Protocol

Study ID:NN1250-4129

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.

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional study

Protocol originator:-

[redacted]

[redacted] India

Title	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 version identifier	1.0
Date of last version of protocol	25 July 2013
EU PAS Register number	Study not registered
Active substance	Insulin degludec
Medicinal product	Tresiba®
Product reference	Not Applicable
Procedure number	Not Applicable
Marketing authorisation holder(s)	Novo Nordisk India Pvt Ltd
Joint Post Authorisation Safety Study (PASS)	Yes
Research question and objectives	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.
Country(-ies) of study	India
Author	[redacted], [redacted] Novo Nordisk India Pvt Ltd

Marketing authorisation holder(s)

Marketing authorisation holder (s) (MAH (s))	Novo Nordisk India Private Ltd.
MAH contact person	Novo Nordisk India Private Ltd. Plot No.32, 47 - 50, EPIP Area, Whitefield, Bangalore - 560 066 India

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1 List of abbreviations

ADR	*Adverse Drug Reaction*
AE	*Adverse Event*
BMI	*Body Mass Index*
CRF	*Case Report Form*
CRO	*Contract Research Organisation*
CV	*Curriculum Vitae*
DCF	*Data Clarification Form*
EAS	*Efficacy Analysis Set*
EDC	*Electronic Data Capture*
ENCePP	*European Network of Centres for Pharmacoepidemiology and Pharmacovigilance*
FAS	*Full Analysis Set*
FBG	*Fasting Blood Glucose*
FPG	*Fasting Plasma Glucose*
GVP	*Good Pharmacovigilance Practice*
GPP	*Good Pharmacoepidemiology Practice*
HbA1c	*Glycated Haemoglobin*
ICF	*Informed consent form*
IEC	*Independent Ethics Committee*
IRB	*Institutional Review Board*
LAR	*Legally Acceptable Representative*
OAD	*Oral anti-diabetic drugs*
PASS	*Post Authorisation Safety Study*
PMS	*Post Marketing Surveillance*
PI	*Package Insert*
PPBG	*Postprandial Blood Glucose*
PPPG	*Postprandial Plasma Glucose*
PRAC	*Pharmacovigilance Risk Assessment Committee*
SAE	*Serious Adverse Event*

SADR	*Serious Adverse Drug Reaction*
SOC	*System Organ Class*
TC	*Technical Complaint*
T1DM	*Type 1 Diabetes mellitus*
T2DM	*Type 2 Diabetes mellitus*
UTN	*Universal Trial Number*
W HO	*World Health Organization*

2 Responsible parties

Novo Nordisk will be responsible for the preparation of the protocol. Data management will be delegated under an agreement of transfer of responsibilities to an external CRO. Statistics and the study report will be performed by Novo Nordisk or delegated under an agreement of transfer of responsibilities to an external CRO. All Novo Nordisk procedures and policies will be met by the CRO.

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties. The medical care given to, and medical decisions made on behalf of patients should always be the responsibility of a qualified physician

The physician must follow the instructions from Novo Nordisk when processing data. The physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The physician must prevent any unauthorised access to data or any other processing of data against applicable law. Upon request from Novo Nordisk, the physician must provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.

3 Abstract

3.1 Title

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.

3.2 Rationale and background

The rationale for conduct of this study in India is that it is a primary regulatory requirement by the Indian health authority to assess the safety of all medicinal products approved for clinical use

3.3 Research question and objectives

The purpose of this post marketing surveillance (PMS) study (also called post authorization safety study (PASS) study) is to assess long-term safety and efficacy of Tresiba® in patients with diabetes mellitus requiring insulin therapy under normal clinical practice conditions

3.4 Study design

This is a multi-centre, prospective, single-arm, open-label, non-interventional, post marketing surveillance (PMS) study (post authorization safety study (PASS) study) to evaluate safety and efficacy during long-term treatment with Tresiba® in patients with diabetes mellitus requiring insulin therapy under normal clinical practice conditions in India. Patients who qualify for starting treatment with Tresiba® based on the clinical judgment by their treating physician will be treated with Tresiba® according to routine clinical practice at the discretion of the treating physician. The assignment of the patient to Tresiba® is decided in advance of this protocol. The patients will be decided to be prescribed with Tresiba® by physicians before the enrolment in the study based on requirement and clinical judgement in diabetes management.

3.5 Population

Patients with diabetes mellitus requiring insulin therapy who qualify for starting treatment with Tresiba® based on the clinical judgment by their treating physician during enrolment period. Patients are excluded if they have 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.

3.6 Variables

AEs/SAEs/ADRs/SADRs will be collected for safety evaluation and HbA1c, FPG and confirmed hypoglycaemic events will be evaluated for efficacy aspect of Tresiba®

3.7 Data sources

The PMS/PASS study is conducted in a real-life setting and without extensive monitoring of the data collected. Only data obtained under normal clinical practice (i.e. available in patient´s medical record or recall) will be recorded. Patients will not undergo any additional testing for the purposes of this PMS/PASS study. Hence there is a risk that complete data stated in the protocol are not always collected from all patients, though relevant measures will be employed to secure that all relevant data are reported and collected

3.8 Study size

The number of patients to be included in this study is 1000

3.9 Study duration

1 year

3.10 Data analysis

Safety and efficacy will be evaluated using descriptive statistics.

3.11 Milestones

FPFV will be attained by 31 Jan 2014 with LPLV by 31 Jan 2016 and study report by 30 May 2016

4 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason

5 Milestones

Milestone	**Planned date**
Start of data collection	31 Jan 2014
End of data collection	31 Jan- 2016
End (or completion) of study	31 Jan 2016
Final report of study results	30 May 2016

The study has to be registered with CTRI (Clinical Trial Registry India) before the enrolment of first patient in the study in the following site www.ctri.nic.in as per regulations of health authority of India.

6 Rationale and background

The rationale for conduct of this study in India is 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® has been granted in India, there is a continuous need to monitor the safety of medicinal products as post-approval surveillance while they are used under normal clinical practice. Spontaneous reporting helps detect signals of safety concern and is a part of continuous safety surveillance. However, more formal studies or surveys constitute a proactive approach to planned collection of safety information and will in some instances identify unexpected ADRs.

7 Research question and objectives

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

7.1 Primary objective

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.

7.2 Secondary objective(s)

To assess safety and efficacy of long term (1 year) treatment with Tresiba®

7.3 Endpoints

Primary endpoint

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

Secondary safety endpoint

- 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

- Change from baseline in HbA1c after 1 year of treatment
- Change from baseline in FPG after 1 year of treatment
- Incidence of confirmed hypoglycaemia during 1 year of treatment

8 Research methods

In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

8.1 Study design

8.1.1 Type of study

This is a multi-centre, prospective, single-arm, open-label, non-interventional, post marketing study(PMS)/post authorization safety study (PASS) study to evaluate safety and efficacy during long-term treatment (1 year) with Tresiba® in patients with diabetes mellitus requiring insulin therapy under normal clinical practice conditions in India. A total of 1000 patients will be enrolled to investigate safety of Tresiba® of which approximately 10 patients per site will be selected by 100 physicians (both primary and secondary care physicians). Data will be collected at baseline (Visit 1), 3 months (Visit 2), 6 months (Visit 3) and finally at one year (Visit 4).

8.1.2 Rationale for study design

The study is 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 is expected to be sufficient to capture untoward medical occurrences that are likely to be associated with long-term use of Tresiba®. Frequency and timing of visit are based on normal clinical practice for patients with diabetes mellitus requiring insulin therapy in India.

8.1.3 Treatment of patients

Patients with diabetes mellitus requiring insulin therapy who qualify for starting treatment with Tresiba® based on the clinical judgment by their treating physician will be treated with Tresiba® according to routine clinical practice at the discretion of the treating physician. The assignment of the patient to Tresiba® is not decided in advance by the protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. Tresiba® will be prescribed by the physician under normal clinical practice conditions and will be obtained/ purchased from the chemist based on physician prescription. The physician will determine the starting dose, as well as later changes to dose, if any. Tresiba® should be used in accordance with the Indian package insert

8.1.4 Rationale for treatment

Diabetes patients will often require insulin in treatment continuum to control their blood glucose when the other available therapy options fail to keep to the recommended target appropriate to respective age group. The clinical practice in India is to add insulin, either basal or premixed depending on the requirement by the patient on existing therapy. The physician will decide as per patient requirement and add basal insulin therapy Tresiba® as per the Indian Package insert. Dosage and administration are based on the Indian package insert of Tresiba®. Further details about Tresiba® can be found in the Indian package insert.

8.1.5 Study supplies

Study product:

The following marketed products will be used in this PMS/PASS. They will not be provided by Novo Nordisk.

- Tresiba® FlexTouch® prefilled pen injector (100 U/mL)

Packaging and labelling of study product(s):

These must be as available in the market by prescription and purchase/supply as in routine practice and according to local regulations.

Auxiliary supply:

Not Applicable

8.2 Setting

8.2.1 Number of patients to be studied

Planned number of patients to be included: 1000

Planned number of patients to complete the study: 800

Anticipated number of patients to be included in each country: India only-1000

8.2.2 Inclusion 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., HbA1c, 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.

8.2.3 Exclusion 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

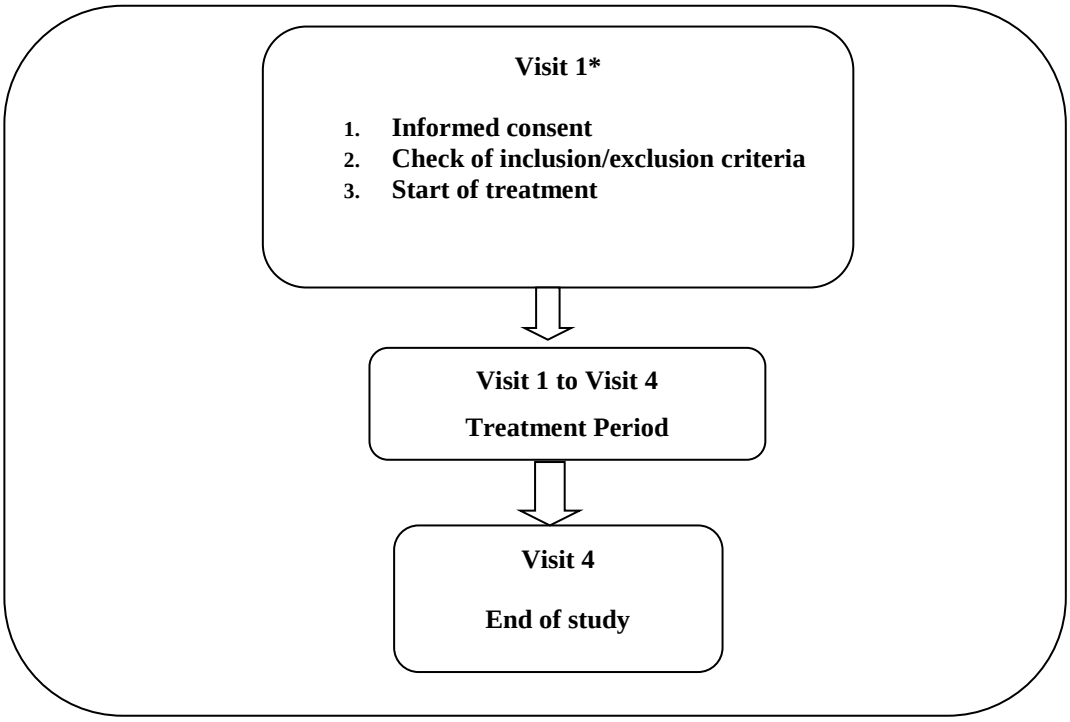
8.2.4 Withdrawal criteria

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.

8.2.5 Rationale for selection criteria

The assignment of the patient to Tresiba® is decided in advance of this the protocol and as part of current practice. Hence, the prescription of Tresiba is clearly separated from the decision to include the patient in the study.

8.2.6 Flowchart



*** 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.**

8.3 Variables

Details of all concomitant illnesses and medication must be 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. A clinically significant worsening of concomitant illness must be reported as an AE.

Definitions:

- Concomitant illness: any illness that is present at the start of the study.
- Concomitant medication: any medication other than Tresiba® and other anti-diabetic medications that is taken during the study.

- Confirmed hypoglycaemia: In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL). Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.
- Confirmed hypoglycaemic episodes are defined as episodes that are severe (ie, an episode requiring assistance of another person to 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

8.3.1 Assessments for safety and efficacy

	Visit 1 (0 weeks)	**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[2] since last visit		X	X	X
Most recent HbA1c value and date of measurement (if available)[3]	X	X	X	X
Most recent FPG/FBG 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 of 3.1 mmol/L (56 mg/dL). Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.

Confirmed hypoglycaemic episodes are defined as episodes that are severe (ie, an episode requiring assistance of another person to 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 1, the term recent means "over the past 4 weeks before starting on insulin degludec".

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

8.3.2 Other assessments

Patients will not undergo any additional testing or assessments for the purposes of this study.

8.4 Data sources

The PMS/PASS study is conducted in a real-life setting and without extensive monitoring of the data collected. Hence there is a risk that complete data stated in the protocol are not always collected from all patients. However data includes routine clinical measurements which can be recorded and analyzed for measuring safety and efficacy of Tresiba®

8.4.1 Visit procedures

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

A patient who meets all inclusion criteria and none of exclusion criteria will be enrolled in the study and assigned a patient number. Patients enrolled in the study will be provided with contact address (es) and telephone number(s) of the physician and/or site staff.

Visit 1

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

- 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 insulin degludec treatment (if available)
- DM treatment prescribed during PMS/PASS study
- Reasons why decision was taken to start therapy with insulin degludec (increased HbA1c, 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

Visits 2, 3 & 4

The physician will gather the following information from either the patient's medical record, patient recall, and/or the patient's SMBG diary:

- All AEs/SAEs/ADRs/SADRs 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 HbA1c 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

8.5 Study size

The sample size calculation is based on the primary objective to evaluate the safety and tolerability of Tresiba®. A sample size of 1000 patients, assuming 20% dropouts who have been exposed to insulin degludec during the treatment will provide a probability of 80% of detecting at least one event that occurs 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 would be 0.375 per year. In other words for an unobserved event, a rate of 0.375 per year or larger can be excluded with 95% probability.

8.6 Data management

Data management is the responsibility of Novo Nordisk Headquarters

8.6.1 Data management

Data management will be carried out by Novo Nordisk or delegated under an agreement of transfer of responsibilities to an external CRO. Data will be processed using an Oracle-based, validated data management system. The patients will be identified by patient number, site, and study identification number. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements.

Electronic data transfer of any CRF or patient related data must be approved by the responsible Data Management Unit(s). In cases where data is transferred via non-secure electronic networks, data must follow applicable data protection regulations. Appropriate measures such as encryption or deletion must be enforced to protect the identity of patients in all presentations and publications as required by local/regional/national requirements.

8.6.2 Case report forms and rules for completing

Print legibly using a ballpoint pen. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.

If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the respective answer field in the CRF. If the question is irrelevant (eg is not applicable) indicate this by writing "NA" (not applicable) in the respective answer field. Further guidance can be obtained from the instruction in the CRF.

By signing the affirmation statement, the physician confirms that the information is complete and correct.

8.6.3 Corrections to CRFs

Corrections to the data on the CRFs must only be made by drawing a straight line through the incorrect data and by writing the correct value next to data that has been crossed out. Each correction must contain initials, date and explanation (if necessary) by the physician or the physician's authorised staff. If corrections are made by the physician's authorised staff after the date of the physician's signature on the affirmation statement, the statement must be signed and dated again by the physician. Corrections necessary after the CRFs have been removed from the physician's site must be documented on a Data Clarification Form (DCF). Such corrections must be approved by the physician or her/his authorised staff.

8.6.4 CRF flow

The sponsor will provide the investigator with CRF. The investigator is to provide patient data according to the sponsor's instruction, in the designated data collection form, compliant with Good Clinical practice/ GPP.

Physicians (or appropriately trained designee) will complete paper CRFs at each patient visit. These CRFs will be collected by the Novo Nordisk India or the CRO acting as Novo Nordisk representative upon completion. The method by which the CRFs are transmitted is dependent on the location of the site. Possible methods include fax, courier or post. Once received at the CRO, the information on the CRFs will be entered into the database and processed according to the data management plan. Physicians (or appropriately trained designee) will be encouraged to complete and send all relevant CRFs pertaining to each patient's visit promptly.

8.7 Data analysis

No formal statistical testing will be done in this non-interventional trial.

All continuous and categorical endpoints will be analysed using descriptive statistics

8.7.1 Evaluability of patients for analysis

The following analysis sets are defined.

Safety Analysis Set (SAS): will consist of all patients who have received at least one dose of Tresiba® during this PMS/PASS.

Efficacy Analysis Set (EAS): will consist of all patients in the SAS who have at least one post-baseline measurement concerning HbA1c, FPG or confirmed hypoglycaemic event(s).

The descriptive analyses of AEs will be based on the SAS. Also demographic data will be presented using SAS.

The summaries of HbA1c, FPG and confirmed hypoglycaemic events will be based on the EAS.

8.7.2 Statistical methods

The primary endpoint will be summarized using descriptive statistics by SOC and preferred term showing number of subject with events, number of events, incidence rate and rate per 100 PYE. Exposure to be used in the calculation in rate should be defined as the timeframe from time of first Tresiba® dose to last contact in this PMS/PASS trial. All secondary endpoints related to AEs (ADR/SADR/SAEs) will be presented in a similar way.

These endpoints will also be presented by the severity grade.

Hypoglycaemic episodes will be summarised in a similar way presenting confirmed and severe episodes separately.

The continuous variables HbA1c and FPG, demographic data will be summarized with descriptive statistics (N, N miss (number of missing values), mean, standard deviation, and median). Baseline, end of trial values and change from baseline values will be presented. Missing values will be subject to last observation carried forward (LOCF)

8.7.3 Interim analysis

Not Applicable

8.7.4 Sequential safety analysis/safety monitoring

Not Applicable

8.7.5 Health economics and/or patients reported outcome

Not Applicable

8.8 Quality control

Novo Nordisk ensures 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.

8.8.1 Monitoring procedures

As this is a PMS/PASS study, Novo Nordisk reserves the right to conduct monitoring on a case-to-case basis when need is determined.

8.8.2 Critical documents

Before the physician starts the study (i.e. obtains informed consent from the first patient), the following documents must be available at Novo Nordisk:

- Regulatory approval and/or notification as required
- Curriculum Vitae (CV) of physician (current, dated and signed and/or supported by an official regulatory document)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IRB/IEC approved patient information/informed consent form/any other written information/advertisement (or document of waiver by IRB/IEC of informed consent)
- Non-interventional study agreement
- List of IRB/IEC Committee members/constitution (if applicable)
- Financial contract and study agreement document(s).

8.8.3 Retention of study documentation

Patient notes must be kept for the maximum period permitted by the hospital, institution or private practice.

Novo Nordisk will comply with all the requirements of Good Pharmacoepidemiological Practice (GPP) and relevant national legislation related to archiving of study documentation. Records containing patient sensitive data must not be archived by Novo Nordisk, but must be kept with physician and patient and according to local regulations pertaining to personal data protection

The physician must agree to archive the documentation pertaining to the study in an archive after completion or discontinuation of the study, if not otherwise notified. The physician should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

8.9 Limitations of the research methods

Due to the non-interventional nature of this trial and the study conducted in a real-life setting there will not be a comparator/control arm and there won't be extensive monitoring of data collected. Hence there is a risk that complete data stated in the protocol are not always collected from all patients.

8.10 Other aspects

None

9 Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practice (GPP)[2].

9.1 Informed consent form for study patients

Informed consent from all study participants is taken and documented. In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki[3].

Prior to any study-related activity, the physician must give the patient and/or the patient's Legally Acceptable Representative (LAR) oral and written information about the study in a form that the patient or the patient's LAR can read and understand. This includes the use of impartial witness where required.

A voluntary, signed and personally dated, informed consent form will be obtained from the patient and/or the patient's LAR prior to any study-related activity. The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must sign and date the patient information/informed consent form. If information becomes available that may be relevant to the patient's willingness to continue participating in the study, the physician must inform the patient and/or the patient's LAR in a timely manner and a revised written informed consent must be obtained.

9.2 Data handling

If the patient (or the patient's LAR) withdraws the previously given informed consent, the patient's data will be handled as follows:

- Data collected will be used as part of the study population.
- Safety events will be reported to the department responsible for Global Safety, Novo Nordisk/regulatory authorities.

Data will be collected and handled in accordance with local law and IRB/IEC procedures.

9.3 Institutional Review Boards/Independent Ethics Committee

Before commencement of the study, the protocol, any amendments, patient information/informed consent form, any other written information to be provided to the patient, patient enrolment procedures, if any, the physician's current CV and/or other documentation evidencing qualifications and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify (by study identification number, including version, title and/or date of the document) which documents have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC (or other appropriate bodies as required locally) before commencement of the study.

During the study, the physician must promptly in accordance with local requirements report the following to the IRB/IEC: unexpected serious adverse reactions, amendments to the protocol according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the study status and other documents as required by the local IRB/IEC.

Amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate immediate hazards to the patients.

The physician must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the physician's study file and copies must be sent to Novo Nordisk.

9.4 Regulatory authorities

Regulatory authorities will receive the non-interventional study application, amendments to the protocol, reports on serious adverse reactions and the non-interventional study report according to national requirements.

9.5 Premature termination of the study

The sponsor, physician or a pertinent regulatory authority may decide to stop the study or part of the study at any time, but agreement on procedures to be followed must be obtained.

- If a study is prematurely terminated or suspended, the physician and/or sponsor should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

- If after the termination of the study the risk/benefit analysis has changed, the new evaluation should be provided to the IEC/IRB in case it will have an impact on the planned follow-up of the patients who have participated in the study. If so, the actions needed to protect the patients should be described.

9.6 Responsibilities

Novo Nordisk will be responsible for the preparation of the protocol. Data management will be delegated under an agreement of transfer of responsibilities to an external CRO. Statistics and the study report will be performed by Novo Nordisk or delegated under an agreement of transfer of responsibilities to an external CRO. All Novo Nordisk procedures and policies will be met by the CRO.

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties. The medical care given to, and medical decisions made on behalf of, patients should always be the responsibility of a qualified physician

The physician must follow the instructions from Novo Nordisk when processing data. The physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The physician must prevent any unauthorised access to data or any other processing of data against applicable law. Upon request from Novo Nordisk, the physician must provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.

9.7 Indemnity statement

Novo Nordisk carries product liability for its products and liability as assumed under the special laws, acts and/or guidelines for conducting non-interventional studies in any country, unless others have shown negligence. Novo Nordisk assumes no liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible. Novo Nordisk accepts liability in accordance with applicable laws and guidelines.

10 Management and reporting of adverse events/adverse reactions

10.1 Safety information to be collected

In this study, the following safety information will be **systematically collected**:

- Adverse events
- Adverse drug reactions
- Serious adverse events

- Serious adverse drug reactions
- Pregnancies in female patients and adverse events in the foetus or newborn infant

Severe hypoglycaemic episodes (according to definition in section 8.3.1) always qualify for AE/SAE reporting.

Other safety information during the use of a Novo Nordisk product, ie safety information which is not collected as part the systematic collection, includes: AEs in infants exposed via breastfeeding, overdose, drug abuse or misuse, medication errors, lack of efficacy and technical complaints.

Voluntary reporting of other safety information by the physician should follow the same reporting process flow as for systematic collection. The local department responsible for drug safety will handle the voluntary reports and may request follow-up information as per their statutory requirements.

If during this non-interventional study, a Novo Nordisk representative is informed of any other safety information related to a Novo Nordisk product, he/she should report this as solicited safety information **within 24 hours** to the local department responsible for drug safety.

10.2 Safety definitions

10.2.1 Safety Information

All reports of Adverse Events or adverse device events occurring during the use of a Novo Nordisk Product (this includes Occupational Exposure). In addition, any other information relevant to the safety of a Novo Nordisk Product

10.2.2 Adverse Drug Reaction

An adverse drug reaction is an untoward medical occurrence in a patient administered the study product for which a causal relationship between the product and the occurrence is suspected, ie judged possible or probable (for definitions, see below) by the reporter or by Novo Nordisk.

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 is considered related to the product. An adverse drug reaction is either a serious adverse drug reaction or a non-serious adverse drug reaction (for definitions, see below).

This includes adverse drug reactions 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 is known should not be reported as adverse drug reactions or adverse events.

10.2.3 Adverse event

An adverse event is 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 is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to an aetiology other than the study product

Seriousness criteria

An adverse drug reaction or adverse event is a **serious adverse drug reaction** or **serious adverse event**, respectively, if the reaction or event results in any of the following seriousness criteria:

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

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

[b] The term "hospitalisation" is used when a patient is: admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays 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 hospitalisation. Hospitalisations for administrative, study related and social purposes do not constitute adverse reactions or events and should therefore not be reported as adverse reactions or events including serious adverse reactions or events. Likewise, hospital admissions for surgical procedures planned prior to study inclusion are not considered adverse reactions or events including serious adverse events or reactions.

[c] A substantial disruption of a patient's ability to conduct normal life functions, eg following the event or clinical investigation the patient has 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 do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse drug reaction or adverse event

An adverse drug reaction or adverse event that does not meet a seriousness criteria is considered to be non-serious.

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.

Outcome categories and definitions

- Recovered/resolved – The patient has fully recovered from the condition, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the patient has signed the informed consent.
- Recovering/resolving – The condition is improving and the patient is expected to recover from the condition/event.
- Recovered/resolved with sequelae – The patient has recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If the sequelae meets a seriousness criterion, the adverse drug reaction or adverse event must be reported as a serious adverse drug reaction or serious adverse event.
- Not recovered/not resolved – The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- Fatal – (only applicable if the patient died from a condition related to the reported adverse drug reaction or adverse event. Outcomes of other reported adverse drug reaction or adverse event in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An adverse drug reaction or adverse event with fatal outcome must be reported as a serious adverse drug reaction or serious adverse event).
- Unknown – This term should only be used in cases where the patient is lost to follow-up.

10.2.4 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 serious adverse event/serious adverse drug reaction criteria are fulfilled or not.

10.3 Collection and reporting of safety information

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

All adverse events (AEs)/reactions, either observed by the physician or reported by the patient, must be recorded by the physician and evaluated.

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

In addition to this, for serious adverse drug reactions (SADRs)/serious adverse events (SAEs), further information must be reported by the physician on the applicable safety information form.

Medication errors should be reported by use of the medication error form. For other safety information, i.e. safety information which is not collected as part the systematic collection (see section 10), a customer complaint form should be used.

The physician must report to Novo Nordisk within the following timelines:

For SADRs/SAEs:

- Initial information must be reported **within 24 hours** of the physician's knowledge of the event.
- Further information must be 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 must be 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 should be signed and sent to Novo Nordisk when the event is resolved or at the end of the study
- Initial and further information must be reported on the applicable adverse event form within **14 calendar days** of the physician's knowledge of the event.

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

Novo Nordisk India Pvt. Ltd.

Plot # 32, 47-50, EPIP Area, Whitefield, Bangalore-560066

Ph: +91-080-40303225

Fax: +91-080-41123517

Email: INAgree@novonordisk.com

The physician should record the diagnosis, if available. If no diagnosis is available, the physician should record each sign and symptom as individual adverse events or adverse drug reactions. When a diagnosis becomes available, the diagnosis should be reported and the signs and symptoms covered by the diagnosis should be described.

If more than one sign or symptom is to be reported, use a separate form for each sign and symptom. However, if several symptoms or diagnoses occur as part of the same clinical picture, only one safety information form can be used to describe all the serious adverse reactions or events.

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

In accordance with regulatory requirements, including GVP, the sponsor will inform the regulatory authorities of study product related serious adverse drug reactions. In addition, the sponsor or external CRO will inform the IECs/IRBs of study product related serious adverse drug reactions, in accordance with the local requirements in force. The sponsor or CRO will notify the physician of study product related suspected serious adverse drug reactions, in accordance with the local requirements.

10.4 Follow-up of safety information

Follow-up information concerning previously reported serious adverse drug reactions/serious adverse events, must be 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 must be forwarded to Novo Nordisk within **14 calendar days** from the date specified on the request, unless otherwise specified in the follow-up information request.

The physician must ensure that the worst case severity and seriousness is 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 reflects the situation at the time of the physician's signature.

All serious and non-serious adverse events/reactions classified as severe or possibly/probably related to the study product must be followed until the outcome of the reaction or event is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse events/reactions ongoing at the time of the death (ie the patient dies from another serious adverse event/reaction) can be closed with the outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the last visit (as stated in this protocol) and is expected by the physician to recover.

All other non-serious adverse events must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the last visit whichever comes first, and until all queries related to these adverse events have been resolved. Adverse events ongoing at time of death (ie patient dies from another adverse event) can be closed with an outcome of "recovering" or "not recovered".

10.5 Collection and reporting of pregnancies in female patients

In female patients, pregnancy must be 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 must be collected at 1 month of age at the earliest. Information must be reported **within 14 calendar days** of the physician's first knowledge of the pregnancy outcome. All adverse events experienced by the foetus or newborn infant should be collected and reported regardless of causality assessment.

Reporting of adverse drug reactions or adverse events in foetus, newborn infant or in connection with the pregnancy must be done on the same forms as described for reporting of adverse drug reactions and events. It must be clearly stated in the diagnosis field on the form if the event occurred in the patient, foetus or newborn infant. The reporting timelines are as described for other adverse events or reactions and other serious adverse events or reactions.

10.6 Precautions/Over-dosage

Follow recommendations in the Indian package insert

10.7 Safety committee(s)

Internal Novo Nordisk safety committee

Novo Nordisk has an internal safety committee that performs ongoing safety surveillance of the Tresiba®

11 Plans for disseminating and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of the study product. All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Novo Nordisk.

11.1 Communication and publication

No permission to publish must be granted to any Clinical Research Organisation (CRO) involved in the study described in this protocol.

Novo Nordisk commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means. Novo Nordisk reserves the right not to release data until specified milestones, eg a non-interventional study report is available. This includes the right not to release interim results from non-interventional studies, because such results may lead to conclusions that are later shown to be incorrect.

At the end of the study, one or more public disclosures for publication may be prepared collaboratively by physician(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property. The results of this study will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

11.2 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors' Uniform Requirements (sometimes referred to as the Vancouver Criteria).[4]

11.3 Publications

In accordance with Novo Nordisk commitment to transparency on our clinical trial activities this study will be registered by Novo Nordisk at www.clinicaltrials.gov and www.novonordisk-trials.com in accordance with Novo Nordisk Clinical Trials Disclosure Code of Conduct.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the physicians' and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

Novo Nordisk maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

11.3.1 Site-specific publication(s) by physician(s)

For a multi-centre study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, and therefore may not be supported by Novo Nordisk. It is Novo Nordisk's policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the study.

Novo Nordisk reserves the right to prior review of such publication and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

11.4 Physician access to data and review of results

As owners of the study database, Novo Nordisk has discretion to determine who will have access to the database. Generally, study databases are only made available to regulatory authorities.

Individual physician(s) will have their own research participants' data.

12 References

1. ENCEPP Considerations on the definition of non-interventional trials under the current legislative framework (Clinical trials directive 2001/20/EC). ENCEPP 22 November 2011
2. EMA/330405/2012 Rev 1, 19 April 2013 - GVP Module VIII: Post-authorization safety studies (together with EMA/395730/2012 Rev 1, 19 April 2013 - Annex: Member States' requirements for transmission of information on non-interventional post authorization safety studies)

3. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). Initially issued: 1996. Revision 2, April, 2007
4. World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, Korea, October 2008
5. International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals (current official version available at www.ICMJE.org)
6. EMA/873138/2011, 22 June 2012 - Guideline on good pharmacovigilance practices (GVP) Module VI - Management and reporting of adverse reactions to medicinal products.