1.9)
	Minerals Nos	1 (0.1)
	Potassium Chloride	2 (0.2)
Muscle Relaxants		2 (0.2)
	Thiocolchicoside	2 (0.2)
Other Alimentary Tract And Metabolism Products		9 (0.9)
	Arginine, Folic Acid, Lycopene, Selenium Oxide, Ubidecarenone, Zinc Sulfate	1 (0.1)
	Levocarnitine, Tocopherol	1 (0.1)
	Sodium Bicarbonate	1 (0.1)
	Thioctic Acid	6 (0.6)
Other Dermatological Preparations		2 (0.2)
	Diclofenac	1 (0.1)
	Hydroquinone	1 (0.1)
Other Gynecologicals		9 (0.9)
	Ascorbic Acid, Biotin, Boron, Calcium Pantothenate, Chromium, Colecalciferol, Copper, Cyanocobalamin, Folic Acid, Iodine,ironpentacarbonyl, Magnesium, Manganese, Nicotinamide, Pyridoxine, Retinol, Riboflavin, Selenium, Soya Isoflavones, Thiamine, Tocopher	9 (0.9)
Other Hematological Agents		2 (0.2)
	Chymotrypsin, Trypsin	2 (0.2)
Other Nervous System Drugs		8 (0.8)
	Betahistine	4 (0.4)
	Cinnarizine	1 (0.1)
	Gabapentin, Mecobalamin	2 (0.2)
	Metadoxine	1 (0.1)
Peripheral Vasodilators		3 (0.3)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Ginkgo Biloba Extract	1 (0.1)
	Pentoxifylline	2 (0.2)
Psychoanaleptics		39 (3.7)
	Amitriptyline	5 (0.5)
	Citicoline Sodium, Piracetam	1 (0.1)
	Clonazepam, Escitalopram	6 (0.6)
	Diazepam, Imipramine Hydrochloride	1 (0.1)
	Donepezil Hydrochloride	1 (0.1)
	Duloxetine	3 (0.3)
	Duloxetine Hydrochloride, Mecobalamin	1 (0.1)
	Escitalopram	8 (0.8)
	Memantine	1 (0.1)
	Mirtazapine	2 (0.2)
	Nortriptyline	9 (0.9)
	Rivastigmine Hydrogen Tartrate	1 (0.1)
	Sertraline	1 (0.1)
Psycholeptics		35 (3.3)
	Alprazolam	14 (1.3)
	Alprazolam, Melatonin	1 (0.1)
	Chlordiazepoxide	1 (0.1)
	Chlordiazepoxide, Trifluoperazine Hydrochloride	1 (0.1)
	Clobazam	1 (0.1)
	Clonazepam	4 (0.4)
	Hydroxyzine	1 (0.1)
	Melatonin, Zolpidem	2 (0.2)
	Olanzapine	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Pregabalin	3 (0.3)
	Zolpidem	9 (0.9)
Sex Hormones And Modulators Of The Genital System		1 (0.1)
	Medroxyprogesterone Acetate	1 (0.1)
Stomatological Preparations		1 (0.1)
	Amlexanox	1 (0.1)
Thyroid Therapy		112 (10.6)
	Levothyroxine	110 (10.4)
	Liothyronine	2 (0.2)
Topical Products For Joint And Muscular Pain		1 (0.1)
	Nimesulide	1 (0.1)
Unspecified Herbal And Traditional Medicine		8 (0.8)
	Arnica Montana	1 (0.1)
	Capsicum Spp. Extract	1 (0.1)
	Commiphora Wightii, Glycyrrhiza Glabra, Phyllanthus Emblica, Rubia Cordifolia, Saussurea Lappa, Tinospora Cordifolia	1 (0.1)
	Echinacea Spp., Platycladus Orientalis	2 (0.2)
	Ginseng Nos	3 (0.3)
Urologicals		13 (1.2)
	Dutasteride, Tamsulosin	5 (0.5)
	Flavoxate Hydrochloride	1 (0.1)
	Oxybutynin	1 (0.1)
	Sildenafil Citrate	1 (0.1)
	Silodosin	1 (0.1)
	Solifenacin Succinate	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Tamsulosin	4 (0.4)
Vitamins		331 (31.3)
	Acetylcysteine, Biotin, Chromium Picolinate, Cyanocobalamin, Folic Acid, Glutamic Acid, Glycine, Inositol, Nicotinamide, Pyridoxine, Sodium , Zinc	1 (0.1)
	Aminobenzoic Acid, Biotin, Calcium Pantothenate, Choline Chloride, Cyanocobalamin, Folic Acid, Nicotinic Acid, Pyridoxine Hydrochloride, Riboflavin, Thiamine Hydrochloride	5 (0.5)
	Ascorbic Acid	17 (1.6)
	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.	1 (0.1)
	Ascorbic Acid,biotin,calcium Pantothenate,folic Acid,nicotinamide,pyridoxine Hydrochloride,riboflavin,vitamin B1 Nos,vitamin B12 Nos,zinc Sulfate Monohydrate	1 (0.1)
	Ascorbic Acid,calcium Pantothenate,chromic Chloride,colecalciferol,cupric Oxide,folic Acid,manganese Chloride,nicotinamide,pyridoxine Hydrochloride,retinol Acetate,riboflavin,sodium Selenate,thiamine Hydrochloride,tocopheryl Acetate,vitamin	1 (0.1)
	Ascorbic Acid,calcium Pantothenate,chromic Chloride,colecalciferol,cupric Oxide,folic Acid,manganese Chloride,nicotinamide,pyridoxine Hydrochloride,retinol Acetate,riboflavin,sodium Selenate,thiamine Hydrochloride,tocopheryl Acetate,vitamin B12 Nos,zinc Oxide	1 (0.1)
	Ascorbic Acid,calcium Pantothenate,cyanocobalamin,nicotinamide,pyridoxine Hydrochloride,riboflavin,thiamine Hydrochloride	1 (0.1)
	Ascorbic Acid,calcium Pantothenate,ergocalciferol,nicotinamide,pyridoxine Hydrochloride,retinol,riboflavin,thiamine Hydrochloride	17 (1.6)
	Ascorbic Acid, Betacarotene, Bioflavonoids,chromium,copper,cystine,folic Acid,iodine,iron,levocarnitine,magnesium,manganese,menadione,nicotinic Acid,pantothenic Acid,pyridoxine Hydrochloride,retinol,riboflavin,selenium,thiamine,tocopherol,vitamin B12 Nos,vitamin D Nos,zinc	1 (0.1)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Ascorbic Acid, Betacarotene, Lycopene, Selenium, Vitamin E Nos, Zinc	1 (0.1)
	Ascorbic Acid, Betacarotene, Selenium, Tocopherol, Zinc	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	17 (1.6)
	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	3 (0.3)
	Ascorbic Acid, Biotin, Calcium Pantothenate, Cyanocobalamin, Folic Acid, Nicotinamide, Pyridoxine Hydrochloride, Riboflavin, Thiamine Mononitrate	1 (0.1)
	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	6 (0.6)
	Ascorbic Acid, Biotin, Calcium, Chromic Chloride, Colecalciferol, Cupric Oxide, Ferrous Sulfate, Folic Acid, Magnesiumoxide, Magnesiumchloride, Mecobalamin, Nicotinamide, Pyridoxine, Retinol, Riboflavin,sodiumthiamine, Tocopherol, Zinc	11 (1.0)
	Ascorbic Acid, Biotin, Cyanocobalamin, Folic Acid, Nicotinamide, Pantothenic Acid, Pyridoxine Hydrochloride, Riboflavin, Thiamine Hydrochloride	1 (0.1)
	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	1 (0.1)
	Ascorbic Acid, Calcium Pantothenate, Cyanocobalamin, Folic Acid, Nicotinamide, Pyridoxine Hydrochloride, Riboflavin, Thiamine Hydrochloride	23 (2.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Ascorbic Acid, Calcium Pantothenate, Ergocalciferol, Nicotinamide, Pyridoxine Hydrochloride, Retinol, Riboflavin, Thiamine Hydrochloride	1 (0.1)
	Ascorbic Acid, Calcium Pantothenate, Folic Acid, Nicotinamide, Pyridoxine Hydrochloride, Riboflavin, Thiamine Hydrochloride, Vitamin B12 Nos, Zinc Sulfate Monohydrate	2 (0.2)
	Ascorbic Acid, Cod-Liver Oil, Colecalciferol, Nicotinamide, Pyridoxine, Retinol, Riboflavin, Sodium Phosphate, Thiamine	4 (0.4)
	Ascorbic Acid, Cyanocobalamin, Folic Acid, Nicotinic Acid, Pantothenic Acid, Pyridoxine, Riboflavin, Thiamine, Zinc	2 (0.2)
	Ascorbic Acid, Dexpanthenol, Nicotinamide, Pyridoxine, Riboflavin, Thiamine	2 (0.2)
	Ascorbic Acid, Lycopene, Omega-3 Fatty Acids, Tocopherol	9 (0.9)
	Ascorbic Acid,calcium Pantothenate, Chromium Picolinate, Colecalciferol,copper,cyanocobalamin,dunaliella Salina,folic Acid,inositol,magnesium,manganese,molybdenum,nicotinamide,phaseolus Vulgaris,pyridoxine Hydrochloride,retinol Palmitate,riboflavin,selenium, Thiamine Mononitrate, Vanadium, Vitamin E Nos, Zinc	10 (0.9)
	Aspartic Acid, Iodine, Magnesium Aspartate, Magnesium Oxide, Manganese Citrate, Nicotinamide, Nicotinic Acid, Potassium Aspartate, Riboflavin, Thiamine Hydrochloride, Tyrosine, Zinc Picolinate	1 (0.1)
	Benfotiamine,chromium,folic Acid,mecobalamin,pyridoxine Hydrochloride,riboflavin,thioctic Acid	1 (0.1)
	Benfotiamine, Mecobalamin, Pyridoxine	1 (0.1)
	Betacarotene,biotin	1 (0.1)
	Betacarotene, Biotin, Chromic Chloride, Colecalciferol, Inositol, Lysine Hydrochloride, Manganese Chloride Tetrahydrate, Nicotinamide, Potassium Iodide, Pyridoxine, Hydrochloride, Sodium Molybdate Dihydrate, Sodium Selenate, Zinc Gluconate	21 (2.0)
	Bisbutiamine	1 (0.1)
	Calcium Pantothenate, Chromium Picolinate, Folic Acid, Mecobalamin, Nicotinamide, Pyridoxine Hydrochloride, Thiamine Hydrochloride, Zinc Sulfate	5 (0.5)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Chromium Picolinate,cyanocobalamin,folic Acid,nicotinamide,pyridoxine Hydrochlorid,selenium,zinc Sulfate	13 (1.2)
	Chromium Picolinate,folic Acid,lycopene,nicotinamide,pyridoxine Hydrochloride,selenious Acid,vitamin B12 Nos,zinc Sulfate.	1 (0.1)
	Colecalciferolcyanocobalamin,dexpanthenol,lysine Hydrochloride,manganese Chloride,nicotinamide,potassium Iodide,pyridoxine Hydrochloride,retinol Palmitate,riboflavin Sodium Phosphate,sodium Molybdate,sodium Selenate,thiamine Hydrochloride,tocopherol,zinc Sulfate	5 (0.5)
	Colecalciferol	104 (9.8)
	Colecalciferol,folic Acid,mecobalamin,pyridoxine Hydrochloride,thioctic Acid	6 (0.6)
	Colecalciferol, Cyanocobalamin, Dexpanthenol, Lysine Hydrochloride, Manganese Chloride, Nicotinamide, Potassium Iodide, Pyridoxine Hydrochloride, Retinol Palmitate, Riboflavin Sodium Phosphate, Sodium Molybdate, Sodium Selenate, Thiamine Hydrochloride, Tocopherol, Zinc Sulfate	4 (0.4)
	Colecalciferol, Folic Acid, Mecobalamin, Pyridoxine, Thioctic Acid	23 (2.2)
	Colecalciferol, Mecobalamin	6 (0.6)
	Cyanocobalamin,pyridoxine Hydrochloride,thiamine Disulfide	13 (1.2)
	Cyanocobalamin,pyridoxine Hydrochloride,thiamine Hydrochloride,tocopheryl Acetate	1 (0.1)
	Cyanocobalamin, Panthenol, Pyridoxine Hydrochloride, Thiamine Hydrochloride	1 (0.1)
	Dexpanthenol, Nicotinamide, Nicotinic Acid, Pyridoxine Hydrochloride, Riboflavin, Thiamine Mononitrate	1 (0.1)
	Folic Acid, Lycopene, Minerals Nos, Vitamins Nos, Xantofyl	4 (0.4)
	Folic Acid, Mecobalamin, Pyridoxal	1 (0.1)
	Ginseng Nos, Minerals Nos, Vitamins Nos	1 (0.1)
	Herbal Nos, Minerals Nos, Vitamins Nos	4 (0.4)
	Minerals Nos, Vitamins Nos	9 (0.9)
	Pyridoxine	2 (0.2)

Drug Class, n (%) [1]	Generic Name of Drug, n (%) [1]	Overall (N = 1057)
	Tocopherol	3 (0.3)
	Vitamins Nos	57 (5.4)

Source Data: Table 14.3.3.1, Listing 16.4.2
Note:
[1] Percentage of drug class and generic name of drug were calculated by taking count of corresponding column header group as denominator.
General Note:
[1] Medications were 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, IDeg was well tolerated. A total of only 44 AEs and 2 SAEs were observed during the Study in patients treated with IDeg. Majority of AEs were mild and only few were moderate in nature. Both serious AEs were not life threatening. Moreover, majority of AEs were unlikely associated with the Study Drug and also recovered/resolved during the Study period. Treatment-emergent hypoglycaemia using IDeg, was reported in 0.1% of patients. No episode of severe hypoglycemia was observed during the study.

13 DISCUSSION AND OVERALL CONCLUSIONS

This multi-centre, prospective, open-label, single-arm, non-interventional, PMS Study was conducted in India to assess the safety and effectiveness of IDeg in accordance to the regulatory authority's requirement. Patients with DM requiring insulin therapy and qualified for starting treatment with Tresiba® were enrolled in this Study. In this real-world clinical practice, the safety and efficacy was assessed in patients who started or switched to IDeg, mostly from another conventional anti-diabetic medication including OADs and different insulins. Several important benefits were observed; HbA1c and FPG was improved by 1.8% and 64.7 mg/dL, in conjunction with reduction in Post breakfast and Post lunch glucose by 86.1 ± 94.80 and 87.8 ± 100.2 mg/dL from baseline.

The improvement in glycaemic control with low risk of hypoglycemia in the current Study, compared with conventional basal insulins was consistent with results of phase 3 trials, observational studies and real world clinical studies.[12, 14, 22-24] In a real-world analysis of 51 consecutive patients (35 had T1DM and 16 had T2DM) switching to IDeg due to problems with hypoglycaemia on their prior basal insulin, reported a mean reduction in HbA1c by 0.5% and 0.7% in patients with T1DM and T2DM, respectively. Furthermore, the hypoglycaemic events were decreased by >90%.[24] Another real-world Study in patients with T1DM (n = 357) reported an improvement in HbA1c by 0.3%, when switched to IDeg. The switch to IDeg was also associated with a 20% reduction in the rate of overall hypoglycaemia.[25] A retrospective Study in Japanese patients with T1DM reported a significant reduction ($p < 0.01$) in mean HbA1c (%) in weeks 4, 8, 12, and 16, compared to baseline when patients were switched to IDeg (once daily) during routine medical care.[26] This Study further showed a transient increase in hypoglycaemic events, however, the change did not reach at statistical significance.[26] A Patient-level meta-analyses has shown an equivalent HbA1c control, but significantly greater reductions in FPG with IDeg, compared to IGlar, in basal-bolus-treated T1DM and insulin-naive T2DM patients.[22]

Analyzing reasons for switching patients to IDeg demonstrate that majority of 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. Similar findings were also reported by Landstedt-Hallin (2015), wherein the inability or unwillingness to administer basal insulin twice daily was the most common reason (66% patients), followed by unsatisfactory HbA1c (59%), hypoglycaemias (45%) and difficulties in taking insulin at a specific time point (13%) were reasons for switching on IDeg.[25] IDeg has an ultra-long duration of action (greater

than 42 hours), with flat and stable steady-state pharmacokinetic and pharmacodynamic profile, which might allow flexibility in dosing times. It forms multihexamers that result in its subcutaneous deposition and ultimately cause protracted time-action profile.[20] Day-to-day variability in total glucose-lowering effect was 4-times lower for IDeg than IGlar, hence showed less hypoglycaemic episodes.[27] Moreover, once-daily dosing of IDeg yields a virtually "peakless" profile, more closely mimicking the profile of physiological basal insulin secretion.

The safety of IDeg was evaluated in 9 clinical trials lasting 6 to 12 months in 1102 patients with T1DM and in 2713 patients with T2DM. Mean treatment durations in these cohorts were 34 weeks and 36 weeks, respectively.[21] Common adverse reactions with IDeg in these trails (excluding hypoglycaemia) were nasopharyngitis, upper respiratory tract infection, headache, sinusitis, diarrhea, and gastroenteritis. Hypersensitivity, lipodystrophy, injection-site reactions, weight gain, and peripheral edema were also reported during these trials. 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, Ear and labyrinth disorders, Eye disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders and vascular disorder.

A baseline history of neuropathy, ophthalmopathy, nephropathy, and cardiovascular disease was reported in 11%, 16%, 7%, and 0.5%, respectively, in patients with type 1 diabetes.[9] A baseline history of the same conditions was reported in 14%, 10%, 6%, and 0.6%, respectively, of patients with type 2 diabetes.[21] In our Study, among the microvascular complications, majority of patients (19.2%) had Peripheral Neuropathy. This was followed by Nephropathy (8.7%), Retinopathy (7.2%), and autonomic neuropathy (6.2%). Among the macrovascular complications, Coronary Heart Disease (8.5%) was highly prevalent, followed by Macroangiopathy (including Peripheral Vascular Disease) (1.8%) and Stroke (0.9%).

In conclusion, this study demonstrates the long-term safety profile of IDeg for 1 year in routine clinical practice in Indian patients. Starting or switching to IDeg has the potential to improve glycaemic control with a reduced risk of hypoglycaemia. It is possible that these advantages with IDeg, in particular, efficacious lowering of HbA1c (%), FPG (mg/dL) and PPG (mg/dL) values together 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 Subject Disposition

Not applicable

14.2 Efficacy Data

Not applicable

14.3 Safety Data

Table 14.3.6.1.2	Visit Wise Summary of change from Baseline of lab parameters - SAS Population (N = 1057)
Table 14.3.4.2	Visit wise Summary of change in Body Measurements and Vital Signs-SAS Population (N = 1057)
Table 14.3.8.2	Visit wise Summary of Change in Dose Administration - SAS Population (N = 1057)
Table 14.3.3.3	Visit wise Summary of Antihypertensive Medications - SAS Population (N = 1057)
Table 14.3.3.3.1	Shift Table to show changes in different visits in Antihypertensive medications - SAS Population (N = 1057)
Table 14.3.3.4	Visit wise Summary of lipid-lowering Medications - SAS Population (N = 1057)
Table 14.3.3.4.1	Shift Table to show changes in different visits in lipid-lowering medications - SAS Population (N = 1057)

14.3.1 Displays of Adverse Events

Table 14.3.1.7	Summary of adverse events by System Organ Class and Preferred Term by relation to a technical complaint - SAS Population (N = 1057)

14.3.2 Listings of Death, Other Serious and Significant Adverse Events

Not applicable

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable

14.3.4 Abnormal Laboratory Value Listing (each patient)

Not applicable

15 REFERENCE LIST

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE and Makaroff LE. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*. 2017;128:40-50.
2. International Diabetes Federation. IDF Diabetes Atlas teB, Belgium: and International Diabetes Federation 2017.
3. Das AK. Type 1 diabetes in India: Overall insights. *Indian Journal of Endocrinology and Metabolism*. 2015;19:S31-S33.
4. da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, Guariguata L, Seuring T, Zhang P, Cavan D and Makaroff LE. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. *Diabetes research and clinical practice*. 2016;117:48-54.
5. Petznick A. Insulin management of type 2 diabetes mellitus. *American family physician*. 2011;84:183-90.
6. Devries JH, Nattrass M and Pieber TR. Refining basal insulin therapy: what have we learned in the age of analogues? *Diabetes/metabolism research and reviews*. 2007;23:441-54.
7. Heise T and Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes, obesity & metabolism*. 2007;9:648-59.
8. Haahr H and Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clinical pharmacokinetics*. 2014;53:787-800.
9. Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund PO and Ribel U. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharmaceutical research*. 2012;29:2104-14.
10. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S and Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes, obesity & metabolism*. 2012;14:859-64.
11. Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D, Larsen J, Tamer SC and Bain SC. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *The Journal of clinical endocrinology and metabolism*. 2013;98:1154-62.
12. Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, Endahl L and Zinman B. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes, obesity & metabolism*. 2013;15:175-84.

13. Meneghini L, Atkin SL, Gough SC, Raz I, Blonde L, Shestakova M, Bain S, Johansen T, Begtrup K and Birkeland KI. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes care*. 2013;36:858-64.
14. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Francisco AM, Pei H and Bode B. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet (London, England)*. 2012;379:1489-97.
15. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Munoz-Torres M, Rosenstock J, Endahl LA, Francisco AM and Hollander P. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet (London, England)*. 2012;379:1498-507.
16. Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S and Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes care*. 2013;36:2536-42.
17. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC and Park S. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: A 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *Journal of Diabetes Investigation*. 2013;4:605-612.
18. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L and Mathieu C. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes care*. 2012;35:2464-71.
19. Philis-Tsimikas A, Del Prato S, Satman I, Bhargava A, Dharmalingam M, Skjoth TV, Rasmussen S and Garber AJ. Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents. *Diabetes, obesity & metabolism*. 2013;15:760-6.
20. 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;9:144-8.
21. Tresiba (insulin degludec injection) [prescribing information]. Plainsboro, NJ Novo Nordisk September 2015.
22. Vora J, Christensen T, Rana A and 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 : research, treatment and education of diabetes and related disorders. 2014;5:435-46.

23. Iwamoto Y, Clauson P, Nishida T and Kaku K. Insulin degludec in Japanese patients with type 1 diabetes mellitus: A randomized controlled trial. *J Diabetes Investig*. 2013;4:62-8.
24. Evans M, McEwan P and Foos V. Insulin degludec early clinical experience: does the promise from the clinical trials translate into clinical practice--a case-based evaluation. *Journal of medical economics*. 2015;18:96-105.
25. Landstedt-Hallin L. Changes in HbA1c, insulin dose and incidence of hypoglycemia in patients with type 1 diabetes after switching to insulin degludec in an outpatient setting: an observational study. *Current medical research and opinion*. 2015;31:1487-93.
26. Suzuki J, Yamakawa T, Nagakura J, Shigematsu E, Kadonosono K and Terauchi Y. Efficacy of switching from insulin glargine to insulin degludec in patients with type 1 diabetes: a 16-week retrospective study. *Diabetology International*. 2017;8:45-51.
27. Kohnert K-D, Heinke P, Vogt L, Zander E, Fritzsche G, Augstein P and Salzsieder E. Reduced glucose variability is associated with improved quality of glycemic control in patients with type 2 diabetes: a 12-month observational study. *Journal of Endocrinology and Metabolism*. 2011;1:64-72.

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)