Protocol

Study ID:NN1250-4189

A multi-centre, prospective, non-interventional study of insulin degludec investigating the safety and effectiveness in a real world population with type 1 and 2 diabetes mellitus

ReFLeCT

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional Study, Post Authorisation Safety Study (PASS)

Protocol originator:

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Post Authorisation Safety Study information

Title	A multi-centre, prospective, non-interventional study of insulin degludec investigating the safety and effectiveness in a real world population with type 1 and 2 diabetes mellitus
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Medicinal product	Insulin degludec (Tresiba®) 100 units/mL and 200 units/mL
Product reference	N/A
Procedure number	EMEA/H/C/002498
Marketing authorisation holder(s)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	The objectives of this study are to evaluate the safety and effectiveness of Tresiba® 100 units/mL or Tresiba® 200 units/mL once daily (OD) in a real world population of type 1 and type 2 diabetes mellitus patients who use insulin that reflects routine clinical care. The primary objective is to monitor and assess the safety of Tresiba®, used with any other anti-diabetic treatment and according to label, by analysing whether treatment with Tresiba® OD is associated with a change in the rate of any hypoglycaemic episodes occurring during the observation period, compared to the rate of any hypoglycaemic episodes occurring during the baseline period, where the patient continues the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin can be any type of basal insulin. The secondary objectives are to monitor and assess the safety and effectiveness of Tresiba®, used with any other anti-diabetic treatment, by analysing whether the treatment with Tresiba® OD is

	associated with a change in safety, effectiveness, patient reported outcomes, and health-economic endpoints compared to the baseline period, where the patient continues the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin can be any type of basal insulin.
Countries of study	Denmark, Germany, The Netherlands, Spain, Sweden, Switzerland, Italy, and the United Kingdom. Novo Nordisk ceased the distribution of Tresiba® in Germany at the end of September 2015. Germany will be removed from this study, thus patients enrolled in Germany based on the protocol version 2.0 will be discontinued. Data obtainable up to the discontinuation date will be included in the analysis, as appropriate and specified in the Statistical Analysis Plan (SAP).
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1 List of abbreviations

ADA	American Diabetes Association
AE	adverse event
CDMS	Clinical Data Management System
CI	confidence interval
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration formula
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
DM	diabetes mellitus
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire - change
DTSQs	Diabetes Treatment Satisfaction Questionnaire - status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	EU Electronic Register of Post-Authorisation Studies
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GP	General Practitioner
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practice
HbA1c	glycated haemoglobin A1c
HE	health economic(s)
HR-QoL	health-related quality of life
IDeg	insulin degludec 100 units/mL or 200 units/mL
IEC	Independent Ethics Committee
IRB	Institutional Review Board

MESI	medical events of special interest
OD	once daily
PASS	post authorisation safety study
PG	plasma glucose
PRO	patient reported outcome
PYE	patient year of exposure
SADR	serious adverse drug reactions
SAP	statistical analysis plan
SC	subcutaneous
SF-36	short form-36
SIF	safety information form
SMBG	self-measured blood glucose
SmPC	Summary of Product Characteristics
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UK	United Kingdom
US	United States
UTN	Universal Trial Number
WHO	World Health Organisation

2 Responsible parties

In this document 'physician' refers to the individual who is overall responsible for and accountable for all treatment decisions and the conduct of the study at a study site. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons whom he/she has delegated specific 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 instructions from Novo Nordisk when processing any 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.

During any period of unavailability, the physician should delegate responsibility for medical care of patients to a specific qualified physician who will be readily available to patients during that time. If the physician is no longer able to fulfil the role of physician (eg, if he/she retires), a new physician will be appointed in consultation with Novo Nordisk. The physician and site personnel must have sufficient English skills according to their assigned task(s).

3 Abstract

3.1 Title

A multi-centre, prospective, non-interventional study of insulin degludec investigating the safety and effectiveness in a real world population with type 1 and 2 diabetes mellitus.

3.2 Rationale and background

Insulin degludec (IDeg) is an approved recombinant analogue of human insulin indicated for the treatment of diabetes mellitus (type 1 and type 2 [T1DM and T2DM], respectively) in adults, providing a basal insulin supply after once daily (OD) subcutaneous (SC) injection. Insulin degludec, marketed as Tresiba® and herein referred to as Tresiba®, received marketing authorisation in Europe by the European Medicines Agency (EMA) on 21 January 2013, and is available in 2 strengths, 100 units/mL and 200 units/mL.

Hypoglycaemia is the biggest obstacle to tight glucose control (1) and a major cause of worry and anxiety amongst patients. The development of newer basal insulin aims to introduce longer acting insulin with lower variability in blood glucose. The clinical development programme for Tresiba® was designed to demonstrate whether Tresiba® is at least as effective as comparators in sustaining glycaemic control, but is associated with a lower frequency of hypoglycaemic episodes. Although including a broad population, the standardised populations used to minimise bias in the clinical development programme do not completely represent the population of patients with diabetes mellitus (DM) receiving care under routine conditions.

Prospective data on the effects of different insulin treatment regimens in general are limited. As no long-term prospective epidemiological studies examining safety and effectiveness of Tresiba® in DM patients and hypoglycaemia have been conducted, such prospective data reflecting the safety and therapeutic effectiveness of Tresiba® are highly warranted.

This study provides the opportunity to deliver valuable insight into the safety and effectiveness of Tresiba® from multiple perspectives, including clinical outcomes, patient reported outcomes (PROs) and health economic (HE) evaluations. The decision as to whom to switch to Tresiba® will be left to the treating physician and falls within routine practice. This approach to patient inclusion in a study is different from that seen in the clinical development programme for Tresiba®.

3.3 Research question and objectives

The objectives of this study are to evaluate the safety and effectiveness of Tresiba® 100 units/mL or Tresiba® 200 units/mL OD in a real world population of T1DM and T2DM patients who use insulin that reflects routine clinical care.

The primary objective is to monitor and assess the safety of Tresiba®, used with any other anti-diabetic treatment and according to label, by analysing whether treatment with Tresiba® OD is associated with a change in the rate of any hypoglycaemic episodes occurring during the observation period, compared to the rate of any hypoglycaemic episodes occurring during the baseline period, where the patient continues the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin can be any type of basal insulin.

The secondary objectives are to monitor and assess the safety and effectiveness of Tresiba®, used with any other anti-diabetic treatment, by analysing whether the treatment with Tresiba® OD is associated with a change in safety, effectiveness, PROs, and HE endpoints compared to the baseline period, where the patient continues the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin can be any type of basal insulin.

3.4 Study design

This is a 12-month, multi-centre, prospective, non-interventional study assessing the safety and effectiveness of Tresiba® 100 units/mL or Tresiba® 200 units/mL OD, used with any other anti-diabetic treatment according to local label, in patients with T1DM or T2DM where the physician has decided to start the patient on Tresiba® treatment. This is under the category of post-authorisation safety study (PASS).

The study is expected to be conducted within the following countries: Denmark, Germany, The Netherlands, Spain, Sweden, Switzerland, Italy, and the United Kingdom (UK).

Novo Nordisk ceased the distribution of Tresiba® in Germany at the end of September 2015. Germany will be removed from this study, thus patients enrolled in Germany based on the protocol version 2.0 will be discontinued. Data obtainable up to the discontinuation date will be included in the analyses, as appropriate and specified in the Statistical Analysis Plan (SAP).

Patients with T1DM and T2DM who are treated with insulin will be followed for a minimum of 4 weeks before (baseline period), and a maximum of 12 months after switching to Tresiba® (observation period).

As indicated in the Summary of Product Characteristics (SmPC), close glucose monitoring is recommended during the transfer from other insulin medicinal products and in the following weeks (2). Using patient diaries, prospective clinical assessments for hypoglycaemia will occur leading up to Months 0, 3, 6, 9, and 12. Visit 1 (-4 weeks) initiates the baseline period; physicians who plan to

start Tresiba® treatment, as part of standard clinical practice, begin evaluating the patients treatment needs based on reviewing diaries on hypoglycaemia and glycaemic control, in order to confirm their treatment decision to switch to Tresiba®. At visit 2 (0 months) only those patients who are switched to Tresiba® treatment are entered into the observation period. In clinical practice, some patients will switch insulin treatment immediately because they require instant changes to their treatment for safety or for effectiveness reasons. Other patients will after evaluation not change treatment at all. And again, other patients will be evaluated, and this will then reveal that their situation may actually be improved by changing treatment regimen. This baseline period will provide a portrait of the patient's risk of developing hypoglycaemia.

The assignment of the patients to Tresiba® is not decided in advance by the protocol but falls within routine practice. The physician will determine the starting dose, based on local label, as well as later changes to dose, if any. Any other anti-diabetic treatments can be changed or doses adjusted according to the treating physician's decision.

Key study observational endpoints include change from the baseline period in the number of any hypoglycaemic episodes and the number of episodes within each category of hypoglycaemia eg, non-severe, severe, and nocturnal, change from baseline in glycated haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), insulin dose, body weight, frequency of serious adverse drug reactions (SADRs), medical events of special interest (MESI) (medication errors), pregnancies, and PROs.

Patients will be analysed separately based on being T1DM or T2DM patients who use insulin.

3.5 Population

Male or female patients aged ≥18 years of age with either T1DM or T2DM (insulin using) (clinically diagnosed) prior to visit 1, who signed an informed consent form, and whose physician plans to start Tresiba® treatment are eligible for entry in this study.

Patients with contraindications as detailed in the SmPC (2) or previous participation in this study (ie, provision of informed consent) are excluded from taking part in this study. Patients who have previously been treated with Tresiba® may not enter this study.

Patients may be withdrawn or may withdraw themselves at any time, for any reason. There is no clinical experience with use of Tresiba® in pregnant women; women who become pregnant or intend to become pregnant will be withdrawn from the study.

3.6 Observational endpoints

Clinical assessments (interviews, questionnaires, and blood samples) will be performed as part of routine clinical practice. Patients will be encouraged to fill out PROs and other non-clinical assessments that are not part of standard routine care, in order to ensure fulfilment of the study

objectives. Data will be collected during the baseline period (4 weeks before Tresiba® treatment, at visits 1 and 2) and at the following time points after treatment initiation: 3 months (±45 days), 6 months (±45 days), 9 months (±45 days), and 12 months (±45 days), when available.

3.6.1 Primary observational endpoint

The primary observational endpoint is the change from the baseline period (4-week baseline period) in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba® (analysed as the change in rate per patient year of exposure [PYE]). Results will also be used in external registration of the study at clinicaltrials.gov and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register.

3.6.2 Secondary observational endpoints

The main secondary endpoints are:

- Change from baseline (visit 2) in FPG after 12 months of treatment
- Percentage of patients reaching HbA1c targets at end of study (listed in Section 7.3.2.1)
- Change from baseline (visit 2) in HbA1c after 3, 6, 9, and 12 months of treatment
- Change from the baseline period in the number of any hypoglycaemic episodes during “the maintenance period” (ie, after 16 weeks of treatment)
- Change from the baseline period in the number of any nocturnal (00:01-05.59 am) hypoglycaemic episodes during “the maintenance period” (ie, after 16 weeks of treatment)
- Change from the baseline period in the number of hypoglycaemic episodes within each category of hypoglycaemia (nocturnal, during sleep, non-severe, severe, according to the American Diabetes Association (ADA) (3) and Novo Nordisk definitions, as listed in Sections 7.3.2.1 and 7.3.2.2) after 12 months of treatment
- Change from baseline (visit 2) in daily insulin dose (total, Tresiba®, and bolus) after the observation period
- Change from baseline (visit 2) in the number of self-measured blood glucose (SMBG) test strips used during the 12 months of treatment
- Change from baseline (visit 2) in body weight after 12 months of treatment
- Frequency of SADRs, MESI (medication errors), and pregnancies during 12 months of treatment
- Change from the baseline period in the number of any hypoglycaemic episodes in high dose users (>80 U daily) after 12 months of treatment
- Change from the baseline period in the number of any hypoglycaemic episodes in hypoglycaemia prone (hypo-prone) patients after 12 months of treatment; hypo-prone patients are defined as having any of the below:
  a) Experienced at least 1 severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013 (3)

b) Moderate chronic renal failure, defined as glomerular filtration rate 30-59 mL/min/1.73 m^2 per Chronic Kidney Disease Epidemiology Collaboration formula (CKD-Epi), as specified by physician statement (or according to national reference definitions if they differ from the values stated)
c) Hypoglycaemic symptom unawareness (history of impaired autonomic responses (tremulousness, sweating, palpitations, and hunger)) during hypoglycaemia
d) For T1DM: DM duration for more than 15 years
e) For T2DM: exposed to insulin for more than 5 years

- Change from baseline (visit 2) in health-related quality of life (HR-QoL) questionnaire scores (PROs: Short form-36 [SF-36] and Diabetes Treatment Satisfaction Questionnaire [DTSQ]) after 12 months of treatment
- Change from baseline in HE-endpoints (eg, number of physician visits, emergency room visits, etc, listed in Section 7.3.2.4) after 12 months of treatment
- Patient preference compared to previous treatment
- FlexTouch® pen; preference of this device compared to previous injection method before Tresiba® use at the end of the study
- Change from baseline in dose-time flexibility endpoints after 12 months of treatment

The following secondary endpoints will be used in external registration of the study at clincialtrials.gov and the ENCePP register:

- Change from baseline in HbA1c and FPG after 12 months
- Change from the baseline period in the number of severe hypoglycaemic episodes after 12 months
- Change from baseline in HR-QoL questionnaire scores (PROs: SF-36, and DTSQ) after 12 months of treatment

All data reported as counts will be converted to rates per PYE for analysis purposes.

3.7 Data sources

Data will be collected from the patients' medical records, diaries, questionnaires, and interviews at each visit and entered into the electronic case report form (eCRF).

At each visit (estimated to at the start of the study ie, provision of informed consent, at 4 weeks and then every 3 months thereafter):

- patients will be given a study diary, to document any episodes of hypoglycaemia, their insulin dosage and timing, number of self-measured blood glucose (SMBG) test strips used, details of resource use due to hypoglycaemia, and use of dose-time flexibility. At each visit, the patient will return his/her diary and will be given a new one

- patients will be encouraged to complete PRO questionnaires
- patients will be asked about any adverse events (AEs) (only SADRs, MESI, pregnancies, and severe hypoglycaemic episodes [regardless of physician's evaluation of seriousness and causality]) will be recorded by the physician) and provide details of any other medication they have received
- patients' medical records will be updated as per normal clinical practice (eg, with results of any measurements taken, adjustment to insulin dosage, concomitant medication, and any new concomitant illnesses)

3.8 Study size

The sample size calculation is based on the primary observational endpoint, which is the change from the baseline period (4-week baseline period) in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba®. The change from baseline measure is operationalised as the mean of the per-patient paired differences in hypoglycaemic episodes/PYE.

For both the T1DM and T2DM patients, the mean of paired differences is expected to be 1 episode/PYE with a standard deviation of 7 (a conservative estimate based on our understanding of possible variation in the measures). At α=0.05 and 90% power, the number of patients who switch to Tresiba® and complete the 12-month observation period is $n_{T1DM}=n_{T2DM}= 517$. Assuming a 15% rate of withdrawal (loss of a patient for any reason prior to completing 12-month observation period), 608 T1DM and 608 T2DM patients will need to complete the 4-week baseline period and switch to Tresiba® to achieve 517 patients for T1DM and 517 patients for T2DM completing the observation period.

The data from participating countries will be pooled. Analysis on data from the patients in Germany up to the discontinuation date will be specified in the SAP.

3.9 Data analysis

All observational endpoints will be analysed on the full analysis set (FAS). The FAS includes all patients who received at least 1 dose of Tresiba® at visit 2. Patients who complete visit 1 but do not initiate Tresiba® at visit 2 will be excluded from the analysis.

Patients will be analysed separately based on being T1DM or T2DM patients treated with insulin.

The primary observational endpoint is the change from the baseline period (4-week baseline period) in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba®. The count data will be converted to rates per PYE prior to analysis. The primary endpoint will be estimated as a baseline-adjusted change using an appropriate regression estimator

(eg, negative binomial estimator) with additional covariates, along with the associated 95% confidence interval (CI), and p-value.

Secondary endpoints that are interval and ratio-level endpoints will be analysed in the same manner as the primary endpoint using an appropriate regression estimator. Categorical endpoints will be displayed in frequency tables (N, %).

All statistical tests will be performed as two-sided tests with a significance level of 0.05.

3.10 Milestones

The planned duration of the study is from start of data collection (planned date: 16 March 2015) through to end of data collection (expected date: 16 March 2018). The end of the non-interventional study is defined at last patient last visit (expected date: 16 March 2018). The non-interventional study report for this is planned to be completed by 30 July 2018.

4 Amendments and updates

None.

5 Milestones

Expected timelines are as outlined below:

Milestone	Planned date
Start of data collection	16 March 2015
End of data collection	16 March 2018
End (or completion) of study	16 March 2018
Interim data cuts*	To be prepared during the study (eg, after 6 months and then every quarter)
Final report of study results	30 July 2018

* Interim data analysis will only be used internally, potentially only shared with regulatory agencies, and will not be shared publically.

This study is subject to registration no longer than 21 days after enrolment of the first study participant according to Novo Nordisk requirement on non-interventional study disclosure. For countries outside the Unites States (US), only the main study site per country will be disclosed via facility name, city and country on the study registration.

For PASS in Europe, the study information should be available in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the EMA) and accessible through the European medicines web portal.

Note: Study registration is regarded as the publication of an internationally-agreed set of information (which can be found at the World Health Organisation [WHO] homepage) about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards (also found at the WHO homepage), eg, www.clinicaltrials.gov.

The study will be registered in accordance with current legal and regulatory requirements, in addition to www.clinicaltrials.gov.

6 Rationale and background

Tresiba® (IDeg is a recombinant analogue of human insulin indicated for the treatment of T1DM and T2DM in adults. Tresiba®, received marketing authorisation in Europe by the EMA on 21 January 2013, and is available in 2 strengths, 100 units/mL and 200 units/mL.

Treatment objectives in T1DM and T2DM patients are to achieve and maintain patient specific, adequate glycaemic control, in order to reduce long-term risk for micro and macro vascular complications, while minimising adverse effects, especially number of episodes of hypoglycaemia and its severity.

Hypoglycaemia is the biggest obstacle to tight glucose control (1). The clinical development programme for Tresiba® was designed to demonstrate whether Tresiba® is at least as effective as comparators in sustaining glycaemic control, but is associated with a lower frequency of hypoglycaemic episodes. All trials had a treat-to-target design. This programme of studies included standardised patient populations, to minimise bias, thus enabling clearer descriptions of the treatment effect of Tresiba® in alignment with EMA (4) and US Food and Drug Administration (FDA) (5) guidelines. Although including a relatively broad population, the clinical development programme does not completely represent the real world population of patients with DM, in particular patients prone to hypoglycaemic episodes.

Prospective data on the effects of different insulin treatment regimens in general are limited. As no long-term prospective epidemiological studies examining safety and effectiveness of Tresiba® in DM patients and hypoglycaemia have been conducted, such prospective data reflecting the safety and therapeutic effectiveness of Tresiba® are highly warranted.

Novo Nordisk will establish a prospective non-interventional study of insulin using DM patients that have been recommended to initiate Tresiba® by their treating physician. The present study constitutes a unique opportunity for large-scale data collection that will allow comparisons and

analysis between the patient's treatment regimen at baseline and up to 12 months after switching to Tresiba®.

This study aims to investigate the use of IDeg in a patient population that reflects clinical reality. Due to the nature of the observational, non-interventional design of the current study, the decision as to whom to switch to Tresiba® will be left to the treating physician. Data collected will thereby provide information on the safety and effectiveness of Tresiba® as used in clinical practice in the real world population.

The clinical development programme has consistently shown a lowered risk of hypoglycaemia in patients treated with Tresiba® against comparators with similar efficacy, and a lowered fasting plasma glucose (FPG); in addition to the flexibility of changing the dosing when missing a dose (intervals of at least 8 hours are required between injections). This study will investigate the rates of hypoglycaemia 4 weeks before and during/after 12 months of continuous Tresiba® treatment, as used in accordance with local clinical practice and labelling.

Furthermore, the secondary observational endpoint, HbA1c, is the most widely accepted measure of overall, long-term blood glucose control in patients with DM. Glycaemic targets HbA1c <7% were used in all Phase 3 studies in accordance with current guidelines (6), (3). Using the same endpoint, and taking into consideration country-specific difference in guidelines and what is clinically meaningful to patients (ie, HbA1c <7.5%), will allow the effectiveness of Tresiba® as used in clinical practice to be compared with completed Phase 3 studies and provide a greater understanding of its effectiveness in the real world management of DM. Secondary endpoints will be calculated based on a dataset that is collected without enforcement to minimise influence on daily clinical practice.

Complete information for Tresiba® may be found in the most recent version of the SmPC (2).

All data collection and statistical analysis will be done in accordance with global and local regulations and legal data protections requirements.

7 Research question and objectives

The objectives of this study are to evaluate the safety and effectiveness of Tresiba® 100 units/mL or Tresiba® 200 units/mL OD in a real world population of T1DM and T2DM patients who use insulin that reflects routine clinical care.

7.1 Primary objective

The primary objective is to monitor and assess the safety of Tresiba®, used with any other anti-diabetic treatment and according to label, by analysing whether treatment with Tresiba® OD is associated with a change in the rate of any hypoglycaemic episodes occurring during the

observation period, compared to the rate of any hypoglycaemic episodes occurring during the baseline period, where the patient continues the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin can be any type of basal insulin.

7.2 Secondary objective(s)

The secondary objectives are to monitor and assess the safety and effectiveness of Tresiba®, used with any other anti-diabetic treatment, by analysing whether the treatment with Tresiba® OD is associated with a change in safety, effectiveness, PROs, and HE endpoints compared to the baseline period, where the patient continues the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin can be any type of basal insulin.

7.3 Observational endpoints

All observational endpoints will be collected during the baseline period (4 weeks before Tresiba® treatment, at visits 1 and 2) and at the following time points after treatment initiation: 3 months (±45 days), 6 months (±45 days), 9 months (±45 days), and 12 months (±45 days), when available.

7.3.1 Primary observational endpoint

The primary observational endpoint is the change from the baseline period (4-week baseline period) in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba® (analysed as the change in rate per PYE). Results will also be used in external registration of the study at clincialtrials.gov and the ENCePP register.

Hypoglycaemic episodes will be collected throughout the study using a 4-week patient hypoglycaemia diary (collected at visits 2, 3, 4, 5, and 6) and 6-month recall for severe hypoglycaemia (visit 1).

7.3.2 Secondary observational endpoints

7.3.2.1 Secondary effectiveness endpoints

- Change from baseline (visit 2) in FPG after 12 months of treatment
- Responder for HbA1c at end of study:
  - HbA1c <7% at end of study
  - HbA1c <7.5% at end of study
  - HbA1c <7% at end of study without severe hypoglycaemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks
  - HbA1c <7.5% at end of study without severe hypoglycaemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks
  - HbA1c lowered according to national guidelines
- Change from baseline (visit 2) in HbA1c after 3 months of treatment

- Change from baseline (visit 2) in HbA1c after 6 months of treatment
- Change from baseline (visit 2) in HbA1c after 9 months of treatment
- Change from baseline (visit 2) in HbA1c after 12 months of treatment
- Hypoglycaemia
  - Change from the baseline period in the number of hypoglycaemic episodes according to the Novo Nordisk definition as well as to the ADA definition of hypoglycaemia (3), after 12 months of treatment
  - Change from the baseline period in the number of any hypoglycaemic episodes during "the maintenance period" (ie, after 16 weeks of treatment)
  - Change from the baseline period in the number of any nocturnal (00:01-05:59 am) hypoglycaemic episodes during "the maintenance period" (ie, after 16 weeks of treatment)
  - Change from the baseline period in the number of any nocturnal (00:01-05:59 am) hypoglycaemic episodes after 12 months of treatment
  - Change from the baseline period in the number of any hypoglycaemic episodes occurring during sleep in the time span 22.01pm and 07.59am, that results in the patient being awoken after 12 months of treatment
  - Change from the baseline period in the number of non-severe hypoglycaemic episodes after 12 months of treatment
  - Change from the baseline period in the number of any hypoglycaemic episodes in high dose users (defined as patients using >80 U daily) after 12 months of treatment
  - Change from the baseline period in the number of any hypoglycaemic episodes in hypoglycaemia prone (hypo-prone) patients after 12 months of treatment; hypo-prone patients are defined as having any of the below:
    a) experienced at least 1 severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013 (3))
    b) moderate chronic renal failure, defined as glomerular filtration rate 30-59 mL/min/1.73 m^2 per the CKD-Epi, as specified by physician statement (or according to national reference definitions if they differ from the values stated)
    c) hypoglycaemic symptom unawareness (history of impaired autonomic responses [tremulousness, sweating, palpitations, and hunger] during hypoglycaemia)
    d) for T1DM: DM duration for more than 15 years
    e) for T2DM: exposed to insulin for more than 5 years

7.3.2.2 Secondary safety endpoints

- Change from the baseline period in the number of severe hypoglycaemic episodes after 12 months of treatment
- Change from baseline (visit 2) in daily insulin dose (total, Tresiba®, bolus) after the observation period

- Change from baseline (visit 2) in the number of SMBG test strips used during the 12 months of treatment
- Change from baseline (visit 2) in body weight after 12 months of treatment
- Frequency of SADRs, MESI (medication errors), and pregnancies during 12 months of treatment

All data reported as counts will be converted to rates per PYE for analysis purposes.

7.3.2.3 Secondary patient reported outcome (PRO) endpoints

HR-QoL questionnaire (SF-36 v2) and DTSQ, and change from baseline on each measure, as appropriate, after 12 months of treatment. The PRO endpoints are described in Section 8.3.2.7.

7.3.2.4 Health economic and dose-time flexibility endpoints

- Physicians primary reason for switching to treatment with Tresiba® (see Section 8.3.3.2)
- Physicians primary reason for not switching to treatment with Tresiba® (see Section 8.3.3.2)
- Physicians primary reason for switching to treatment with Tresiba® during the baseline period ie, early switchers (see Section 8.3.3.2)
- Change from baseline in the following HE-endpoints:
  - Number of outpatient visits due to hypoglycaemia
  - Number of physician or diabetic nursing visits due to hypoglycaemia
  - Number of treatments by a paramedic at home
  - Number of emergency room visits due to hypoglycaemia
  - Number of ambulance transportations due to hypoglycaemia
  - Number of hospitalisations due to hypoglycaemia, and duration of hospitalisation
  - Duration of absence from work due to hypoglycaemia
  - Used SMBG test strips and how many
- Patient preference compared to previous treatment
- FlexTouch® pen; preference of this device compared to previous injection method before Tresiba® use at the end of the study
- Change from baseline in dose-time flexibility endpoints:
  - Number of missed doses
  - Reason for missed dose
  - Action taken when dose missed
  - Changes in any social, leisure, and working activities due to insulin treatment
  - Number of times Tresiba® flexibility option used

All data reported as counts will be converted to rates per PYE for analysis purposes.

7.3.2.5 Secondary endpoints for external study registration

The following secondary endpoints will be used in external registration of the study at clincialtrials.gov and the ENCePP register:

- Change from baseline in HbA1c and FPG after 12 months
- Change from the baseline period in the number of severe hypoglycaemic episodes after 12 months
- Change from baseline in HR-QoL questionnaire scores (PROs: SF-36 and DTSQ) after 12 months 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 12-month, multi-centre, prospective, non-interventional study assessing the safety and effectiveness of Tresiba® 100 units/mL or Tresiba® 200 units/mL OD, used with any anti-diabetic treatment according to local label, in T1DM or T2DM patients who use insulin where the physician has decided to start the patient on Tresiba® treatment.

The study is non-interventional as the patients are treated according to routine clinical practice and the local label upon the treating physician's decision. This is under the category of PASS. The location of study information within this protocol is available in ENCePP checklist for study protocols (Annex 2).

The study is expected to be conducted within the following countries: Denmark, Germany, The Netherlands, Spain, Sweden, Switzerland, Italy, and the United Kingdom (UK).

Novo Nordisk ceased the distribution of Tresiba® in Germany at the end of September 2015. Germany will be removed from this study, thus patients enrolled in Germany based on the protocol version 2.0 will be discontinued. Data obtainable up to the discontinuation date will be included in the analyses, as appropriate and specified in the SAP.

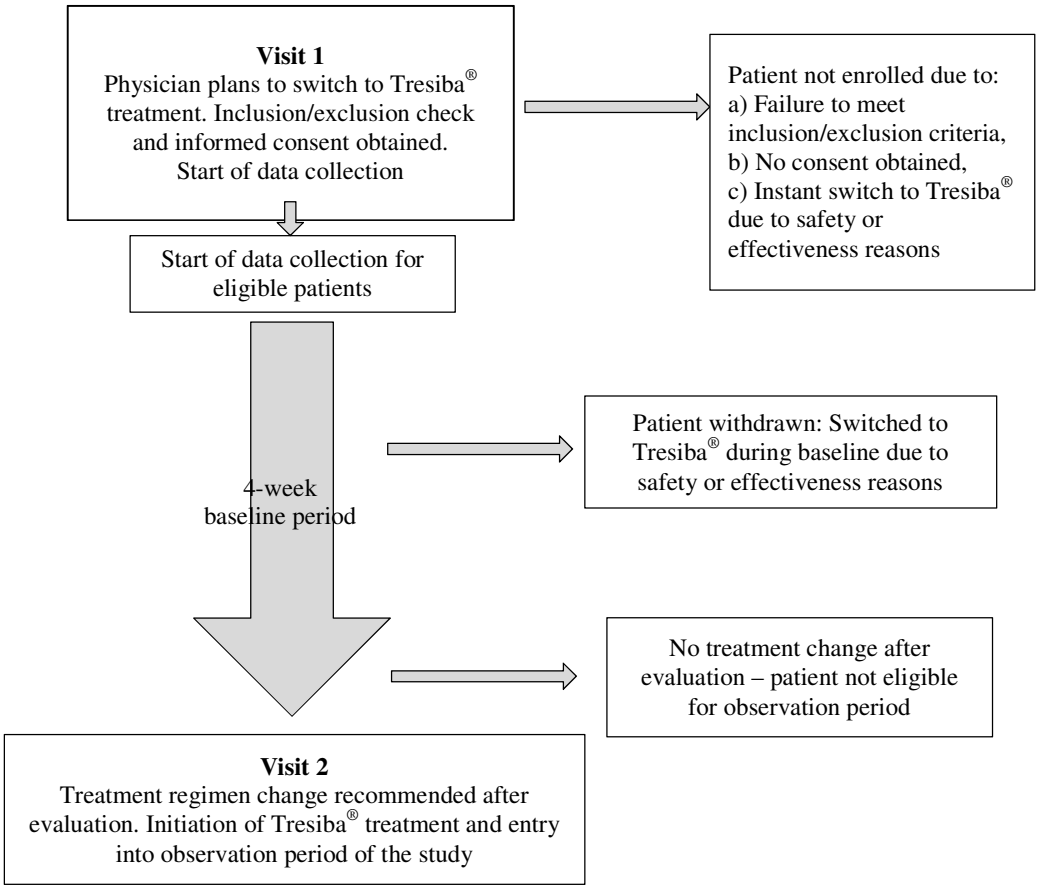
Anonymised patient level data will be collected by the patients' physicians and an eCRF will be used to capture the data.

The total study duration for the individual patients will be a maximum of 63 weeks (baseline: 4 weeks, observation period: up to 52 weeks +/-45 days).

Throughout the study, change in dosage, dose interval and add-on or removal of bolus insulin, other oral anti-diabetic drugs and/or glucagon-like peptide-1 agonists is expected and will not exclude the patients to participate in the study and in the primary and secondary endpoint analyses.

Patients with T1DM and T2DM who are treated with insulin will be followed for 4-weeks before (baseline period), and a maximum of 12 months after switching to Tresiba® (observation period). During the 4-week baseline period, physicians who plan to start Tresiba® treatment begin evaluating the patient's glycaemic control and confirm the decision to switch treatment. As specified in the SmPC, close glucose monitoring is recommended during the transfer from other insulin medicinal products and in the following weeks (2) and allows individualised treatment to be provided. During the 4-week baseline period patients will continue on their current therapy, including any diet and exercise recommendations. This baseline period will provide a portrait of the patient's risk of developing hypoglycaemia. Each patient acts as his/her own reference where the baseline period allows assessment of hypoglycaemic episode rates on current insulin and thus enables comparisons with the hypoglycaemic episode rates after switching to Tresiba®. In clinical practice, possible outcomes during and after the 4-week baseline period are presented in Figure 8–1 below.

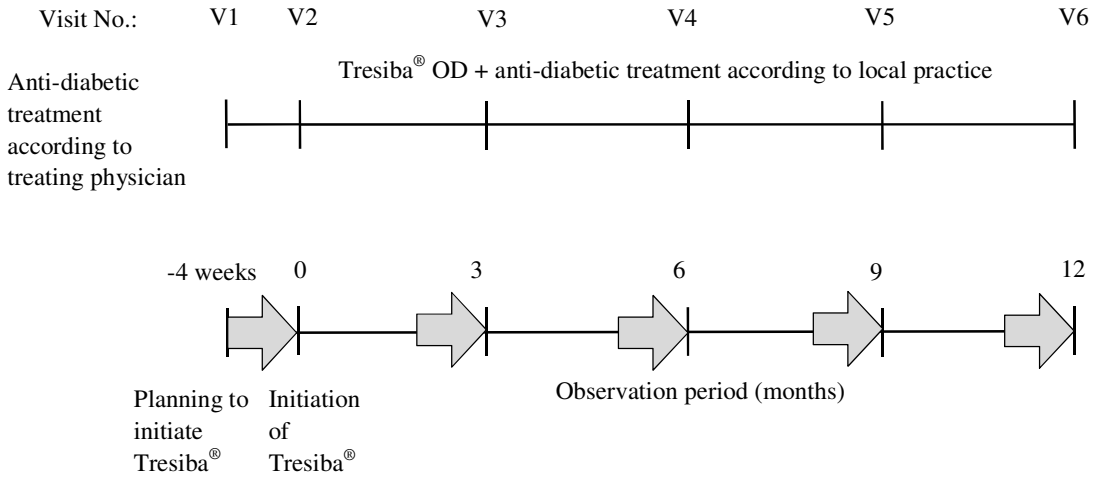
Figure 8–1 Flowchart of patient disposition during and after the 4-week baseline period



At the end of the baseline period, patients eligible for the study who continue to qualify for Tresiba® treatment (according to the treating physician) will initiate Tresiba® treatment (visit 2). Prospective hypoglycaemic episode data will be collected at the following time points during Tresiba® treatment: 0 months (+14 days, visit 2), 3 months (±45 days, visit 3), 6 months (±45 days, visit 4), 9 months (±45 days, visit 5) and finally at 12 months (±45 days, visit 6). Visits are not protocol defined and will be conducted as part of routine clinical monitoring of patients. Key study observational endpoints are outlined above in Section 7.3.

The study design is summarised schematically in Figure 8–2.

Figure 8–2 Schematic of study design



Abbreviations: OD=once daily; V=visit.

Grey arrows indicate 4-week periods when hypoglycaemic episodes will be recorded prospectively in patient diaries. At visit 1 patients will be asked to recall any severe hypoglycaemic episodes over the previous 6 months. Visits are defined as contact with health care provider (physician or nurse).

8.1.2 Rationale for study design

The non-interventional study design reflects clinical practice in a way that a randomised controlled study cannot, as it allows for the inclusion of patients and the treatment to be solely at the discretion of the treating physician.

The study design is a non-interventional study with a 4-week baseline reporting period. The 4-week baseline period provides an opportunity to collect a portrait of the patient's risk of developing hypoglycaemia. Each patient acts as his/her own reference where the baseline period allows assessment of hypoglycaemic rates on current insulin and thus, enables comparisons with the hypoglycaemic rates after switching to Tresiba®.

In the clinical development programme Tresiba® has consistently demonstrated similar efficacy to other insulin analogues in the treat-to-target trial designs, but a more favourable safety profile with fewer hypoglycaemic episodes. Thus the primary observational endpoint, change from the baseline period (4-week baseline period) in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba® is relevant to assess in a real world setting.

The secondary effectiveness endpoint, HbA1c, is the most widely accepted measure of overall, long-term blood glucose control in patients with diabetes (7). In addition, it is a laboratory parameter and consequently the probability of assessment bias is limited. Other measures could have non-ignorable measurement errors, however these are not pivotal observational endpoints, and regardless, it is not possible to alleviate assessment bias in a similar way.

The study is based on prospectively collected clinical data and PROs as part of normal clinical practice. The prospective non-interventional study design in a large-scale setting with a sufficient number of patients, and thus an adequately powered study, is needed to analyse the safety and effectiveness of Tresiba® with regard to the primary and secondary endpoints in a real-world population of T1DM and T2DM patients.

In order to minimise potential reporting and prescribing bias and to ensure face validity of the study, data will be collected from patients that the physician plans to switch to Tresiba® over a similar time frame (approximately 6 months) within each country.

The 12-month observation period is expected to be sufficient to initiate and optimise the study treatment regimen and to obtain long-term real world data for safety and effectiveness evaluation.

8.1.3 Treatment of patients

Patients with T1DM as well as patients with T2DM requiring insulin therapy will be treated 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 routine practice.

The initiation of Tresiba® is at the discretion of the treating physician. All anti-diabetic treatment will be prescribed and used in accordance with local label, including the study product Tresiba®, marketed as Tresiba® (100 units/mL / 200 units/mL) in a prefilled pen injector (FlexTouch®).

Tresiba® will be prescribed by the physician under routine clinical practice conditions (see Section 8.1.5). The physician will determine the starting dose, based on local label, as well as later changes to dose, if any. Patients will be instructed as per usual practice to use Tresiba® as specified in local package insert (ie, OD subcutaneous [SC] administration at any time of the day, preferably at the same time every day). Any other anti-diabetic treatments can be changed or doses adjusted at the discretion of the treating physician.

Diet and exercise counselling may be conducted as per the standard of care at the investigational site.

All other prescription and non-prescription drugs may be used.

8.1.4 Rationale for treatment

Patients with T1DM or T2DM (insulin users) are eligible for treatment with Tresiba® in accordance with the approved SmPC.

8.1.5 Study supplies

Study product:

The study product is IDeg, marketed as Tresiba® (100 units/mL / 200 units/mL) in a prefilled pen injector (FlexTouch®) for SC injection.

Packaging and labelling of study product:

Tresiba® will be prescribed by the physician under normal clinical practice and will be obtained/purchased from the pharmacy based on the physician's prescription and according to local regulations.

8.2 Setting

A broad population of patients with T1DM or insulin using patients with T2DM is eligible for this study. The purpose of this study is to monitor the safety and effectiveness of Tresiba® in a general real world diabetic population. The decision to initiate treatment is entirely the treating physician's, as is the treatment regimen and adjustment of the treatment.

Patients who meet the eligibility criteria, outlined in Section 8.2.2, will be eligible regardless of sex, race or ethnicity. Both general practitioners (GPs)/specialists and hospital sites will be included. The study will include multiple geographical sites to potentially enhance generalisability and ensure sufficient numbers of patients with T1DM or T2DM who use insulin are included for adequately powered analysis of the primary and secondary endpoints. Inclusion and exclusion criteria applied in this study should ensure comparability of study results for a general broad population of patients with T1DM or T2DM.

In order to facilitate identification of suitable sites by the Contract Research Organisation (CRO), Novo Nordisk will, where possible and relevant, supply the CRO, [redacted], with information on local primary care formulary status for Tresiba® and information about local primary care prescription density by geographical area. Both GPs/specialists and hospital sites will be included.

8.2.1 Number of patients to be studied

Patients with T1DM or T2DM, eligible for this study will be included. All data collected will be included in the analysis.

Planned number of patients to be included: 1216 patients are expected to switch treatment to Tresiba® following the 4-week baseline period, including the patients from sites in Germany, according to the SAP.

Planned number of patients to complete the study in the participating countries: in total, 1034 are planned to complete the study (based on a withdrawal rate of 15%).

8.2.2 Inclusion criteria

Patients must meet the following inclusion criteria to be eligible for the study.

1. Informed consent obtained before any study-related activities (Study-related activities are any procedure related to recording of data according to the protocol)
2. Male or female patients ≥18 years of age at time of informed consent
3. T1DM (diagnosed clinically) prior to inclusion in the study, and/or T2DM, insulin using patients (diagnosed clinically) prior to inclusion in the study
4. Planned initiation with Tresiba®

8.2.3 Exclusion criteria

Patients presenting with any of the following will not be eligible to participate in the study:

1. Known or suspected hypersensitivity to Tresiba® or any of the excipients listed in Section 6.1 of the SmPC or related products
2. Previous participation in this study (ie, provision of informed consent)
3. Patients who have previously been treated with Tresiba®
4. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation

Patients who are non-compliant with any of the inclusion/exclusion criteria, but included in the study, must be excluded immediately.

8.2.4 Withdrawal criteria

The patient may withdraw at will at any time, for any reason. Patients may also be withdrawn early because of pregnancy or intention to become pregnant.

Management of subjects who are withdrawn

The treating physician as part of normal clinical practice should follow-up with the patients who have been withdrawn regarding any unresolved SADRs, MESI and pregnancies, as well as severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality).

The physician should inquire about the reason for discontinuation.

The reason for discontinuation should be recorded in the eCRF. A discontinuation occurs when a patient who has provided informed consent ceases participation in the study, regardless of the circumstances, prior to collection of data on visit 6.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who have been withdrawn from the study cannot be re-included in the study if they have already started Tresiba® treatment. The patient number must not be reused.

8.2.5 Rationale for eligibility criteria

The inclusion criteria are broad reflecting the real world population of T1DM and T2DM patients, i.e., patients treated under conditions of routine care, eligible for Tresiba® treatment.

Informed consent will only be valid for patients ≥18 years of age. The questionnaires are not designed for paediatric populations.

Patients with mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation are excluded to ensure the collection of robust and reliable data.

8.2.6 Flowchart

All visits and data collections are outlined below in Table 8–1.

Table 8–1 Flow chart of study-related data collection

Study NN1250-4189	Planning to initiate	Initiation	Observation period			
Visit Number (V)	V1[1]	V2[1]	V3[1]	V4[1]	V5[1]	V6[1]
Time of visit (Months)	-1	0	3	6	9	12
Visit window (days)		+14	±45	±45	±45	±45
PATIENT RELATED INFO/ASSESSMENTS						
Informed consent	X					
In/Exclusion criteria	X	X				
Initiation		X				
Withdrawal criteria		X	X	X	X	X
Demographic data	X					
Height, systolic and diastolic blood pressure (if available)	X					
Body weight (if available)	X	X	X	X	X	X
Diagnosis of diabetes	X					
Insulin use – is the patient a high dose insulin user (>80 U/day)	X					
Hypoglycaemia risk: is the patient prone to hypoglycaemia	X					
Concomitant ill/ medical history	X					
Anti-diabetic treatment type and dose[2]	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Reason for switching or not switching to Tresiba®		X				
First date on study insulin (Tresiba®)		X				

Study NN1250-4189	Planning to initiate	Initiation	Observation period			
SAFTY AND EFFECTIVENESS						
Distribution and collection of patient diaries[3]	X	X	X	X	X	X
Most recent FPG and date of measurement (if available)	X	X	X	X	X	X
Most recent HbA_{1c} and date of measurement (if available)	X	X	X	X	X	X
Total daily dose of bolus insulin on day prior to visit (if applicable)		X	X	X	X	X
Changes in any social, leisure and working activities due to insulin treatment		X	X	X	X	X
SADRs, MESI and pregnancies[4]		X	X	X	X	X
Hypoglycaemic episodes[5]	X	X	X	X	X	X
PRO questionnaires[6]: SF-36 (version 2) DTSQ[7]	X	X	X	X	X	X
Patient preference			X	X	X	X
End of study						X[8]

Abbreviations: DTSQ=diabetes treatment satisfaction questionnaire; FPG=fasting plasma glucose; HbA1c=glycated haemoglobin A1c; MESI=medical events of special interest; SADR=serious adverse drug reaction; PRO=patient reported outcomes; SF-36=Short form-36; V=visit.

[1] Decision to initiate the study will take place 4 weeks prior to actual initiation of Tresiba® treatment, and with this a statement reported by the physician that use of current medication (for 4 weeks) will not be a safety problem for the patient. Patient material will be handed out at visit 1 to explain the importance of the baseline reporting period. It is not guaranteed that all patients will attend all visits.

[2] For anti-diabetic treatment also collect the insulin dosing regimen.

[3] Patient diaries will include sections for recording information such as details of hypoglycaemia, insulin dosage, dose-time flexibility, and health economics resource use.

[4] Each SADR will be spontaneously reported and recorded on a separate AE and safety information form according to existing reporting procedures. MESI includes medication errors.

[5] Four weeks prospective hypoglycaemia assessment leading up to visits at Months 0, 3, 6, 9, and 12, in addition to a 6 month severe hypoglycaemia recall at visit 1.

[6] Patients will be encouraged to fill the PRO questionnaires, preferably before any other study related procedures.

[7] Status version of DSTQ at visits 1, 2, 3, 4, 5 and 6, change version of DSTQ at visit 6.

[8] Preference of FlexTouch® over previous injection method.

8.3 Endpoints

Data will be collected during the baseline period (4 weeks before Tresiba® treatment, at visits 1, and 2) and at the following time points after treatment initiation: 3 months (±45 days), 6 months (±45 days), 9 months (±45 days), and 12 months (±45 days), when available.

All safety and effectiveness assessments (interviews, questionnaires and blood samples) should be performed as part of routine clinical practice. They are generally recognised as reliable, accurate and relevant to this indication (DM in adults). The biochemical assessments, FPG, and HbA1c, will be included in the analyses if available. They will not be performed unless according to clinical practice at the site. The hypoglycaemia reporting and the PRO assessments may require some questions that are not part of standard routine care.

8.3.1 Primary endpoint

Hypoglycaemic episodes will be collected throughout the study using a 4-week patient hypoglycaemia diary (collected at visits 2, 3, 4, 5, and 6) and 6 month recall for severe hypoglycaemia (visit 1). Each episode of hypoglycaemia will be reported on a dedicated eCRF page and all severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality) must be reported on the AE form and the safety information form (SIF) (see Section 10).

For the primary observational endpoint any hypoglycaemic episode will be recorded.

8.3.2 Secondary endpoints

8.3.2.1 Classification of hypoglycaemic episodes

At visit 1 the physician will indicate on the eCRF if his/her patient is a high dose insulin user - defined as patients requiring doses >80 U daily, and/or is prone to hypoglycaemic episodes. Hypo-prone patients are defined as having any of the below:

1. Experienced at least 1 severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013 (3))
2. Moderate chronic renal failure, defined as glomerular filtration rate 30 – 59 mL/min/1.73 m^2 per CKD-Epi as specified by physician statement (or according to national reference definitions if they differ from the values stated)
3. Hypoglycaemic symptom unawareness (history of impaired autonomic responses [tremulousness, sweating, palpitations, and hunger] during hypoglycaemia)

4. For T1DM: DM duration for more than 15 years
5. For T2DM: exposed to insulin for more than 5 years

For the secondary effectiveness/safety endpoints the number of hypoglycaemic episodes within the different categories of hypoglycaemia will be reported. At each visit, the treating physician, or appropriately qualified and trained delegate, will indicate in the eCRF the category (severe, non-severe, nocturnal, during sleep, or confirmed hypoglycaemia, as defined below) of each hypoglycaemic episode, based on the information recorded in the patient diary.

Severe hypoglycaemia

Severe hypoglycaemia is an event that requires assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (3).

These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose (PG) measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event is induced by a low PG concentration.

The definition of severe symptomatic hypoglycaemia includes all episodes in which neurological impairment is severe enough to prevent self-treatment and which are thus thought to place patients at risk of injury to themselves or others.

All severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality) must be systematically reported as safety information.

Non-severe hypoglycaemia

Non-severe hypoglycaemia is an event in which the patient is able to treat themselves and includes:

a) an event during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL)

OR

b) an event during which symptoms of hypoglycaemia are not accompanied by a PG determination, but is presumably caused by a PG concentration ≤3.9 mmol/L (70 mg/dL); symptoms treated with oral carbohydrate without a test of PG, glucagon or intravenous glucose, and leading to a significant improvement or prompt recovery

OR

c) an event not accompanied by typical symptoms of hypoglycaemia but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL)

Clinical symptoms that are considered to result from a hypoglycaemic episode include increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.

A distinction will be made between day-time hypoglycaemia, either severe or non-severe, occurring during the waking period and nocturnal hypoglycaemia.

Nocturnal hypoglycaemia

Nocturnal hypoglycaemia is defined as any hypoglycaemia (defined by time of the day) that occurs between 00:01 and 05:59 hours, regardless of whether the patient is awake or wakes up because of the event.

Hypoglycaemia during sleep

Any hypoglycaemia occurring during sleep (defined by time of the day) of the above categories that occurs between 22:01 and 07:59 hours, that results in the patient being woken up because of the event.

Novo Nordisk definition of hypoglycaemia

Confirmed hypoglycaemic episodes are defined as severe hypoglycaemia and/or a measured PG value of <3.1 mmol/L:

- Total hypoglycaemia (severe or blood glucose confirmed) is defined as episodes that are severe and/or blood glucose confirmed by a PG value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia.
- Severe or blood glucose confirmed symptomatic hypoglycaemia is defined as episodes that are severe and/or blood glucose confirmed by a PG value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.
- Severe hypoglycaemia is defined according to the ADA classification as stated below.

ADA classification of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG values may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL)

- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration >3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤3.9 mmol/L (70 mg/dL).

8.3.2.2 HbA1c and FPG

Blood samples for FPG and HbA1c measurements will be collected and analysed (in local laboratories) as part of standard clinical practice at each site. The date and results of the most recent test will be recorded at every visit.

The secondary effectiveness endpoint HbA1c (see Section 7.3.2.1) (change from baseline to during treatment) is the most widely accepted measure of overall, long-term blood glucose control in patients with diabetes.

8.3.2.3 Body weight

Body weight (kg) measurements will be collected, if available. Patients should ideally be weighed in their underwear or without shoes, on an appropriately calibrated weighing scale, as per standard clinical practice. Where possible the same weighing scales should be used throughout the study.

8.3.2.4 Serious adverse drug reactions (SADRs), medical events of special interest (MESI) and pregnancies

SADRs, severe hypoglycaemic events (regardless of seriousness or causality), MESI (medication errors), and pregnancies will be recorded throughout the study, from the signature of the informed consent form until the end of the study as defined by the protocol for that patient (see Section 10).

All SADRs will be coded using the latest version of Medical Dictionary for Regulatory Activities.

8.3.2.5 Documentation of insulin dose and time of injection

Patients will be provided with a study diary and requested to prospectively document daily Tresiba® doses for 4 weeks prior to each physician visit.

At each visit the Tresiba® dosage details (time, amount, and date of each dose) should be transcribed from the patient dose record into the eCRF.

At each visit, the patient will be asked what their total daily dose of bolus insulin was on the day prior to the visit, if applicable and this will be entered into the eCRF.

8.3.2.6 Self-measured blood glucose (SMBG)

Patients will be provided with a study diary and requested to document the number of SMBG test strips used over the 4 weeks prior to each physician visit. The SMBG measurements should not be performed unless according to clinical practice at the site.

8.3.2.7 Patient reported outcomes (PROs)

All PRO questionnaires should be completed by the patients at every visit (see Table 8–1); preferably before any other study-related activities. All PROs will be available in the local languages.

Health-related quality of life (HR-QoL)

The SF-36 health status survey assesses general health status. HR-QoL will be measured via the SF-36 v2 instrument. The SF-36 has 36 questions grouped into eight domains termed: physical functioning; bodily pain; role-physical; general health; vitality; social functioning; role-emotional; and mental health, which again can be combined to give two summary component scores.

The patient should complete SF-36 (version 2) at every visit.

Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The status DTSQ (DTSQs) provides a measure of how satisfied patients are with their treatment and how they perceive hyper- and hypoglycaemia in the real world clinical setting. It consists of 8 questions, which are to be answered on a Likert scale from 0 to 6. The change version (DTSQc) has the same 8 items as the status version, but is reworded to measure the change in satisfaction rather than absolute satisfaction. Each item is scored on a scale of -3 to +3.

Patient should complete the DTSQs at visits 1, 2, 3, 4, 5, and 6 and the DTSQc at visit 6.

8.3.3 Other assessments

8.3.3.1 Health economics (HE)

HE endpoints will be collected using the patient diary (collected at visits 2, 3, 4, 5, and 6).

Patient diary:

At visits 1, 2, 3, 4, and 5, patients will be provided with a study diary and requested to document the resources used due to hypoglycaemia, over a 4-week period prior to each physician visit. The treating physician, or an appropriately trained member of staff, should enter the HE data into the eCRF which will contain specific fields based on the diary.

Patients will be encouraged to record information such as, if they have:

- had any outpatient visits due to hypoglycaemia
- had any physician or diabetic nursing visits due to hypoglycaemia
- had any treatment at home by a paramedic, due to hypoglycaemia
- had any emergency room visits, due to hypoglycaemia
- needed ambulance transportation, due to hypoglycaemia
- been hospitalised due to hypoglycaemia and duration of any hospital stays
- had any days absent from work due to hypoglycaemia
- used SMBG test strips and how many.

8.3.3.2 Reason for switching or not switching to Tresiba®

When recording data at visit 2, the treating physician will also be asked to identify, and enter into the eCRF, the most important factor determining his/her decision to switch the patient to Tresiba® (for all patients who sign the informed consent including those who switch during the 4-week baseline period) or not to switch the patient to Tresiba®, as applicable.

8.3.3.3 Flexibility of dose time and FlexTouch® pen device

The effects of dose-time flexibility on compliance and effectiveness will be measured by collecting data from patient diaries. At each visit, the treating physician, or an appropriately trained member of staff, should document the dose-time flexibility responses in the eCRF which will contain specific fields based on the diary.

Patients will be provided with a study diary and requested to prospectively document information on missed doses and dose-time flexibility 4 weeks prior to each physician visit.

Patients will be asked to record/indicate information such as:

- If they miss a dose
- Why they missed a dose
- What did they do when they missed a dose
- How often they needed to take their Tresiba® at a different time/used the possibility of dose-time flexibility

In addition, at visits 2-6, the patient will be asked if their insulin treatment required them to change any social, leisure, and working time activities.

At the end of the study, patients will be asked which they found easier to use a) the FlexTouch® pen or b) previous injection method.

8.3.3.4 Patient preference

At each physician visit after initiation of Tresiba® treatment (visits 3, 4, 5, and 6), the physician will ask for the patient's preference for Tresiba® or their previous treatment and enter it in the eCRF.

8.4 Data sources

Physicians or an appropriately qualified and trained delegate will enter data from the patient's medical records in the eCRF.

8.4.1 Patient diaries

Upon providing informed consent, each patient will be given a study diary and provided guidance in its use. There will be 2 diaries, the first one will cover 4 weeks of baseline data (between visits 1 and 2) and the second one will cover the 4 weeks prior to each physician visit (visits 3 to 6). At the visit following completion of the diary, the patient will return his/her diary and will be given a new one. Data from the diary will be entered into the eCRF. The diary will be kept in the source files at the investigational site.

The 4-week diaries will include sections for information such as:

- Insulin dose and time of administration
- Details of missed doses and dose-time flexibility
- Number of SMBG test strips used
- Information related to hypoglycaemic episodes. Each time the patient has a symptom of hypoglycaemia or his/her blood sugar level is below or equal to 3.9 mmol/L (70 mg/dL), the patients will be encouraged to complete the diary (exact time, PG value, assistance required or not)
- Resource use due to hypoglycaemia.

8.4.2 Visit procedures

The physician must keep a patient enrolment log and a log of patients evaluated for but not included in the study throughout the enrolment period. These can be combined in one document.

A sequence of patient numbers will be assigned to each study site. All patients entering the baseline period will receive a patient number that will be used to identify the patient throughout the study. Patients withdrawn from the study retain their patient number, if already given. New patients must always be allocated a new patient number.

Patients who are enrolled in the study will be provided with contact address(es) and telephone number(s) of the physician site and/or staff.

Patients will be asked about any AEs during each visit by 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 visit?" However, only SADRs, MESI, pregnancies and severe hypoglycaemic events (regardless of seriousness or causality) will be collected in this study as specified in Section 10.

In case a patient is being prematurely withdrawn from the study the physician will ensure that the procedures for the last visit are recorded, if possible. The primary reason (adverse reaction or other) for discontinuation must be specified in the eCRF.

The study consists of a 4-week baseline period followed by a 12-month (±45 days) observation period. All visit dates are based on the date the patient started Tresiba® medication (Month 0, visit 2). The time window for visits 3, 4, 5, and 6 (Months 3, 6, 9 and 12) is ±45 days. Visits are not protocol defined but based on the estimated regularity of visits to a treating physician under normal clinical practice. It is not expected that all patients will attend all visits.

8.4.3 Visit 1 Physician plans to initiate Tresiba® (Week -4)

The patient will receive complete information about the study both orally and in writing. Informed consent must be given prior to any trial-related data being collected.

The visit will include:

- Signature of informed consent and recording of the date informed consent was given
- Determination of eligibility by checking the inclusion/exclusion criteria (Section 8.2.2 and Section 8.2.3). The decision as to which T1DM and T2DM patients will start Tresiba® treatment is determined by the treating physician
- Distribution of all PROs to be completed by the patient. This will be done prior to any following steps. The questionnaires will be administered while the subject is in the waiting room or another dedicated room
- Demography – collecting age, sex, ethnicity
- Blood pressure (systolic and diastolic) and height measurements, if available
- Body weight (kg), if available
- Medical history
- Physician will document if the patient is hypo-prone
- Concomitant medications (related to diabetes - including insulin dosing regimen)
- Physician will document if the patient is a high dose insulin user (>80 U/day)
- Collection of the most recent HbA1c and FPG and date of the measurements
- Patients will be interviewed and asked to recall any severe hypoglycaemic episodes in the 6 months prior to this visit
- Distribution of diary and guidance on use.

The patient will be instructed to:

- Continue on current therapy, as prescribed by the physician and lifestyle interventions
- Record in the diary every episode of hypoglycaemia occurring over the following 4 weeks
- Record in the diary insulin dose, time, and date (over the following 4 weeks)
- Record in the diary if any doses are missed and what the patient did
- Record in the diary how many SMBG strips they use over the following 4 weeks
- Record in the diary any resource use due to hypoglycaemia over the following 4 weeks
- Bring the diary to the next clinical visit.

An appointment will be made for their next usual clinical visit (visit 2, initiation) in approximately 4 weeks (+14 days).

8.4.4 Visit 2, Initiation/Baseline (Month 0)

The decision to treat patients is entirely based on the physician's decision in accordance with local practice.

This visit will include:

- Check of inclusion, exclusion and withdrawal criteria (see Sections 8.2.2, 8.2.3 and 8.2.4)
- Distribution of all PRO questionnaires to be completed by the patient. This will be done prior to any following steps
- Body weight (kg), if available
- Concomitant medications, including current insulin dosing regimen, will be recorded
- Collection of the most recent HbA1c and FPG and date of the measurements
- Collection of safety information. Patients will be asked about any AEs as part of standard care. Each SADR, severe hypoglycaemic episode (regardless of physician's evaluation of seriousness and causality), MESI, and pregnancies will be recorded on a separate AE form and SIF according to existing reporting procedures and timelines
- Collection of diary and distribution of a new one
- The patient will be asked what their total daily dose of bolus insulin was on the day prior to the visit, if applicable
- The patient will be asked if their insulin treatment required them to change any social, leisure, and working time activities
- Physician will document the reason for switching or not switching to Tresiba® treatment as applicable
- Based on physician decision, patients will commence treatment on Tresiba®

The patient will be instructed to:

- Continue on current therapy including Tresiba®, as prescribed by the physician and lifestyle interventions
- Record in the diary every episode of hypoglycaemia occurring over the 4 weeks prior to the next visit
- Record in the diary insulin dose, time, and date (for 4 weeks prior to the next visit)
- Record in the diary if any doses are missed and what the patient did, and details of dose-time flexibility
- Record in the diary how many SMBG strips they used over the 4 weeks prior to the next visit
- Record in the diary any resource use due to hypoglycaemia over the 4 weeks prior to the next visit
- Bring the diary to the next clinical visit.

8.4.5 Observation period (standard routine visits)

The time window for visits 3, 4, 5, and 6 (Months 3, 6, 9, and 12) are ±45 days. Visits are based on the regularity of visits to a treating physician under normal clinical management of a diabetic patient.

These visits will include:

- Patients will be assessed to determine if they meet any of the withdrawal criteria (Section 8.2.4).
- Distribution of all PRO questionnaires to be completed by the patient. This will be done prior to any following steps. The questionnaires will be administered while the subject is in the waiting room or another dedicated room.
- Body weight (kg), if available.
- Collection of the most recent HbA1c and FPG and date of the measurements.
- The patient will be asked what their total daily dose of bolus insulin was on the day prior to the visit, if applicable.
- The patient will be asked if their insulin treatment required them to change any social, leisure, and working time activities.
- Concomitant medications, including current insulin dosing regimen, will be recorded
- Collection of safety information. Patients will be asked about any AEs as part of standard care. Each SADR, severe hypoglycaemic episode (regardless of physician's evaluation of seriousness and causality), MESI, and pregnancies will be recorded on a separate AE form and SIF according to existing reporting procedures and timelines.
- Collection of diary (at all visits) and distribution of a new one at visits 3, 4 and 5 only.

- Patients will be asked their preference for Tresiba® or their previous treatment.

The patient will be instructed to (except for the end of study visit 6, Month 12):

- Continue on current therapy including Tresiba®, as prescribed by the physician and lifestyle interventions
- Record in the diary every episode of hypoglycaemia occurring over the 4 weeks prior to the next visit
- Record in the diary insulin dose, time, and date (for 4 weeks prior to the next visit)
- Record in the diary if any doses are missed and what the patient did, and details of dose-time flexibility
- Record in the diary how many SMBG strips they used over the 4 weeks prior to the next visit
- Record in the diary any resource use due to hypoglycaemia over the 4 weeks prior to the next visit
- Bring the diary to the next clinical visit.

8.4.6 End of Study (Visit 6, Month 12)

Treating physicians will perform and record details of the last visit as described in Section 8.4.5. Patients will continue to be treated as directed by their physician. Patients will be asked to return any diaries; after this visit no further data will be collected. Patients will be asked at the end of study visit which they found easier to use a) the FlexTouch® pen or b) previous injection method.

End of the study will have no impact on the treatment decision made by the physician.

8.5 Study size

The sample size calculation is based on the primary observational endpoint, which is the change from the baseline period (4-week baseline period) in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba®. The change from baseline measure is operationalised as the mean of the per-patient paired differences in hypoglycaemic episodes/PYE.

For both T1DM and T2DM, the mean of paired differences is expected to be 1 episode/PYE with a standard deviation of 7 (a conservative estimate based on our understanding of possible variation in the measures). At α=0.05 and 90% power, the number of patients who switch to Tresiba® and complete the 12-month observation period is $n_{T1DM}=n_{T2DM}= 517$. Assuming a 15% rate of withdrawal (loss of patient for any reason prior to completing 12-month observation period), 608 T1DM and 608 T2DM patients will need to be enrolled and complete the 4-week baseline period and switch to Tresiba® to achieve 517 T1DM and 517 T2DM patients completing the observation period.

The data from the participating countries will be pooled. Analysis on data from the patients in Germany up to the discontinuation date will be specified in the SAP.

8.6 Data management

8.6.1 Data management

Data from individual patient's charts will be remotely collected through a password-protected web-based electronic data capture (EDC) system. The prescribing physician or an authorised and appropriately trained delegate will enter the data into the web-based eCRF based on the individual patient's charts. No source documents will be sent off-site. To protect privacy, data will be anonymised and processed in accordance with local regulations regarding privacy protection.

Data management is the responsibility of Data Management, Novo Nordisk Headquarters. Data management will be delegated under an agreement of transfer of responsibilities to [redacted]

Data must be loaded at least one time during the conduct of the trial and as well as after Database Lock into Novo Nordisk Clinical Data Management System (CDMS). Data must be in a loadable format for Oracle Clinical.

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.

Appropriate measures such as encryption of data files must be used to ensure confidentiality of patient data when it is transmitted over open networks.

8.6.2 Case report forms and rules for completing

As used in this protocol, the term eCRF should be understood to refer to an electronic data record.

Novo Nordisk will provide a system for EDC. This system and support services for the system will be supplied by [redacted]. The activities of [redacted] will be under the direction and supervision of Novo Nordisk.

Pregnancy and MESI forms will be paper-based and will be supplied by Novo Nordisk.

An eCRF is required and should be completed for each included patient. The completed original eCRFs are the sole property of Novo Nordisk and should not be made available in any form to third parties except for authorised representatives of Novo Nordisk or appropriate regulatory authorities, without written permission from Novo Nordisk.

The treating physician has responsibility for the accuracy and authenticity of all clinical safety and laboratory data entered on the eCRFs. In most cases, the source documents are the physician's patient chart.

Ensure that all relevant questions are answered and that no empty data blocks exist.

If a test/assessment has not been done and will not be available, or if the question is irrelevant (eg, is not applicable) indicate this according to the instructions for completing eCRFs.

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

Data will be anonymised and collected by physicians, or appropriately trained delegates, so no direct patient contact with Novo Nordisk or [redacted] staff is envisaged.

8.6.3 Corrections to case report forms (CRFs)

e CRF data can be corrected only by the physician or the physician's authorised staff. For PROs, the patient will be responsible for notifying the physician of any errors which can then be corrected in the eCRF by the physician or the physician's authorised staff. An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry and the corrected entry. 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 again by the physician.

The following paragraphs apply to corrections to data on the paper-based MESI and pregnancy forms only.

Corrections to the data on the case report forms (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 eCRF flow

The physician must ensure that data is recorded in the eCRFs as soon as possible after the visit (preferably within 5 days if source data is available otherwise in connection to the visit of obtaining data). When data is entered, it will be available to Novo Nordisk for data verification activities.

When the final non-interventional study report is available, the data will be archived by Novo Nordisk.

8.7 Data analysis

8.7.1 Evaluability of patients for analysis

All observational endpoints will be analysed on the FAS. The FAS includes all patients who received at least 1 dose of Tresiba® at visit 2. Patients who complete visit 1 but do not initiate Tresiba® at visit 2 will be excluded from the analyses.

The safety population will consist of all patients who received at least 1 dose of Tresiba® (FAS).

Patients will be analysed separately based on being T1DM or T2DM patients who use insulin.

8.7.2 Statistical methods

Novo Nordisk A/S is responsible for the statistical analysis.

A full SAP will be developed. In brief, all observational endpoints will be analysed on the FAS (Section 8.7.1).

8.7.2.1 Analysis of primary endpoint

The primary observational endpoint is the change from the baseline period in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba®. The count data will be converted to rates per PYE for analysis purposes.

For purposes of descriptive statistics, the endpoint will be calculated as the change in patient paired differences and will be summarised, by visit, as number of observations with available values, number of observations with missing values, mean (of paired differences), 95% CI of the mean, standard deviation, minimum, median, and maximum.

The primary endpoint will also be estimated as a baseline-adjusted change using an appropriate regression estimator (eg, negative binomial estimator) with additional covariates, along with the associated 95% CI and p-value. Additional covariates may be added to the model (e.g., clinical, country, etc.). The list of covariates to be included, along with the baseline endpoint value, will be specified in the SAP.

The baseline value for the primary endpoint is calculated from the entire 4-week baseline period.

Patients will be analysed separately based on being T1DM or T2DM patients who use insulin.

8.7.2.2 Analysis of secondary endpoints

Analysis of secondary endpoints will be performed on the FAS. Secondary endpoints that are interval and ratio-level endpoints will be analysed in the same manner as the primary endpoint using an appropriate regression estimator.

The baseline value for number data is calculated in the same manner as for the primary endpoint. For all other endpoints the baseline is the value recorded at visit 2.

For the following categorical endpoints, data will be displayed in frequency tables as percentages with numerator counts, based upon the appropriate denominator:

- Any hypoglycaemia
- Responder for HbA1c:
  - HbA1c <7% at end of study
  - HbA1c <7.5% at end of study
  - HbA1c <7% at end of study without severe hypoglycaemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks
  - HbA1c <7.5% at end of study without severe hypoglycaemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks
  - HbA1c lowered according to national guidelines.

Additional exploratory hypothesis-generating analyses may also be performed as deemed relevant.

All statistical tests will be performed as two-sided tests with a significance level of 0.05.

Patients will be analysed separately based on being T1DM or T2DM patients who use insulin.

8.7.2.3 Additional analyses

It is possible that if a patient experiences a severe episode of hypoglycaemia during the 4-week baseline period, the treating physician may elect to switch them immediately to Tresiba® (or another product), making that patient ineligible to continue in this study. This could affect estimation of the change from baseline in hypoglycaemic episode rate as the baseline measure could be underestimated, thus making it harder, *ceteris paribus*, to get a large effect from Tresiba® during the observation period (ie, large change from baseline, because the baseline rate was lower than it should have been). Consequently, the baseline rates of patients who are switched early to Tresiba® will be examined. If there is sufficient evidence that the omission of these patients biases baseline rates, appropriate methods may be employed (eg, weighting data for patients included in the study)

to adjust data of the patients enrolled in the study. Details for these analyses will be provided in the SAP.

8.7.3 Interim reporting

There is no interim reporting, there will be data cuts for data analysis but the data will be used internally, potentially only shared with regulatory agencies, and not for publications.

8.7.4 Health economics and/or patient reported outcomes

8.7.4.1 PROs

PRO evaluation will be performed for each country. The score for each PRO questionnaire will be summarised descriptively as outlined in Section 8.7.2.2 and statistical analysis will be performed. The change in PRO scores will be presented graphically for each QoL measure.

8.7.4.2 HE endpoints

The changes in HE endpoints (outlined in Section 8.3.3.1) will be presented graphically for the T1DM and T2DM patients and statistical analyses performed. Evaluations will be performed for each country.

8.8 Quality control

8.8.1 Monitoring procedures

During the course of the study, the monitor should visit the study site to ensure that the protocol has been adhered to and that relevant data have been recorded.

During study conduct, monitoring will be performed by a CRO according to the same standards as set out in Novo Nordisk's SOP for Non-interventional Studies. The CRO will conduct periodic monitoring at least monthly, via telephone contacts and visits, to ensure that the protocol and Good Pharmacoepidemiological Practice (GPP) and Good Pharmacovigilance Practice (GVP) guidelines are being followed. The monitors may review source documents to confirm that the data recorded on the eCRFs and on paper-based MESI and pregnancy forms are accurate. The treating physician and institution will allow Novo Nordisk monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and /or quality assurance audits performed by Novo Nordisk, and/or to inspection by appropriate regulatory authorities.

It is important that the physician(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

The monitor must ensure that the eCRFs are completed; this may be performed remotely or on-site.

8.8.2 Critical documents

Before the physician starts the study (ie, 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 IRB/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, and patient consent procedures
- Copy of IRB/IEC approved patient information/informed consent form/any other written information/advertisement
- Non-interventional study agreement.

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 GPP, GVP, 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 or in accordance with national regulations if they require a longer retention period.

8.9 Limitations of the research methods

The enrolled patients in the current non-interventional study are acting as their own control. Thus, the baseline period of 4 weeks prior to planned initiation of Tresiba® is crucial in order to obtain reference data for the enrolled patients. The baseline period also constitutes an evaluation period for the physician, in order to aid in the final decision whether to initiate Tresiba®. While no causal

relationships can be concluded based on a non-interventional study design, the aim is to explore the associations between Tresiba® and other anti-diabetic treatment regimens with regard to any hypoglycaemic episodes.

The absence of a comparator group results in a number of threats to internal validity of the study design, the most critical of which is that the design will not provide the ability to rule out many alternative explanations for changes from baseline.

Whilst this is a study of real world clinical practice, enhanced glucose monitoring during the 4-week baseline period may potentially bias the physician's decision to commence Tresiba® treatment. More frequent blood glucose monitoring and maintaining a diary is an important factor in improved blood glucose control. Based on the enhanced monitoring and hypoglycaemic episode data collected during the 4-week baseline period, patients who the physician considered candidates for a treatment switch to Tresiba® at visit 1, may have improved blood glucose control and, at visit 2, may no longer be considered candidates for switching treatment.

Furthermore, due to data collection procedures conducted at visit 1 (see Table 8–1), it is possible that treating physicians may selectively enrol only those patients deemed, by past medical history, to be less likely to experience a hypoglycaemic episode during the 4-week baseline period before switching to Tresiba®. This differential selection of patients introduces a form of systematic selection bias that will result in an underestimation of the true rate of hypoglycaemia among all T1DM and T2DM patients switched to Tresiba®. The impact of this type of selection bias is that rates obtained from this study population will represent only those patients with an a priori lower rate of hypoglycaemia.

If treating physicians do not selectively enrol patients based on knowledge of past medical history, it is still likely that if a patient experiences a severe episode of hypoglycaemia during the 4-week baseline period, the treating physician may elect to switch them immediately to Tresiba® (or another product), making that patient ineligible to continue in this study. If this type of patient selection occurs systematically, then the study population will consist predominantly of patients with a history of non-severe hypoglycaemia, which will result in an underestimation of the true rate of hypoglycaemia among all T1DM and T2DM patients switched to Tresiba®. This could affect estimation of the change from baseline in hypoglycaemia rate as the baseline measure could be underestimated, thus making it harder (*ceteris paribus*) to get a large effect after Tresiba® (ie, a large change from baseline).

Once patients have entered the observation period it is not anticipated that the physician's perception and understanding of a patient by the detailed collection of hypoglycaemic episode data will influence the physician's decision to continue Tresiba® treatment.

The inclusion criteria have been made deliberately broad to reflect the real world diabetic population. However, the use of diaries and questionnaires in this study may bias data towards those patients, either through socio-economic or educational reasons, better able to monitor and maintain a diary and thus maintain improved blood glucose. It is anticipated that the broad inclusion criteria will provide data from a sufficiently wide demographic and thus reduce the impact of this bias.

Laboratory measurements will be performed locally as per standard clinical practice, results are therefore expected to show greater variability than if performed centrally.

Recall of event or dosage information is frequently associated with either high numbers of errors of missing values/fields in collected data. The use of a prospective diary will limit collection of erroneous or missing data.

8.10 Other aspects

None.

9 Protection of human subjects

The study will be conducted in accordance with GPP (8) and GVP (9).

9.1 Informed consent form for study patients

Informed consent from all study participants is required prior to any study-related activities.

In obtaining and documenting informed consent, the physician must comply with the applicable local regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki (10).

Prior to any study-related activity, the physician must give the patient oral and written information about the study in a form that the patient can read and understand. This includes the use of impartial witness where required. Processes for study entry will be similar at each site.

A voluntary, signed and personally dated, informed consent form will be obtained from the patient 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 in a timely manner and a revised written informed consent must be obtained.

9.2 Data handling

If the patient 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 information 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 according to national requirements. 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

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.

10 Management and reporting of adverse events/adverse reactions

The requirements for collection of safety data are described in Sections 10.1 and 10.5.

10.1 Safety information to be collected

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

- SADRs
- Severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality)
- MESI – medication errors
- Pregnancies in female patients including the outcome
- Safety information required by local laws and/or IECs/IRBs.

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

Voluntary reporting of any other AE information other than serious adverse reactions, medication errors, and pregnancies (including outcome) is at physician's discretion. For technical complaints, the spontaneous reporting process should be followed. 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 (or agent acting on behalf of Novo Nordisk) is informed of any other safety information related to a Novo Nordisk product that the patient takes concomitantly with Tresiba®, he/she should report this information **within 24 hours** to the local department responsible for drug safety.

10.2 Safety definitions

Safety Information

All reports of AEs 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. In this trial, only the safety information listed in Section 10.1 must be reported.

Adverse reaction

An adverse reaction is an untoward medical occurrence in a patient administered a 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 reaction can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, which is considered related to the product. An adverse reaction is either a serious adverse reaction or a non-serious adverse reaction (for definitions, see below).

This includes adverse reactions which arise from:

- a worsening of a concomitant illness
- occupational exposure to a product.

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

Adverse event

An AE is any untoward medical occurrence in a patient administered a product, which does not necessarily have a causal relationship with the product.

Terms used to describe causal relationship to Tresiba®

- 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 Tresiba®.

Seriousness criteria

An adverse reaction or AE is a **serious adverse reaction** or **SAE**, 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 a SAE – 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 SAEs 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 dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse reaction or adverse event

An adverse reaction or AE that does not meet a seriousness criterion 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 meet a seriousness criterion, the adverse reaction or AE must be reported as a serious adverse reaction or SAE.
- 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 reaction or AE. Outcomes of other reported adverse reaction or AE 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 reaction or AE with fatal outcome must be reported as a serious adverse reaction or SAE).
- Unknown – This term should only be used in cases where the patient is lost to follow-up.

Adverse events fulfilling criteria for MESI

A MESI is an event which, in the evaluation of safety, has a special focus. A MESI should be reported as below (Section 10.3).

The following are defined as MESI:

1. Medication errors concerning Tresiba®.

For medication errors, the following should be reported:

- Administration of wrong drug or use of wrong device
- Wrong route of administration, such as intramuscular instead of SC
- Administration of an overdose with the intention to cause harm, eg suicide attempt
- Administration of an accidental overdose ie, dose which may lead to significant health consequences, as judged by the physician, irrespective of whether the SAE/serious adverse reaction criteria are fulfilled or not.

10.3 Collection and reporting of safety information

Safety information must be reported by the physician on the electronic/paper AE form. At each visit patients will be asked about AEs, eg: “Have you experienced any problems since the last contact?” However, only the safety information listed in Section 10.1 must be reported.

SADRs and severe hypoglycaemic episodes (regardless of physician’s evaluation of seriousness and causality) will be reported using forms within the EDC application. MESI will be reported using forms in the paper format.

In addition to this, for **SADRs, severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality) and MESI**, further information must be reported by the physician on the SIF.

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

For SADRs, severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality) and MESI:

- Initial information must be reported on the AE form **within 24 hours** of the physician's knowledge of the event.
- Further information must be reported on the safety information form **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 on the AE and safety information forms **within 5 calendar days** of the physician's knowledge of the event on the forms, as described above.

The physician must complete the forms in the EDC application and/or in the paper format within the above specified timelines of obtaining knowledge about the event(s). For SAEs the physician must sign the form within 7 days after completing the form. Paper forms must be forwarded electronically, fax or courier copies. The physician should fax/email the completed paper MESI forms to the Novo Nordisk office in their country (contact details are provided below in this section).

The physician should record the diagnosis, if available. If no diagnosis is available, the physician should record each sign and symptom as individual serious adverse 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 SIF can be used to describe all the serious adverse reactions or events.

Sponsor's assessment of expectedness is done according to the Company Core Data Sheet for Tresiba®.

In accordance with regulatory requirements, including GVP, the sponsor will inform the regulatory authorities of study product related serious adverse reactions. In addition, [redacted] will inform the IECs/IRBs (or other appropriate bodies as required locally) of study product related serious adverse reactions, in accordance with the local requirements in force.

[redacted] will notify the physician of study product related suspected serious adverse reactions, in accordance with the local requirements.

Contact details of Novo Nordisk safety:

Denmark
Novo Nordisk Scandinavia AB
Region Danmark
Arne Jacobsens Allé 17, 9. sal
DK-2300 København S -Denmark
Contact person: [redacted]
Telephone: [redacted]
Fax: [redacted]
Email: dkno-safety@novonordisk.com

Germany
Novo Nordisk Pharma GmbH
Attention: Safety Department
Produktsicherheit
Brucknerstr. 1
55127 Mainz
Telephone: + 49 (0) 6131 903 0
Fax: +49 (0)6131 903 327
Email: DE-MedProdSafety1@novonordisk.com

The Netherlands
Novo Nordisk B.V.
Flemingweg 18
2408 AV Alphen aan den Rijn
The Netherlands
Contact person: Drug Safety Officer
Telephone: +31-0172-449494
Fax:+31 172 424 709
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Spain
Novo Nordisk Pharma SA
Via de los Poblados, 3
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Email: 012_SpainFarmacov@novonordisk.com

Switzerland
Novo Nordisk Switzerland
Attention: Safety Department
Untere Heslibachstrasse 46
8700 Küsnacht/ZH
Telephone: +41 (0)44 914 11 26
Fax: +41 (0)44 914 11 00
Email: safety-chkn@novonordisk.com

Sweden
Novo Nordisk Scandinavia AB
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Fax: +46 40 388 995
E-mail: SE-safety@novonordisk.com

Italy
Novo Nordisk S.p.A.
Attention: Safety Department
Via Elio Vittorini, 129
I-00144 Rome
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Telephone: +39 06 50088443
Fax: +39 06 50088354
Email: ITASafetymail@novonordisk.com

United Kingdom
Novo Nordisk Ltd.
Attention: Safety Department
3 City Place
Beehive Ring Road
Gatwick
West Sussex RH6 0PA
United Kingdom
Telephone: +44 (0) 1293 613555
Fax: +44 (0) 1293 611819
Email: NNGB-Safety@novonordisk.com

10.4 Follow-up of safety information

Follow-up information concerning previously reported SADRs, severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality), and MESI 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 the systematically collected safety information 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 or serious adverse reactions ongoing at the time of the death (ie, the patient dies from another SAE) 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 observation period (as stated in this protocol) and is expected by the physician to recover.

10.5 Collection and reporting of pregnancies in female patients

In female patients, pregnancy must be reported **within 14 calendar days** of the physician's first knowledge of the pregnancy using the applicable pregnancy forms (in paper format). The physician should fax/email the completed paper pregnancy forms to the Novo Nordisk office in their country (contact details in Section 10.3). 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 AEs experienced by the foetus or newborn infant should be collected and reported regardless of causality assessment.

Reporting of adverse reactions or AEs in foetus, newborn infant or in connection with the pregnancy must be done on the same forms as described in Section 10.3 "Collection and reporting of safety information". It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the patient, foetus or newborn infant. The reporting timelines are as described in Section 10.3 for other adverse events or reactions and other serious AEs or reactions.

10.6 Precautions/over-dosage

Over-dosage will be managed in accordance with the SmPC. As part of normal clinical practice when patients commence Tresiba® treatment they will be advised to always carry glucose-containing products.

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 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), (11).

11.3 Publications

The physician must ensure submission of the results of the study (either abstract or full study report) to IEC/IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

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.

For PASS in Europe, the study information should be available in the EU PAS Register (see Section 5).

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.

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 American Diabetes Association Workgroup on Hypoglycaemia. Defining and Reporting Hypoglycemia in Diabetes. 2005; 28, 1245-49.

2 Novo Nordisk A/S. Tresiba® Summary of Product Characteristics. 2013.

3 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care. 2013.

4 CPMP/EWP/1080/00. Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus. Committee for Medicinal Products for Human use (CHMP). The European Agency for the Evaluation of Medicinal Products. 2002.

5 FDA Guidance (draft) for industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. US Department of Heath and Human Services, Center for Drug Evaluation and Research (CDER). February 2008.

6 Ryden L, Standl E, Bartnik M, Van den BG, Betteridge J, de Boer MJ et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The task force on Diabetes and Cardiovascular Disease of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007, 28(1), 88-136.

7 CPMP/EWP/1080/00 Rev. 1. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2012.

8 International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiolgy Practices (GPP). Initially issued: 1996. Revision 2, April, 2007.

9 EMA/873138/2011, 22 June 2012. Guideline on good pharmacovigilance practices (GVP) Module VI - Management and reporting of adverse reactions to medicinal products. 2011.

10 World Medical Association (WMA) Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Brazil. October, 2013.

11 International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals. WWW.ICMJE.org.

ANNEX 1. List of Stand-alone Documents

List of Stand-alone Documents

None.

ANNEX 2. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (eg to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	9, 16-17
1.1.2 The objectives of the study?	☒	☐	☐	10, 17-21
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (ie population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9-11,
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	43
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	10
2.2.2 Age and sex?	☒	☐	☐	11, 26, 27
2.2.3 Country of origin?	☒	☐	☐	3, 21
2.2.4 Disease/indication?	☒	☐	☐	11, 26
2.2.5 Co-morbidity?	☐	☒	☐	
2.2.6 Seasonality?	☐	☒	☐	
2.3 Does the protocol define how the study population will be sampled from the source population? (eg event or inclusion/exclusion criteria)	☒	☐	☐	26

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12-13, 18-21
3.2 Is the study design described? (eg cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10, 21
3.3 Does the protocol describe the measure(s) of effect? (eg relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	40
3.4 Is sample size considered?	☒	☐	☐	40-41
3.5 Is statistical power calculated?	☒	☐	☐	14, 40

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (eg pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	24-25, 36-40
4.1.2 Endpoints? (eg clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	24-25, 36-40
4.1.3 Covariates?	☒	☐	☐	15, 24-25, 36-40
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (eg date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24-25, 36-40
4.2.2 Endpoints? (eg date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24-25, 36-40
4.2.3 Covariates? (eg age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc)	☒	☐	☐	24-25, 36-40
4.3 Is the coding system described for:				
4.3.1 Diseases? (eg International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (eg Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (eg WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (eg based on a unique identifier or other)	☒	☐	☐	36

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (eg operational details for defining and categorising exposure)	☐	☒	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (eg precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (eg current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18-21; 30-36
6.2 Does the protocol discuss the validity of endpoint measurement? (eg precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Biases and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	47
7.1.2 Information biases? (eg anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
7.2 Does the protocol address known confounders? (eg collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.3 Does the protocol address known effect modifiers? (eg collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	
7.4 Does the protocol address other limitations?	☒	☐	☐	47

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☒	☐	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	43-44
8.3 Are descriptive analyses included?	☒	☐	☐	44
8.4 Are stratified analyses included?	☐	☒	☐	
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☒	☐	
8.5.2 Effect modifiers?	☐	☒	☐	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	43-44
8.6.2 Effect modification?	☒	☐	☐	43-44

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (eg software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	46
9.2 Are methods of quality assurance described?	☒	☐	☐	45
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☒	☐	
9.4 Does the protocol discuss study feasibility? (eg sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15,
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	15
9.5.2 Study progress?	☒	☐	☐	15
9.5.3 Study completion?	☒	☐	☐	15
9.5.4 Reporting?	☒	☐	☐	15
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15
9.7 Are communication methods to disseminate results described?	☒	☐	☐	58
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	46, 49

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.2Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3Have data protection requirements been described?	☒	☐	☐	17, 46

Comments:

Name of protocol originator: _____

Date: / /

Signature: _____

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