Non-interventional study report

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

PASS 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
Version identifier of the final study report	1.0
Date of last version of the final study report	27 March 2019
EU PAS register number	ENCePP/SDPP/7880
EU PAS register link	http://www.encepp.eu/encepp/viewResource.htm?id=24527
Active substance	ATC code: A10AE06; active substance: Insulin degludec
Medicinal product	Insulin degludec (Tresiba®) 100 units/mL and 200 units/mL
Product reference	N/A
Procedure number	EMEA/H/C/002498
MAH	Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Denmark
Joint PASS	No
Research question and objectives	The objectives of this study were 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. Primary objective: 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 continued the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin could be any type of basal insulin. Secondary objectives: 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 health-economic endpoints compared to the baseline period, where the patient continued the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin could be any type of basal insulin.

Countries of study	Denmark, Germany, Netherlands, Spain, Sweden, Switzerland, Italy, and United Kingdom. Novo Nordisk ceased the distribution of Tresiba® in Germany in September 2015 and Germany was removed from this study; thus, patients enrolled in Germany based on the protocol version 2.0 were discontinued. Data obtainable up to the discontinuation date were included in the analysis, as appropriate and specified in the SAP.
Author	[redacted], [redacted], Novo Nordisk, [redacted] Denmark
UTN	U1111-1158-0248
ClinicalTrials.gov identifier	https://www.clinicaltrials.gov/ct2/show/NCT02392117?term=insulin+tresiba&cond=Diabetes&rank=10
IND number	N/A
Generic name	Insulin degludec
Indication	Type 1 and 2 diabetes mellitus
Investigators	There were 201 physicians appointed as individual overall responsible at each of the sites in the in the study – one at each study site. Signatory physician: [redacted], MD, [redacted]
Study sites	There were 201 sites in 8 countries: Germany, Denmark, Spain, Italy, Netherlands, Sweden, Switzerland, and United Kingdom
Study initiated	FPFV:16 March 2015
Study completed	LPLV: 19 March 2018
Lead study manager	[redacted], Novo Nordisk A/S, [redacted], Denmark
Study manager	[redacted], Novo Nordisk A/S, [redacted], Denmark
Epidemiologists	[redacted], [redacted], [redacted], Novo Nordisk A/S, [redacted], Denmark [redacted], Novo Nordisk A/S, [redacted] Denmark

Abbreviations: ATC = anatomical therapeutic chemical; EnCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EU PAS = European Union electronic register of post-authorisation studies maintained by the European Medicines Agency; FPFV, first patient first visit; IND = investigational new drug; LPLV, last patient last visit; MAH = marketing authorisation holder; N/A = not applicable, OD = once daily; PASS = post-authorisation safety study; PRO = patient-reported outcome; SAP = Statistical Analysis Plan; UTN = Universal Trial Number.

Marketing authorisation holder

MAHs	**Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Denmark**
MAH contact person	[redacted], [redacted] Novo Nordisk, [redacted], Denmark

This study was conducted in accordance with the Declaration of Helsinki[1] and the Guidelines for Good Pharmacoepidemiology Practices[2].

Abbreviation: MAH = marketing authorisation holder

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1 Abstract

Please refer to separate document.

2 List of abbreviations and definitions of terms

ADA	American Diabetes Association
ADR/AR	adverse drug reaction/adverse reaction
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CKD-Epi	chronic kidney disease epidemiology collaboration formula
CRF	case report form
CRO	contract research organisation
DBP	diastolic blood pressure
DM	diabetes mellitus
DPO	dropouts prior to observation
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	European Union
EU PAS	European Union electronic register of post-authorisation studies maintained by the European Medicines Agency
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FPG	fasting plasma glucose
HbA1c	glycated haemoglobin A1c
HR-QoL	Health-related Quality of Life
ICF	informed consent form
IDeg	Insulin degludec 100 units/mL or 200 units/mL
IEC	independent ethics committee
IRB	institutional review board
LPLV	last patient last visit
LS	least squares
MCS	mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
MMRM	mixed model for repeated measurements
N/A	not applicable

OD	once daily
PASS	post-authorisation safety study
PCS	physical component score
PG	plasma glucose
PRO	patient-reported outcome
PT	preferred term
PYE	patient years of exposure
Q	quartile
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR/SADR	serious adverse reaction/serious adverse drug reaction
SBP	systolic blood pressure
SC	subcutaneous
SF-36	Short Form-36
SIF	safety information form
SMBG	self-measured blood glucose
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
US	United States

3 Investigators

This study was conducted at 201 sites in 8 countries (Germany, Denmark, Spain, Italy, Netherlands, Sweden, Switzerland, and United Kingdom). A list of study sites is provided in Annex 1, Appendix 16.1.1 and a list of physicians is provided in Annex 1, Appendix 16.1.4.

4 Other responsible parties

[redacted]	Project management, clinical monitoring, statistical analysis, medical analysis, regulatory affairs, data management, medical writing

5 Milestones

Table 5–1 Milestones

Milestone	Planned date	Actual date
Start of data collection (FPFV)	16 March 2015	16 March 2015
End of data collection (LPLV)	16 March 2018	19 March 2018
Registration in the EU PAS register	15 March 2015	15 March 2015
Interim data cuts*	30 June 2016 31 January 2017 30 June 2017 06 December 2017	30 June 2016 31 January 2017 30 June 2017 06 December 2017
Final report of study results	30 July 2018	27 March 2019

*Interim data were only used internally, potentially only shared with regulatory agencies and not shared publicly.

Note: the planned dates are as per protocol version 5.0.

Abbreviations: EU PAS register, the European Union (EU) electronic register of post-authorisation studies (PAS) maintained by the European Medicines Agency (EMA); FPFV, first patient first visit; LPLV, last patient last visit

6 Rationale and background

Tresiba® (insulin degludec 100 units/mL or 200 units/mL [IDeg]) is a recombinant analogue of human insulin indicated for the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (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. Complete information for Tresiba® may be found in the most recent version of the Summary of Product Characteristics (SmPC)[10].

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 the number of episodes of hypoglycaemia and its severity.

Hypoglycaemia is the biggest obstacle to tight glucose control[3]. The clinical development programme for Tresiba® was designed to demonstrate whether Tresiba® is at least as effective as comparators in sustaining glycaemic control while associated with a lower frequency of hypoglycaemic episodes. The clinical development programme has consistently shown a lowered risk of hypoglycaemia in patients treated with Tresiba® against comparators with similar efficacy.

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 efficacy of Tresiba® in alignment with EMA[4] and United States Food and Drug Administration (US 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.

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 established a prospective non-interventional study of insulin-using DM patients who were recommended by their treating physician to initiate Tresiba®. This study aimed to investigate the use of Tresiba® according to routine clinical practice in a patient population that reflected clinical reality; the decision as to whom to switch to Tresiba® was left to the treating physician. The study constituted a unique opportunity for large-scale data collection that allowed comparisons and analysis between the patient's treatment regimen at baseline and up to 12 months after switching to Tresiba®.

All data collection and statistical analyses were done in accordance with global and local regulations and legal data protection requirements.

Written approval was obtained from the independent ethics committee (IEC) of participating countries before commencement of the study, except for Denmark. Submission of observational

studies in Denmark is not a requirement. In obtaining and documenting informed consent, the physician complied with the applicable regulatory requirements and adhered to the requirements in the Declaration of Helsinki[1].

Prior to any study-related activity, the physician gave the patient oral and written information about the study in a form that the patient could read and understand. A voluntary, signed and personally dated, informed consent form was obtained from the patient prior to any study-related activity. The responsibility for obtaining informed consent was with that of a medically qualified person. The written informed consent was signed and personally dated by the person who obtained the informed consent.

7 Research question and objectives

As stated in the protocol (included in Annex 1, Appendix 16.1.1), the objectives of the study were as follows:

7.1 Primary objective

The primary objective was 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 was 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 continued the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin could be any type of basal insulin.

7.2 Secondary objectives

The secondary objectives were 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 was associated with a change in safety, effectiveness, patient-reported outcomes (PRO), and health economics endpoints compared to the baseline period, where the patient continued the prior basal insulin as part of their anti-diabetic treatment regimen. The prior basal insulin could be any type of basal insulin.

8 Amendments and updates

Protocol version 1.0 was not submitted to any ethics committee. Consequently, protocol version 2.0 was implemented (on 29 October 2014) without the need for a formal amendment.

Protocol version 3.0 (including protocol amendment 2.0) was implemented on 30 September 2015. Protocol amendment 2.0 was needed in order to remove Germany from the study and add Italy to the list of participant countries in the study. This was necessary as a result of a decision made by Novo Nordisk to cease distribution of Tresiba® in Germany in September 2015. All patients from Germany who had been enrolled in the study prior to this amendment had to be discontinued. As a result of this amendment, the total number of patients across all countries decreased to 1,034 patients. Additional changes implemented in protocol amendment 2.0 were: The term analysis of covariance (ANCOVA) was removed as this statistical test was not used for the primary analysis of the primary observational endpoint; the EU PASS register number was added; a clarification was made that all data from participating countries would be pooled from the time of the amendment; the regression estimator used for statistical analyses of the primary observational endpoint was clarified; milestone expected dates and number of patients enrolled in the study were updated; terminology was updated; clarification of patient eligibility criteria was made; the Medical Dictionary for Regulatory Activities (MedDRA) version was updated; the wording about result expectations was removed; clarification as to the contract research organisation (CRO) role was made; contact details for Novo Nordisk Safety (Italy) were added.

Protocol version 4.0 (including protocol amendment 3.0) was implemented on 22 December 2015. Protocol amendment 3.0 was needed in order to have 3 additional countries added to the list of participating countries: Denmark, Netherlands and Spain. In order to allow the new participating countries enough time to enrol patients in the study, the last patient last visit (LPLV) expected date had to be extended to the end of December 2017. Additional changes implemented in protocol amendment 3.0 were: protocol originator contact details were updated; milestone expected dates and number of patients enrolled in the study were updated; contact details for Novo Nordisk Safety (Denmark, Netherlands and Spain) were added.

Protocol version 5.0 (including protocol amendment 4.0) was implemented on 24 October 2016. Protocol amendment 4.0 was needed in order to clarify a discrepancy in the wording used to describe one of the secondary study endpoints: the intention was to measure the change from baseline in the <u>total</u> daily bolus insulin, and not the <u>last</u> dose of bolus insulin, as was described in the description of the procedures. Also, in order to account for the time windows allowed for completion of the study procedures, the LPLV date was extended from 31 December 2017 to 16 March 2018. Additional changes implemented in protocol amendment 4.0 were: the restriction on number of insulin switchers required to complete the study was lifted without modification on the recruitment target of 1,034 patients; formatting errors were corrected; protocol originator and International Medical Director contact details were updated.

For details of the sections affected by protocol amendment 2.0, protocol amendment 3.0 and protocol amendment 4.0 see Table 8–1.

Table 8–1 Amendments to the protocol

Number	Date	Section of study protocol	Amendment	Reason
Protocol amendment 2 (Protocol final version 3.0)	30 Sep 2015	Synopsis Report Header MAH contact details Section 3.4, 3.8, 3.9, 3.10 Section 5 Section 8.1.1, 8.2.1, 8.2.5, 8.3.2.4, 8.3.2.7, 8.5, 8.7.2.1, 8.7.2.2, 8.8.1 Section 10.3	See Section 8 of this report	See Section 8 of this report
Protocol amendment 3 (Protocol final version 4.0)	22 Dec 2015	MAH/Protocol originator contact details Section 3.4, 3.10 Section 5 Section 8.1.1 Section 10.3	See Section 8 of this report	See Section 8 of this report
Protocol amendment 4 (Protocol final version 5.0)	24 Oct 2016	MAH/Protocol originator contact details Section 3.8, 3.10 Section 5 Section 8.2.6, 8.3.2.5, 8.4.4, 8.4.5, 8.5 Section 10.3	See Section 8 of this report	See Section 8 of this report

Abbreviation: MAH = marketing authorisation holder

9 Research methods

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

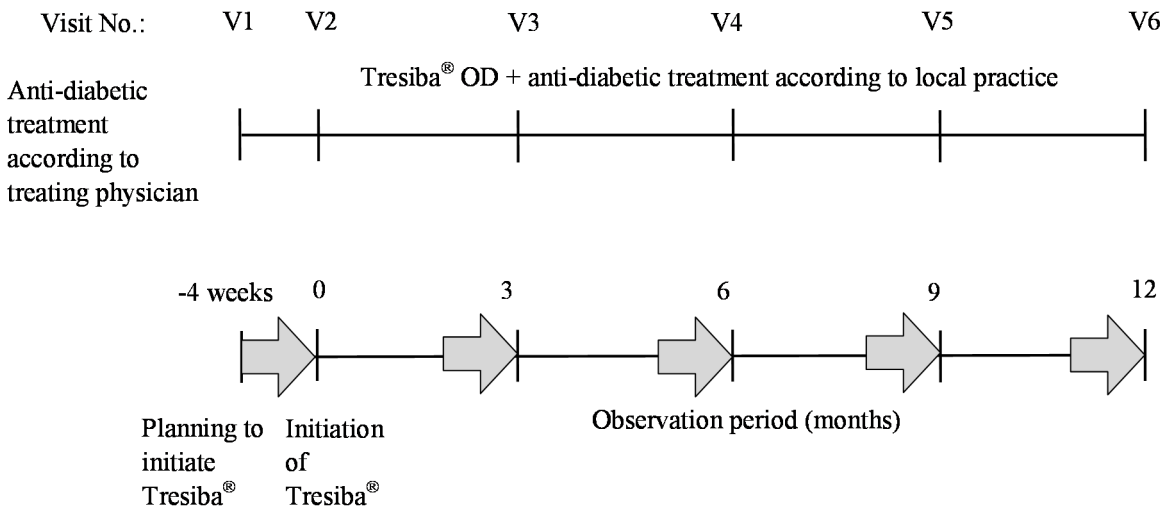
9.1 Study design

This was 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 used insulin where the physician had decided to start the patient on Tresiba® treatment.

The study was non-interventional as the patients were treated according to routine clinical practice and the local label upon the treating physician's discretion. This was under the category of PASS. Patients with T1DM and T2DM who were treated with insulin were followed for 4 weeks before (baseline period) and a maximum of 12 months after switching to Tresiba® (observation period). All visit dates were based on the date the patient started Tresiba® medication (month 0, visit 2). The total study duration for the individual patients was a maximum of 63 weeks (baseline: 4 weeks, observation period: up to 52 weeks ±45 days).

The study design is summarised schematically in Figure 9-1.

Figure 9-1 Schematic of study design



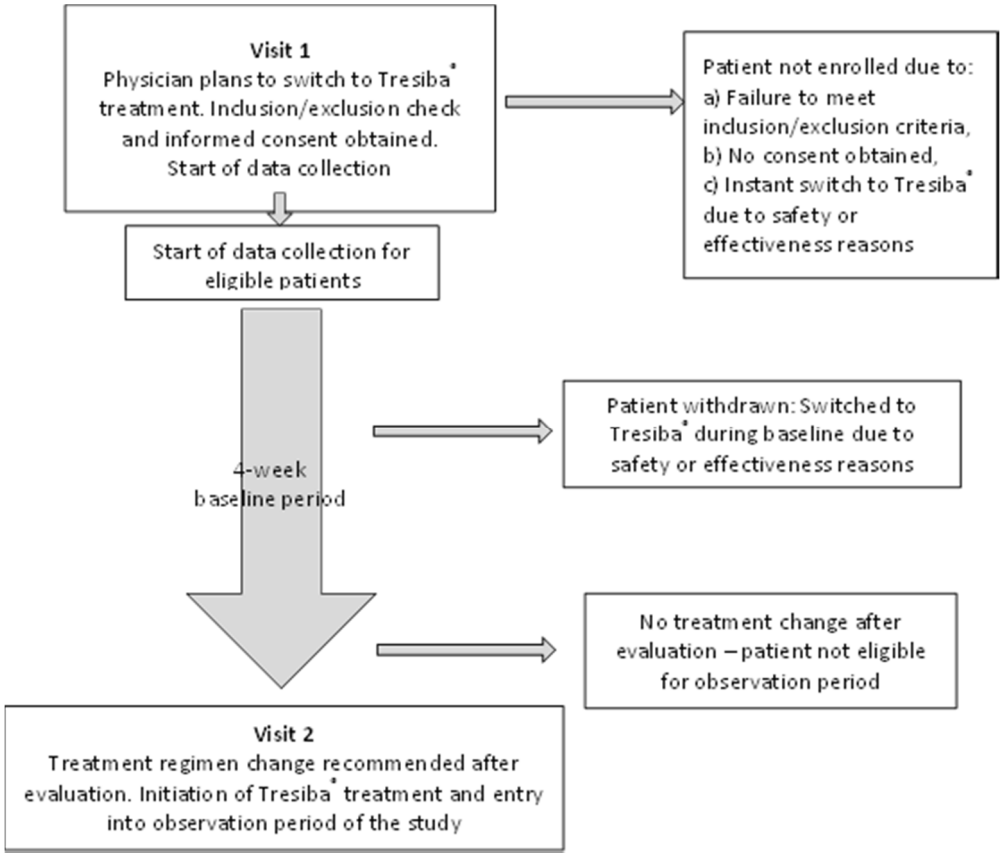
Abbreviations: OD = once daily; V = visit.
Grey arrows indicate 4-week periods when hypoglycaemic episodes were recorded prospectively in patient diaries. At visit 1 patients were asked to recall any severe hypoglycaemic episodes over the previous 6 months. Visits were defined as contact with health care provider (physician or nurse).

As specified in the SmPC[10], close glucose monitoring was recommended during the transfer from other insulin medicinal products and in the following weeks[10] and allowed individualised treatment to be provided according to local clinical practice and at the discretion of the physician. Using patient diaries, prospective clinical assessments for hypoglycaemia were performed leading up to visits at months 0, 3, 6, 9 and 12.

Visit 1 (-4 weeks) initiated the baseline period. Patients were instructed to continue their current therapy, including any diet and exercise recommendations, during the 4-week baseline period. During this time, physicians who planned to start the patient on Tresiba® treatment further evaluated the patient's glycaemic control based on reviewing patient diaries on hypoglycaemia and glycaemic control, in order to confirm the decision to switch treatment. This baseline period provided a portrait of the patient's risk of developing hypoglycaemia. Each patient acted as his/her own reference where the baseline period allowed assessment of hypoglycaemic episode rates on the current insulin and thus enabled comparisons with the hypoglycaemic episode rates after switching to Tresiba®. At visit 2 (month 0), at the end of the baseline period, patients were checked for eligibility to initiate Tresiba® treatment (according to the treating physician); only those patients who were switched to Tresiba® treatment (at the discretion of the treating physician) were entered into the observation period (see Figure 9-2). In clinical practice, some patients may have switched

insulin treatment immediately because they required instant changes to their treatment for safety or for effectiveness reasons. Other patients may not have changed treatment at all, after evaluation.

Figure 9-2 Flowchart of patient disposition during and after the 4-week baseline period



During each visit, patients were asked about any adverse events (AE) by the physician or study site staff. This could be done by posing a simple question such as "have you experienced any problems since the last visit?" However, only serious adverse drug reactions (SADR), medical events of special interest (MESI), pregnancies and severe hypoglycaemic events (regardless of physician's evaluation of seriousness or causality) were collected systematically in this study as specified in Table 9–1.

Clinical assessments (interviews and blood samples) were performed as part of routine clinical practice. These assessments were generally recognised as reliable, accurate and relevant to the indication, DM in adults. The biochemical assessments, fasting plasma glucose (FPG) and glycated haemoglobin A1c (HbA1c), were included in the analyses if available. They were not performed unless according to clinical practice at the site. The hypoglycaemia reporting and the PRO assessments could require some questions that were not part of standard routine care, and the PRO assessments were not part of routine clinical practice. Patient diaries included sections for recording

information such as details of hypoglycaemia, insulin dosage, dose-time flexibility, and health economics resource use.

All observational endpoints (see Section 9.1.1 and Section 9.1.2) were collected during the baseline period (4 weeks before Tresiba® treatment, month 0, at visits 1 and 2) and at the following time points after treatment initiation: 3 months (±45 days, visit 3), 6 months (±45 days, visit 4), 9 months (±45 days, visit 5), and 12 months (±45 days, visit 6), when available. Visits and data collections are outlined in Table 9–1. Visits were not protocol defined and were conducted as part of routine clinical monitoring of patients. It was not expected that all patients attended all visits.

In case a patient was being prematurely withdrawn from the study the physician had to ensure that the procedures for the last visit were recorded, if possible. The primary reason (adverse reaction or other) for discontinuation had to be specified in the electronic case report form (eCRF).

Table 9–1 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

Study NN1250-4189	Planning to initiate	Initiation	Observation period			
Concomitant medications	X	X	X	X	X	X
Reason for switching or not switching to Tresiba®		X				
First date on study insulin (Tresiba®)		X				
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 HbA1c 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[8]			X	X	X	X

Abbreviations: DTSQ = Diabetes Treatment Satisfaction Questionnaire; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin A1c; MESI = medical event of special interest; PRO = patient reported outcome; SADR = serious adverse drug reaction; SF-36 = Short Form-36; V = visit.

[1] Decision to initiate the study took 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) was not a safety problem for the patient. Patient material was handed out at visit 1 to explain the importance of the baseline reporting period. It was not guaranteed that all patients attended all visits.

[2] For anti-diabetic treatment, the insulin dosing regimen was also collected.

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

[4] Each SADR was reported on a separate AE and safety information form according to existing reporting procedures. MESI included 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 were encouraged to fill the PRO questionnaires, preferably before any other study related procedures.

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

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

9.1.1 Primary observational endpoint

The primary observational endpoint was 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 years of exposure (PYE), based on patient diary recorded data).

Hypoglycaemic episodes were collected during the study using a 4-week patient hypoglycaemia diary (collected at visits 2, 3, 4, 5, and 6).

9.1.2 Secondary observational endpoints

Endpoints are presented as per the Statistical Analysis Plan (SAP) owing to amendments to some secondary observational endpoints. Changes from the protocol are noted in the SAP, Section 8.0, Annex 1, Appendix 16.1.7. Changes since SAP approval are provided in Section 9.9.5.

9.1.2.1 Secondary observational effectiveness endpoints

The secondary effectiveness endpoints were:

- Change from baseline (visit 2) in FPG after 12 months of treatment
- Responder rates for HbA1c at the end of study (last visit in observation period):
  - 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 at end of study:

Country	T1DM	T2DM
Denmark	<58 mmol / mol (7.5%)	<58 mmol / mol (7.5%)
Germany	<58 mmol / mol (7.5%)	<58 mmol / mol (7.5%)
Italy	<53 mmol/mol (7.0%)	<53 mmol/mol (7.0%)
Spain	<53 mmol/mol (7.0%)	<53 mmol/mol (7.0%)
Sweden	<52 mmol/mol (6.9 %)	<52 mmol/mol (6.9 %)
Switzerland	<53 mmol/mol (7.0%)	<53 mmol/mol (7.0%)
The Netherlands	<53 mmol/mol (7.0%)	• if age <70 years - HbA1c ≤ 53 mmol/mol • if age ≥70 years and diabetes duration

Country	T1DM	T2DM
		• <10 years, then HbA1c ≤58 mmol/mol • if age ≥70 and diabetes duration ≥10 years, then HbA1c ≤64 mmol/mol
United Kingdom	≤48 mmol/mol (6.5%)	<53 mmol/mol (7.0%)

- Change from baseline (visit 2) in HbA1c at visits 3, 4, 5, and 6 (i.e., 3, 6, 9, and 12 months of treatment)
- Hypoglycaemia (incidence rates were based on the sum of visits 3, 4, 5 and 6 patient diary data for the 12-month observation period and based on the sum of visits 4, 5 and 6 patient diary data for the maintenance period):
  - Change from the baseline period in the number of hypoglycaemic episodes according to the American Diabetes Association (ADA) definition of hypoglycaemia (for definition see Section 9.4.2.1), during and after 12 months of treatment. Incidence rates were presented separately for:
    - Severe hypoglycaemia
    - Asymptomatic hypoglycaemia
    - Documented symptomatic hypoglycaemia
    - Pseudo-hypoglycaemia
    - Probable symptomatic hypoglycaemia
  - Change from the baseline period in the number of confirmed hypoglycaemic episodes according to the Novo Nordisk definition of hypoglycaemia (for definition see Section 9.4.2.1), during and after 12 months of treatment
    - Severe or blood glucose confirmed hypoglycaemia
    - Severe or blood glucose confirmed symptomatic hypoglycaemia
  - Change from the baseline period in the number of any hypoglycaemic episodes during the maintenance period (i.e., the period after 16 weeks of treatment until the end of treatment)
  - Change from the baseline period in the number of any nocturnal (00:01-05:59) hypoglycaemic episodes during the maintenance period
  - Change from the baseline period in the number of any nocturnal (00:01-05:59) hypoglycaemic episodes during and after 12 months of treatment
  - Change from the baseline period in the number of any hypoglycaemic episodes occurring during sleep in the time span 22.01-07.59 during and after 12 months of treatment
  - Change from the baseline period in the number of non-severe hypoglycaemic episodes during and after 12 months of treatment (for definition see Section 9.4.2.1)
  - Change from the baseline period in the number of any hypoglycaemic episodes in high-dose insulin users (defined as patients using >80 U daily at baseline) during and after 12 months of treatment

- Change from the baseline period in the number of any hypoglycaemic episodes in hypoglycaemia-prone (hypo-prone) patients (for definition see Section 9.4.1.1) during and after 12 months of treatment

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

9.1.2.2 Secondary observational safety endpoints

The following secondary safety endpoints were:

- Change from the baseline period (6-month recall, as per eCRF) in the number of severe hypoglycaemic episodes during and after 12 months of treatment (taken from AE data recorded throughout the study)
- 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 (taken from AE data recorded throughout the study)
- Frequency of treatment emergent AEs (TEAE) and serious AEs (SAE) during 12 months of treatment (taken from AE data recorded throughout the study). TEAEs included any AE that started after the start of Tresiba®

All data reported as counts were converted to rates per PYE for analysis purposes

9.1.2.3 Secondary observational patient-reported outcome endpoints

The health-related quality of life (HR-QoL) questionnaire (SF-36 version 2) and DTSQ, and change from baseline on each measure, as appropriate, after 12 months of treatment (see Section 9.4.7).

9.1.2.4 Health economic and dose-time flexibility observational endpoints

The following secondary health economic and dose-time flexibility endpoints were:

- Physicians' reasons for switching to treatment with Tresiba® (see Section 9.4.9)
- Physicians' reasons for not switching to treatment with Tresiba® (see Section 9.4.9)
- Change from baseline period (visit 2) in the following health economics endpoints after 3, 6, 9 and 12 months of treatment:
  - Number of times patient discussed hypoglycaemic event with physician or nurse
  - Number of treatments by a paramedic at home
  - Number of emergency room visits due to hypoglycaemia
  - Number of hospitalisations due to hypoglycaemia, and duration of hospitalisation
  - Duration of absence from work due to hypoglycaemia
  - Used self-measured blood glucose (SMBG) test strips and how many
  - Change from baseline period (visit 2) in daily insulin dose (total, Tresiba®, bolus) after the observation period (up to end of study)
- 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
- Dose-time flexibility endpoints were analysed as appropriate:
  - 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
  - Mean dosing time

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

9.1.2.5 Secondary observational endpoints for external study registration

The following secondary observational endpoints for external registration of the study at clincialtrials.gov and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register, were:

- 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® (see primary observational endpoint: Section 9.1.1)
- Change from baseline in HbA1c and FPG after 12 months (see secondary effectiveness endpoints: Section 9.1.2.1)
- Change from the baseline period in the number of severe hypoglycaemic episodes after 12 months (see Section 9.1.2.1)
- Change from baseline in HR-QoL questionnaire scores (PROs: SF-36 and DTSQ) after 12 months of treatment (see secondary PRO endpoints: Section 9.1.2.3)

9.2 Setting

This was a non-interventional (observational) study, conducted at 201 active geographical sites (Denmark, Germany, The Netherlands, Spain, Sweden, Switzerland, Italy, and United Kingdom). The subjects were treated with Tresiba® (100 units/mL / 200 units/mL) in a prefilled pen injector (FlexTouch®) for subcutaneous (SC) injection.

9.3 Patients

A broad population of patients with T1DM or insulin-using patients with T2DM was eligible for this study. Patients who met the eligibility criteria (Section 9.3.1) were eligible regardless of sex, race or ethnicity. Inclusion and exclusion criteria applied in this study ensured comparability of study results for a heterogeneous adult population of insulin-using patients with T1DM or T2DM.

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 were expected and did not exclude patients from participation in the study and the inclusion of their data in the primary and secondary observational endpoint analyses.

The inclusion criteria broadly reflected the real-world population of T1DM and T2DM patients, i.e., patients treated under conditions of routine care, eligible for Tresiba® treatment. Patients who were non-compliant with any of the inclusion/exclusion criteria, but were included in the study, had to be excluded immediately.

Informed consent was only valid for patients ≥18 years of age. The questionnaires were not designed for paediatric populations.

9.3.1 Inclusion criteria

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

1. Informed consent obtained before any study-related activities (study-related activities were 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®.

9.3.2 Exclusion criteria

Patients presenting with any of the following were not 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[10] or related products.
2. Previous participation in this study (i.e., provision of informed consent).
3. Patients who had previously been treated with Tresiba®.
4. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

9.3.3 Removal of patients from therapy or assessment

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

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

The physician was encouraged to inquired about the reason for discontinuation and recorded the reason in the eCRF. A discontinuation occurred when a patient who had provided informed consent ceased participation in the study, regardless of the circumstances, prior to collection of data on visit 6.

If the patient withdrew from the study no additional data could be collected. The sponsor could retain and continue to use any data collected before the withdrawal of consent.

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

9.3.4 Sources of patients

The target population was male or female patients aged ≥18 years, with either T1DM or T2DM (clinically diagnosed) and insulin-using prior to visit 1, who signed the informed consent form (ICF) and whose physician planned to start them on Tresiba® treatment were eligible for entry in this study. Inclusion of patients was solely at the discretion of the treating physician.

9.3.5 Methods of selection of patients

There was no specified target number of patients for each country; rather each country could continue to enrol patients until the overall study sample size was met.

The physician had to keep a patient enrolment log and a log of patients evaluated for but not included in the study throughout the enrolment period. These could be combined in 1 document.

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

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

Study-defined inclusion and exclusion criteria were considered while selecting the patients for the study (refer to Section 9.3.1 and Section 9.3.2).

9.4 Variables

The primary and secondary observational endpoints are described in Section 9.1.1 and Section 9.1.2.

9.4.1 Visit procedures

Visits were not protocol defined but based on the estimated regularity of visits to a treating physician under normal clinical practice. It was not expected that all patients would attend all visits.

9.4.1.1 Visit 1 (week –4) - Physician plans to initiate Tresiba®

The patient received complete information about the study, both orally and in writing. Informed consent had to be given prior to any study-related data being collected. The decision to treat patients was entirely based on the physician's discretion in accordance with local practice.

Visit 1 included:

- Signature of informed consent and recording of the date informed when consent was given.
- Determination of eligibility by checking the inclusion/exclusion criteria (Section 9.3.1 and Section 9.3.2).
  - Distribution of all PRO questionnaires (SF-36 and Diabetes Treatment Satisfaction Questionnaire – Status [DTSQs]) that were to be completed by the patient. This was done prior to any following steps. The questionnaires were administered while the patient was in the waiting room or another dedicated room.
- Documentation of demography (age, sex, ethnicity).
- Documentation of blood pressure (systolic and diastolic) and height measurements, if available.
- Documentation of body weight (kg), if available.
- Documentation of medical history.
- Documentation if the patient was hypo-prone. Hypo-prone patients were defined as having any of the below:
    - Experienced at least 1 severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013[9]).
    - 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 differed from the values stated).
    - Hypoglycaemic symptom unawareness (history of impaired autonomic responses [tremulousness, sweating, palpitations, and hunger] during hypoglycaemia).
    - For T1DM: DM duration for more than 15 years.
    - For T2DM: exposed to insulin for more than 5 years.
- Documentation of concomitant medications (related to diabetes, including insulin dosing regimen).
- Documentation if the patient was a high-dose insulin user (>80 U/day).
- Collection of the most recent HbA1c and FPG measurements and their date.
- Interviewing of patients to recall any severe hypoglycaemic episodes in the 6 months prior to this visit.

- Distribution of diary and guidance on its use.

Patients were instructed to:

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

An appointment was made for their next usual clinical visit (visit 2, initiation of Tresiba®) in approximately 4 weeks (+14 days).

9.4.1.2 Visit 2 (month 0) - Initiation/baseline

Visit 2 included:

- Check of inclusion and exclusion criteria, and whether any conditions for withdrawal (withdrawal criteria) were met (see Sections 9.3.1, 9.3.2 and 9.3.3).
- Distribution of all PRO questionnaires (SF-36 and DTSQs) that were to be completed by the patient. This was done prior to any following steps.
- Documentation of body weight (kg), if available.
- Documentation of concomitant medications, including current insulin dosing regimen.
- Collection of the most recent HbA1c and FPG measurements and their date.
- Collection of safety information. Patients were 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 were recorded on a separate AE form and safety information form (SIF) according to existing reporting procedures and timelines.
- Collection of diary and distribution of a new one.
- The patients were asked what their total daily dose of bolus insulin was on the day prior to the visit, if applicable.
- The patients were asked if their insulin treatment required them to change any social, leisure, and working time activities.
- Physician documented the reason for switching or not switching to Tresiba® treatment as applicable.
- Based on physician's discretion, patients commenced treatment with Tresiba®.

Patients were instructed to:

- Switch their basal insulin to Tresiba® and continue on other current therapies, 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 basal insulin dose, time, and date (over the 4 weeks prior to the next visit).
- Record in the diary if any doses were 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.

9.4.1.3 Visits 3, 4, 5 and 6 (months 3, 6, 9 and 12) - Observation period (standard routine visits)

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

These visits included:

- Check if patients met any of the conditions for withdrawal (Section 9.3.3).
- Distribution of all PRO questionnaires (SF-36 and DTSQs; Diabetes Treatment Satisfaction Questionnaire – Change [DTSQc] at visit 6 only) that were to be completed by the patient. This was done prior to any following steps. The questionnaires were administered while the patient was in the waiting room or another dedicated room.
- Documentation of body weight (kg), if available.
- Collection of the most recent HbA1c and FPG measurements and their date.
- The patients were asked what their total daily dose of bolus insulin was on the day prior to the visit, if applicable.
- The patients were asked if their insulin treatment required them to change any social, leisure, and working time activities.
- Documentation of concomitant medications, including current insulin dosing regimen.
- Collection of safety information. Patients were 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 was 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 were asked their preference for Tresiba® or their previous treatment.

Patients were 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 basal insulin dose, time, and date (for 4 weeks prior to the next visit).
- Record in the diary if any doses were 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.

9.4.1.4 Visit 6 (month 12) - End of study

Treating physicians performed and recorded details of the last visit as described in Section 9.4.1.3. Patients continued to be treated as directed by their physician. Patients were asked to return any diaries; after this visit no further data were collected. Patients were asked at the end of study visit which one they found easier to use, the FlexTouch® pen or the previous injection method.

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

9.4.2 Assessment of hypoglycaemic episodes

Hypoglycaemic episodes were collected during the study using a 4-week patient hypoglycaemia diary (collected at visits 2, 3, 4, 5 and 6). Each episode of hypoglycaemia was reported on a dedicated eCRF diary page.

Additionally, at visit 1, a six-month recall for severe hypoglycaemia was recorded. All severe hypoglycaemic episodes (regardless of physician's evaluation of seriousness and causality) were to be systematically reported on the AE form and the SIF.

9.4.2.1 Classification of hypoglycaemic episodes

The classification of hypoglycaemic episodes are specified below:

Severe hypoglycaemia

Severe hypoglycaemia was defined according to the ADA definition as an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions[9].

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

The definition of severe symptomatic hypoglycaemia included all episodes in which neurological impairment was severe enough to prevent self-treatment and which were 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) had to be systematically reported as safety information.

Non-severe hypoglycaemia

Non-severe hypoglycaemia was defined as an event in which the patient was able to treat themselves and included:

a) An event during which typical symptoms of hypoglycaemia were accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL).
   OR
b) An event during which symptoms of hypoglycaemia were not accompanied by a PG determination but was 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 were 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.

Nocturnal hypoglycaemia

Nocturnal hypoglycaemia was defined as any hypoglycaemia that occurred in the time span 00:01 and 05:59 hours.

Hypoglycaemia during sleep

Hypoglycaemia during sleep was defined as any hypoglycaemia that occurred in the time span 22:01 and 07:59 hours.

The ADA classifications and Novo Nordisk definition of hypoglycaemia are as follows:

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 could possibly not be available during an event, but neurological recovery following the return of PG to normal was 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 were accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reported 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 were not accompanied by a PG determination but that was presumably caused by a PG concentration ≤3.9 mmol/L (70 mg/dL).

Novo Nordisk definition of hypoglycaemia

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

- Total hypoglycaemia (severe or blood glucose confirmed) was defined as episodes that were 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 was defined as episodes that were 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 was defined according to the ADA classification as stated below.

Patients prone to hypoglycaemic episodes (i.e., hypo-prone patients) are defined in Section 9.4.1.1.

9.4.3 Assessment of HbA1c and FPG

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

9.4.4 Documentation of insulin dose and time of injection

Patients were provided with a study diary and requested to prospectively document daily basal insulin dose during the baseline period (between visits 1 and 2) followed by daily Tresiba® doses for 4 weeks prior to each physician visit (visits 3, 4, 5 and 6).

Previous basal insulin (baseline) and Tresiba® (visits 3, 4, 5 and 6) dosage details (time, amount and date of each dose) was recorded.

At each visit, the patient was asked what their total daily dose of bolus insulin was on the day prior to the visit, if applicable.

9.4.5 Self-measured blood glucose

Patients were 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 were not to be performed unless according to clinical practice at the site.

9.4.6 Assessment of body weight

Body weight (kg) measurements were collected. Patients had to 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 had to be used throughout the study.

9.4.7 Patient-reported outcomes

All PRO questionnaires were completed by the patients at every visit, preferably before any other study-related activities. All PROs were available in the local languages.

Health-related quality of life: General health status was assessed with the HR-QoL questionnaire SF-36 (version 2). The SF-36 consisted of 36 questions grouped into 8 domains termed: physical functioning; bodily pain; role-physical; general health; vitality; social functioning; role-emotional; and mental health.

Patients had to complete the SF-36 at every visit.

Diabetes Treatment Satisfaction Questionnaire: The DTSQs was used to assess how satisfied patients were with their treatment and how they perceived hyper- and hypoglycaemia in the real-world clinical setting. The DTSQs consisted of 8 questions, which were to be answered on a Likert scale from 0 to 6. The change version (DTSQc) had the same 8 items as the status version but was reworded to measure the change in satisfaction rather than absolute satisfaction.

Patients had to complete the DTSQs at visits 1, 2, 3, 4, 5 and 6 and the DTSQc at visit 6.

9.4.8 Assessment of health economic endpoints

Health economics endpoints were assessed using data from the patient diary (collected at visits 2, 3, 4, 5 and 6).

Patient diary: At visits 1, 2, 3, 4, and 5, patients were 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.

Patients were encouraged to record the following information:

- Number of times they had discussed a hypoglycaemic event with any physician or nurse.
- Number of treatments at home by a paramedic due to hypoglycaemia.
- Number of emergency room visits due to hypoglycaemia.
- Number of hospitalisations due to hypoglycaemia and duration of hospitalization.
- Duration of absence from work due to hypoglycaemia.
- Number of SMBG test strips used.

9.4.9 Reason for switching or not switching to Tresiba®

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

9.4.10 Assessment of flexibility of dose-time

Patients were 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 were asked to record/indicate information such as:

- If they missed a dose.
- Why they missed a dose.
- What they did when they missed a dose.

At visits, physicians also asked patients the following:

- How often they needed to take their Tresiba® at a different time.
- How often they needed to use the possibility of dose-time flexibility.
- At visits 2-6, patients were asked if their insulin treatment required them to change any social, leisure and working time activities.

The effects of dose-time flexibility on compliance and effectiveness were measured by collecting data from patient diaries.

9.4.11 Assessment of patient preference for Tresiba® and FlexTouch® pen device

At each physician visit after initiation of Tresiba® treatment (visits 3, 4, 5 and 6), the physician asked for the patients' preference for Tresiba® or their previous treatment and entered the response into the eCRF.

Patients were also asked which one they found easier to use, the FlexTouch® pen or the previous injection method.

9.4.12 Serious adverse drug reactions, MESIs and pregnancies

The following safety information was systematically collected: SADRs, severe hypoglycaemic events (regardless of physician's evaluation of seriousness or causality) (see Section 9.4.2 for reporting and definition), MESI (medication errors), pregnancies in female patients including the outcome, and safety information required by local laws and/or IECs/institutional review boards (IRB). These were recorded throughout the study, from the signature of the ICF until the end of the study as defined by the protocol for that patient (see protocol Section 10, Annex 1, Appendix 16.1.1).

All SADRs were coded using the latest version of MedDRA dictionary.

9.4.13 Management and reporting of adverse events/reactions

Voluntary reporting of any AE information other than the systematically collected safety information described in Section 9.4.12 was at the physician's discretion.

9.4.13.1 Definitions

Adverse reaction

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

An AR 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 AR is either a serious adverse reaction (SAR) or a non-serious AR (for definitions, see below).

This includes ARs 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 was known, were not to be reported as ARs 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®

An AR or AE is defined as a SAR or SAE, respectively, if the reaction or event results in any of the following seriousness criteria:

- Death
- A life-threatening* experience
- In-patient hospitalisation or prolongation of existing hospitalisation**
- A persistent or significant disability/incapacity***
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening* or require hospitalisation** 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****. This also includes suspected transmission of an infectious agent via a study product.

*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.

**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 ARs or events and should therefore not be reported as ARs or events including SARs or events. Likewise, hospital admissions for surgical procedures planned prior to study inclusion are not considered ARs or events including SAEs or reactions.

***A substantial disruption of a patient's ability to conduct normal life functions, e.g., 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.

****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 AR 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 met a seriousness criterion, the AR or AE had to be reported as a SAR 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 AR or AE. Outcomes of other reported AR or AE in a patient before he/she died were to be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An AR or AE with fatal outcome had to reported as a SAR 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 the safety of the medicinal product, had a special focus. In the present study medication errors concerning Tresiba® were defined as MESIs. Medical events of special interest were reported as follows:

- Administration of wrong drug or use of wrong device

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

9.4.13.2 Collection and reporting of safety information

Safety information had to be reported by the physician on the electronic/paper AE form. At each visit, patients were asked about AEs, e.g.: "Have you experienced any problems since the last contact?" Only the safety information listed in Section 9.4.12 had to be reported systematically. SADRs and severe hypoglycaemic episodes (regardless of the physician's evaluation of seriousness and causality) were reported using forms within the electronic data capture (EDC) application. MESIs were reported using forms in the paper format. The physician had to report initial information for SADRs, severe hypoglycaemic episodes and MESIs to Novo Nordisk **within 24 hours** of his/her knowledge of the event and to provide further information **within 5 calendar days**. Follow-up information concerning these types of events was to be reported by the physician **within 24 hours** of his/her knowledge and **within 14 days** for follow-up information requested by Novo Nordisk.

All systematically collected safety information had to be followed until the outcome of the event was "recovered", "recovered with sequelae" or "fatal" and all queries were resolved. Cases of chronic conditions, cancer or SAR ongoing at the time of the death (i.e., the patient died from another SAE) could be closed with the outcome of "recovering" or "not recovered". Cases could be closed with an outcome of "recovering" when the patient completed the observation period and was expected by the physician to recover.

9.4.13.3 Collection and reporting of pregnancies in female patients

In female patients, pregnancy had to be reported **within 14 calendar days** of the physician's first knowledge of the pregnancy using the applicable paper pregnancy forms. Follow-up information on the foetus or newborn infant from a pregnancy in a patient had to be collected at 1 month of age at the earliest. Information had to 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 were to be collected and reported regardless of causality assessment.

The reporting timelines for reporting AEs in the foetus or newborn infant were the same as described in Section 9.4.13.2.

9.5 Data sources and measurement

The study was based on prospectively collected clinical data and PROs as part of normal clinical practice. Physicians, or an appropriately qualified and trained delegate, entered anonymised data from the patient's medical records, diaries, questionnaires and interviews into the eCRF.

Medical records

Patients' medical records were updated as per normal clinical practice (e.g., with results of any measurements taken, concomitant medication, and any new concomitant illnesses).

The following data were entered in the eCRF: Demography, vital signs and body measurements (weight), diagnosis of diabetes, medical history/ concomitant illness, anti-diabetic treatment, concomitant medications, FPG, HbA1c, and total daily of bolus insulin.

Patient diaries

Each patient was given study diaries and was provided guidance in their use. The first diary covered 4 weeks of baseline data (between visits 1 and 2) and the remaining diaries covered the 4 weeks prior to each physician visit (visits 3-6). At the visit following completion of the diary, the patient returned his/her diary and was given a new diary. Data from the diary were entered into the eCRF. The diary was kept in the source files at the investigational site.

The 4-week diaries included sections for information such as:

- Basal 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 had a symptom of hypoglycaemia or his/her blood sugar level was below or equal to 3.9 mmol/L (70 mg/dL), the patient was encouraged to complete a hypoglycaemia page to include the exact time, PG value, resource use, symptoms, and whether assistance was required or not.

Patient questionnaires

Patients were encouraged to complete PRO questionnaires (SF-36, DTSQs and DTSQc) and other non-clinical assessments that were not part of standard routine care, in order to ensure fulfilment of the study objectives.

Patient interviews

Patients were asked about any AEs (only SADRs, MESIs, pregnancies, and severe hypoglycaemic episodes [regardless of physician's evaluation of seriousness and causality]) were systematically reported by the physician) and provide details of any other medication they received.

9.6 Bias

The source population of the current study was limited to eligible patients from the sites included in the study, which might introduce selection bias, as there may be a selection in both the sites and the patients who consented to participate in a study. In order to minimise potential reporting and prescribing bias and to ensure face validity of the study, the physicians enrolled patients who they planned to switch to Tresiba® over a similar time frame (approximately 6 months) within each country.

The inclusion criteria were made deliberately broad to reflect the real-world diabetic population. However, the use of diaries and questionnaires in this study might have biased data towards patients who were better able to monitor and maintain a diary, either through socio-economic or educational reasons, and thus maintained improved blood glucose. It was anticipated that the broad inclusion criteria would provide data from patients with widely varying efficiency for maintaining diaries and completing questionnaires, and thus reduced the impact of this bias.

This was a single-armed study where the patients acted as their own control and thereby the risk of confounding was minimised. However residual confounding may have existed for things that change over time such as use of other anti-diabetic medications, lifestyle, compliance to treatment, and awareness of hypoglycaemia. Adjustments were not made for these factors and this may have biased the results away from the null hypothesis. The statistical phenomenon of regression to the mean also may have biased results away from the null hypothesis. There may have been a placebo effect. Additionally, due to the single-arm study design the treatment effect could not be separated from the study effect.

For details of selection bias as a limitation of the research methods used, see protocol Section 8.9, Annex 1, Appendix 16.1.1.

9.7 Study size

The sample size calculation was based on the primary observational endpoint, which was 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 was operationalised as the mean of the per-patient paired differences in hypoglycaemic episodes/PYE.

For both T1DM and T2DM, the mean of paired differences was 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 switched to Tresiba® and completed the 12-month observation period was $n_{T1DM}=n_{T2DM}= 517$. 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 needed 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 excluding Germany were pooled. Analysis on data from the patients in Germany up to the discontinuation date was specified in the SAP, Annex 1, Appendix 16.1.7.

9.8 Data transformation

9.8.1 Data management

Data from individual patient's charts were remotely collected through a password-protected web-based EDC system. The prescribing physician or an authorised and appropriately trained delegate entered the data into the web-based eCRF based on the individual patient's charts. No source documents were sent off-site. To protect privacy, data were anonymised and processed in accordance with local regulations regarding privacy protection. Appropriate measures such as encryption of data files had to be used to ensure confidentiality of patient data when it was transmitted over open networks.

9.8.2 Case report forms and rules for completing

CISIV provided a system for EDC. This system and support services for the system were supplied by [redacted] The activities of [redacted] were under the direction and supervision of Novo Nordisk.

Pregnancy and MESI forms were paper-based and were supplied by Novo Nordisk. Data collected on these forms were entered into the into the database.

An eCRF was required and had to be completed for each included patient. The treating physician was responsible for the accuracy and authenticity of all clinical safety and laboratory data entered into the eCRFs. In most cases, the source documents were the physician's patient chart. The physician was to ensure that all relevant questions were answered and that there were no empty data blocks.

If a test/assessment had not been done and was not available, or if the question was irrelevant (e.g., was not applicable) this had to be indicated according to the instructions for completing eCRFs.

By signing the affirmation statement electronically, the physician confirmed that the information was complete and correct.

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

9.8.3 Corrections to case report forms

Data in the eCRF could be corrected by the physician or the physician's authorised staff. For PROs, the patient was responsible for notifying the physician of any errors which could then be corrected in the eCRF by the physician or the physician's authorised staff. An audit trail was 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 were made by the physician's authorised staff after the date of the physician's signature on the affirmation statement, the statement had to be signed again by the physician.

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

Corrections to the data on the CRFs could only be made by drawing a straight line through the incorrect data and by writing the correct value next to data that had been crossed out. Each correction had to contain initials, date and explanation (if necessary) by the physician or the physician's authorised staff. If corrections were made by the physician's authorised staff after the date of the physician's signature on the affirmation statement, the statement had to be signed and dated again by the physician.

Corrections necessary after the CRFs had been removed from the physician's site had to be documented on a data clarification form. Such corrections had to be approved by the physician or her/his authorised staff.

9.8.4 Electronic case report form flow

The physician had to ensure that data was recorded in the eCRFs as soon as possible after the visit (preferably within 5 days if source data was available otherwise in connection to the visit of obtaining data). When data was entered, it became available to [redacted] for data verification activities.

Data were to be archived by Novo Nordisk upon availability of the final non-interventional study report.

9.9 Statistical methods

A fully developed SAP was prepared for this study that expanded on details provided in the protocol (see Annex 1, Appendix 16.1.7). All details outlined below are based on the SAP. Changes in the statistical analysis from the protocol to the SAP are summarised in SAP Section 8, Annex 1, Appendix 16.1.7. Additional analyses and post-hoc analyses are described in Section 9.9.5.

9.9.1 Main summary measures

9.9.1.1 Primary analysis of the primary observational endpoint

The primary observational endpoint was the change from the baseline period in the number of any hypoglycaemic episodes occurring during the 12-month observation period with Tresiba®, analysed as the change in incidence rate per patient year of exposure.

For purposes of descriptive statistics, the endpoint was calculated as the change in patient-paired differences and was summarised, as number of observations with available values, mean (of paired differences), 95% confidence interval (CI) of the mean, standard deviation, minimum, median, and maximum.

Incidence rates of hypoglycaemia were calculated for patients who had recorded a diary observation period between 26-30 days in duration, where the dates recorded on the 'hypo page' matched exactly the date on the diary. Descriptive statistics presented the incidence rate for both the baseline period and the 12-month observation period, as well as the crude risk difference for both T1DM and T2DM.

Negative binomial regression models specifying a log-transformed follow-up time offset term were used to examine the change in incidence rate of any hypoglycaemic events between 4 weeks before and 12 months after baseline (using all available diary data for patients who had recorded a diary observation period between 26-30 days in duration, where the dates recorded on the diary page matched exactly the date on the diary), using actual count data for each patient. The analytic approach carried out for analysis of T1DM and T2DM patients to calculate both crude (period only) and adjusted (all possible variables included in the same model) incidence rate ratios is detailed in SAP Section 7.1.2, Annex 1, Appendix 16.1.7. In addition, as a post-hoc analysis (detailed in Section 9.9.5), the crude model (period only) was carried out on all patients included in the fully-adjusted model. The estimated negative binomial regression coefficients for the model and associated 95% CI and p-value as well as the number of observations included in the model were presented.

The primary analysis was performed on the full analysis set (FAS), excluding patients from Germany, by diabetes type.

9.9.1.2 Analysis of the secondary observational effectiveness endpoints

The secondary effectiveness endpoints are described in Section 9.1.2.1).

The secondary observational endpoints of change from baseline in FPG and HbA1c, respectively, at each post-baseline timepoint (visits 3, 4, 5 and 6) were assessed following an analysis of covariance approach using a mixed model for repeated measurements (MMRM) model. Both crude (only baseline FPG/HbA1c and period) and adjusted (all possible variables included in the same model)

estimates were presented with corresponding 95% CIs and p-values. Additionally, as a post-hoc analysis, crude model estimates based on patients with full set of covariates (only baseline FPG/HbA1c and period in the model) were presented with corresponding 95% CIs and p-values. The analytic approach carried out for analysis of T1DM and T2DM patients is detailed in SAP Section 7.2.2, Annex 1, Appendix 16.1.7. Descriptive statistics were provided for FPG and HbA1c at all study visits. Change from baseline in FPG and HbA1c was summarised together with the 95% CI for the mean change from baseline. MMRM was tabulated for both FPG and HbA1c by diabetes type (T1DM and T2DM).

The frequency and percentage of responders for HbA1c at the end of study (last visit in the observation period) were calculated. In addition, the frequency and percentage of responders for HbA1c at visit 6 was analysed for HbA1c <7% and HbA1c <7.5%. The responder rates for HbA1c were tabulated by diabetes type (T1DM and T2DM).

The secondary variables of change from baseline in number of hypoglycaemic events were analysed and presented as per the primary observational endpoint (see Section 9.9.1.1). All secondary effectiveness endpoints were analysed for the FAS excluding patients from Germany, by diabetes type.

9.9.1.3 Analysis of the secondary observational safety endpoints

The secondary safety endpoints are described in Section 9.1.2.2).

The change from the baseline period in the number of severe hypoglycaemic episodes during 12 months of treatment was analysed and presented in a fashion analogous with the primary observational endpoint (see Section 9.9.1.1). Severe hypoglycaemic episodes were recorded throughout the study, identified as 'Is the AE a Severe Hypoglycaemic Episode?'=Yes. The baseline period was the 6-month baseline recall.

Body weight was analysed using an MMRM model and presented as per the secondary effectiveness endpoints (see Section 9.9.1.2).

Frequency counts, percentages and rate of occurrence were calculated for SADRs, MESIs and pregnancies during 12 months of treatment. TEAEs and SAEs, as well as treatment-related TEAEs and TEAEs leading to discontinuation were presented in the same way. Frequency tabulations for these events were presented and included the number, percentage and rate of occurrence.

All secondary safety endpoints were analysed for the FAS patients outside Germany and for patients from Germany, by diabetes type.

9.9.1.4 Analysis of secondary observational patient-reported outcome endpoints

The validated HR-QoL questionnaire (SF-36) and DTSQ were used to ascertain PRO endpoints.

The SF-36 measure eight domains that can be combined to give 2 summary component scores. Each domain and summary component scores could take values between 0-100, where a higher score indicated less disability.

The DTSQs consisted of 8 questions, which were to be answered on a Likert scale from 0 to 6. 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.

The change version (DTSQc) had the same 8 items as the DTSQs but was reworded to measure the change in satisfaction rather than absolute satisfaction. Each DTSQc item was scored on a scale of –3 to +3. DTSQc total scores range potentially from -18 to +18, while DTSQc difference scores range potentially from -36 to +36. Thus, a positive score indicates improvement in total or individual domain[11].

The DTSQc, used in conjunction with the DTSQs, overcomes the problem of ceiling effects encountered when only the status measure is used and provides a means for new treatments to show greater value than is possible with the DTSQs alone[11].

The HR-QoL questionnaire (SF-36) and DTSQ were analysed as per the instrument instructions (see SAP Section 12.3, Annex 1, Appendix 16.1.7).

Descriptive statistics were provided for each domain in the SF-36 as well as the two component scores, DTSQc and DTSQs, at all study visits. For DTSQs, total score and perceived hypoglycaemia were presented. Change from baseline was summarised together with the 95% CI for the mean change from baseline.

9.9.1.5 Analysis of health economic and dose-time flexibility observational endpoints

The secondary observational endpoints presented in Section 9.1.2.4 were analysed.

All observed and change from baseline data were presented by diabetes type and visit.

Frequency counts and percentages were calculated for patient preference compared to previous treatment (calculated at visits 3, 4, 5 and 6), patient preference of FlexTouch® pen compared to previous injection method before Tresiba® use (calculated at visits 3, 4, 5 and 6), reason for missed dose and action taken when dose missed (calculated at baseline and at visits 3, 4, 5 and 6), and changes in any social, leisure, and working activities due to insulin treatment at all visits.

The number of times Tresiba® flexibility option used was summarised descriptively at follow-up. Frequency tabulations for patient preference data, reason for missed dose and action taken were presented. The changes in any social, leisure, and working activities due to insulin treatment were presented as frequencies and percentages in a shift table.

Physicians' reasons for switching or not switching to treatment with Tresiba® were analysed for the DPO population (see Section 9.9.2.1) by diabetes type, excluding patients from Germany and Germany alone. Whilst the physicians' reasons for switching to treatment with Tresiba® were analysed for the FAS population by diabetes type, excluding patients from Germany and Germany alone. All other health economic and dose-time flexibility endpoints were analysed by diabetes type, for the FAS excluding patients from Germany.

9.9.1.6 Analysis of secondary observational endpoints for external study registration

The endpoints for analyses included for external study registration are provided in Section 9.1.2.5; these were exact repeats of the endpoints indicated. These were not additional analyses.

9.9.1.7 Subgroup analyses

The primary observational endpoint was analysed for the subgroups defined on the basis of the following categorized variables:

- Duration of DM: Quartiles (Q1, Q2, Q3, Q4)
- Baseline Bolus: With bolus, without bolus
- Country: Denmark, Netherlands, Spain, Sweden, Switzerland, Italy and United Kingdom
- Baseline HbA1c categories: <7.5; 7.5-<8.5; 8.5-<9.5; ≥9.5
- Reason for switching to Tresiba®: Yes/No to hypoglycaemia

Subgroup analyses were performed by diabetes type, for the FAS excluding patients from Germany.

9.9.2 Main statistical methods

9.9.2.1 Analysis sets

All patients who signed informed consent were included in the 'All Enrolled Patients' population.

Due to the cessation of the distribution of Tresiba® in Germany, German patients were analysed separately from other country data.

The following populations were defined for all countries excluding Germany, and Germany alone:

- Patients who were found to be ineligible, dropped out prior to switching, or who switched early to Tresiba® or who confirmed that they were not considering switching to Tresiba®, were included in the DPO. The DPO included all patients that were excluded from the FAS.
- The FAS included all patients who received at least 1 dose of Tresiba® at or after the initiation visit and who did not take Tresiba® before the initiation visit. The FAS, excluding patients from Germany, was the primary analysis set.

- The safety population was the same as the FAS and therefore all further analyses were completed using the FAS. Patients who switched to Tresiba® prior to visit 2 were not included in the FAS, as there was no follow-up safety data recorded for these patients.

9.9.2.2 Statistical methodology

All statistical tests were performed as 2-sided tests with a significance level of 0.05.

For continuous variables, descriptive statistics included the number of patients (n), the number of patients with missing data (n_{miss}), mean, standard deviation, median, minimum and maximum. Wherever relevant, 2-sided 95% CIs were calculated for mean changes from baseline. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e., added up to 100%. The number of missing values was specified for each categorical variable.

All summaries were presented by T1DM and T2DM patients. Selected summaries were presented by subgroup categories.

All summaries were produced for pooled countries, unless otherwise stated.

9.9.2.3 Analysis timepoints

Visit 1 (Planning to initiate Tresiba® visit) occurred when the patient was enrolled and informed consent for the study was provided, but prior to switching to Tresiba®. Visit 2 (Initiation of Tresiba®/baseline visit) occurred after the patient had been followed up for 4-6 weeks. At that point, the patient was either switched to Tresiba® or discontinued from the study. A baseline value was therefore defined as the final measure recorded prior to switching to Tresiba®.

For baseline medications, the baseline period was defined as the time between visit 1 and the day prior to visit 2. For analyses based on diary data, the baseline period was the time between the first and last diary entry prior to visit 2.

Analyses did not exclude patient data due to the patient's failure to comply with the visit schedule. However, data that were recorded for visits between day 2 and day 45 (i.e., between scheduled visits 2 and 3) and after day 410 (i.e., after scheduled visit 6), including associated diaries, were only listed and not included in the statistical analysis tables, with the exception of the sensitivity analyses. For assessment windows, see SAP, Section 7.8.2, Annex 1, Appendix 16.1.7.

9.9.3 Missing values

Imputation of missing data occurred in cases where the imputation was self-evident, e.g., if a patient had a missing value for 'Did you have any symptoms?' but there were 'Symptoms' recorded for this patient, the missing value was imputed to Yes.

Other imputations were not planned since analyses were based on observed data only.

All imputations were detailed in the Analysis Dataset Specifications.

9.9.4 Sensitivity analyses

Sensitivity analyses were performed on the FAS, excluding patients from Germany.

An additional analysis presenting the number and proportion (with Clopper-Pearson 95% CI) of patients having a hypoglycaemic event, number of events, follow-up time (patient years), estimated incidence rate with corresponding exact 95% CI, and number of patients missing was performed for the 4 weeks before and 12 months after baseline.

The primary analysis was based on patient diary data collected during the observation period between 26-30 days in duration, where the dates recorded on the diary page with details of the hypoglycaemic event were recorded and matched exactly the date on the diary. Due to the nature of patient-reported diary data, the following sensitivity analyses were performed:

- Sensitivity analysis 1: Based on diary periods with 26-30 days, where the dates of hypoglycaemic events recorded on the 'hypo page' fell within the diary period.
- Sensitivity analysis 2: Based on all diaries (except those with missing duration), where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly the diary data.
- Sensitivity analysis 3: Based on all diaries (except those with missing duration), where the dates of hypoglycaemic events recorded on the 'hypo page' fell within the diary period.

A fourth sensitivity analysis was performed to determine the robustness of the primary analysis and the impact of any missing data:

- Sensitivity analysis 4: Based on diary periods with 26-30 days, where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to diary data for patients who completed 12 months observation, i.e., attended visit 6 and completed at least 23 diary days for each diary period during the 12 months observation period.

The sensitivity analyses were conducted as per the primary observational endpoint (see Section 9.9.1.1).

Descriptive statistics presented the incidence rate for both the baseline period and the 12-month observation period, as well as the crude risk difference for both T1DM and T2DM. The estimated negative binomial regression coefficients for the model and associated 95% CI and p-value as well as number of observations included in the model were presented.

9.9.5 Amendments to the Statistical Analysis Plan

The following are changes to the statistical analyses that were described in the protocol and that are not described in Section 8 of the Final Statistical Analysis Plan v2.0 (20 March 2018):

- Anti-diabetic treatment during the baseline period and during the observation period were presented
- Insulin treatment during the baseline period and during the observation period were presented
- Exposure of Tresiba® for patients identified as completed per the end of treatment form was presented
- Summary of HbA1c responder rates for patients who had a visit 6 was presented

The following are changes to the statistical analyses that are not described in the Final Statistical Analysis Plan v2.0 (20 March 2018):

- Time-varying categorical covariates were removed from the MMRM and negative binomial regression models due to the nature of the endpoints (ie summation of the post-baseline events).
- Dosing time by diary period was presented instead of the mean dosing time to allow for further analyses.

9.10 Quality control

The CRO conducted periodic site monitoring at least monthly, via telephone contacts and visits, to ensure that the protocol and Good Pharmacoepidemiology Practice and Good Pharmacovigilance Practice guidelines were being followed. Two sites (both in the United Kingdom) were audited during this study: site [redacted] was audited on [redacted] and site [redacted] was audited on [redacted] The monitors could review source documents to confirm that the data recorded in the eCRFs and in paper-based MESI and pregnancy forms were accurate. The monitors ensure that the eCRFs were complete; this could be performed remotely or on site. The treating physician and institution allowed Novo Nordisk monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

More than 10000 queries were raised during the study period. Approximately 5% of all queries (including German patients and non-responsive sites) were unresolved at database lock. Unresolved queries were recorded on an Unresolved Queries Log as 'Not answered'.

There were cases where documentation of anti-diabetic treatments by the sites was incomplete. On-site monitoring of source documentation for all enrolled patients confirmed that all patients received at least one insulin treatment during the baseline period and that all patients received at least 1 dose of Tresiba®. As instructed in the protocol, patients not meeting these criteria were excluded from the FAS. Given the inclusion criteria were met, patients were enrolled per the protocol inclusion criteria.

10 Results

10.1 Participants

Overall, 690 T1DM patients and 784 T2DM patients were enrolled in the study; of these, 606 T1DM patients and 661 T2DM patients were enrolled outside Germany (Table 10–1).

For the FAS outside Germany, 8.3% of T1DM patients and 7.6% of T2DM patients dropped out of the study prior to the observation period. The most frequent reasons for dropping out of the study prior to the observation period for the FAS outside Germany were: withdrawal by patient (4.0% of T1DM patients and 2.3%of T2DM patients), patient lost to follow-up (1.8% of T1DM patients and 2.7%of T2DM patients), and ”other” (1.7% of T1DM patients and 1.5% of T2DM patients).

The FAS comprised of patients outside Germany included 91.7% of all enrolled T1DM patients and 92.4% of all enrolled T2DM patients. Of these, 12.6% of T1DM patients and 11.0% of T2DM patients discontinued the study. The most frequent reasons for discontinuing the study were: withdrawal by patient (5.9% of T1DM patients and 2.9% of T2DM patients) and “other” (3.6% of T1DM patients and 3.3% of T2DM patients).

Of note, 0.7% of T1DM and T2DM patients each discontinued from the study due to AEs.

Table 10–1 Overall patient disposition (All Enrolled Patients)

	T1DM (N=690) n (%)	**T2DM (N=784) n (%)**
All Enrolled	690	784
All Enrolled - excluding Germany	606	661
Dropouts Prior to Observation Period - excluding Germany [1] [2]	50 (8.3)	50 (7.6)
Reason for Dropout Prior to Observation Period		
Adverse Event	0	0
Protocol Violation	2 (0.3)	2 (0.3)
Lost to Follow Up	11 (1.8)	18 (2.7)
Pregnancy	1 (0.2)	0
Withdrawal by Patient	24 (4.0)	15 (2.3)
Product no Longer Reimbursed	0	1 (0.2)
Other	10 (1.7)	10 (1.5)
No End of Study Form	2 (0.3)	4 (0.6)
Missing	0	0
Full Analysis Set - excluding Germany [1] [3]	556 (91.7)	611 (92.4)
Study Discontinuation - excluding Germany [4]		
Yes	70 (12.6)	67 (11.0)
No	486 (87.4)	544 (89.0)

	T1DM (N=690) n (%)	T2DM (N=784) n (%)
Reason for Discontinuation - excluding Germany		
Adverse Event	4 (0.7)	4 (0.7)
Protocol Violation	2 (0.4)	0
Lost to Follow Up	8 (1.4)	16 (2.6)
Pregnancy	2 (0.4)	0
Withdrawal by Patient	33 (5.9)	18 (2.9)
Product no Longer Reimbursed	0	0
Other	20 (3.6)	20 (3.3)
No End of Study Form	1 (0.2)	9 (1.5)
Missing	0	0

[1] Percentages were calculated using the number of enrolled patients (excluding Germany), which included all patients who signed informed consent.

[2] Patients who were found to be ineligible, dropped out prior to switching, or who switched early to Tresiba® or who confirmed that they were not considering switching to Tresiba®, were included in the Dropouts Prior to Observation Period (DPO).

[3] The full analysis set (FAS) included all patients who received at least 1 dose of Tresiba® at or after initiation visit and Tresiba® was not taken before initiation visit.

[4] Percentages were calculated using the number of patients in the FAS (excluding Germany) as the denominator. Patients with no End of Study form were counted as having discontinued.

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.1.1.1

Patients by analysis visit are summarised in Table 14.1.1.3.1 (outside Germany). The number of patients by visit during the study period ranged from 556 (100%) at baseline to 412 (74.1%) at visit 5 for the T1DM patients and from 611 (100%) at baseline to 491 (80.4%) at visit 6 for the T2DM patients. At month 12, there were 74.1% of T1DM patients and 80.4% of T2DM patients. The proportion of patients who returned diaries during the study period ranged from 65.1% to 98.4% for T1DM patients and 71.0% to 95.7% for T2DM patients. At month 12, 65.1% of T1DM patients and 71.0% of T2DM returned their diaries.

For patients from Germany, analysis visit is summarised in Table 14.1.1.3.2.

Patient disposition by country is summarised in Table 14.1.1.2, patients enrolled by country and site are summarised in Table 14.1.4.3.1 (outside Germany) and Table 14.1.4.3.2 (from Germany).

Individual data of inclusion/exclusion criteria are shown in Annex 2, Listing 16.2.4.1.2. Individual data of analysis sets and analysis visits are shown in Annex 2, Listing 16.2.3.1 and Listing 16.2.4.1.3, respectively. Individual data of patients who were non-completers are shown in Listing 16.2.1.4.2.1 with further details in Listing 16.2.1.4.2.2.

10.2 Descriptive data

10.2.1 Demographics

Patient demographics for the FAS outside Germany are summarised in Table 10–2.

In the T1DM group, the mean age at enrolment was 47.4 years and the majority of patients were younger than 65 years (83.3%). The majority of patients were male (55.8%) and not of Hispanic or Latino ethnicity (85.3%).

In the T2DM group, the mean age at enrolment was 65.2 years and the majority of patients were at least 65 years of age (56.3%). The majority of patients were male (59.6%) and not of Hispanic or Latino ethnicity (73.2%).

Table 10–2 Demographics (Full Analysis Set – excluding Germany)

	T1DM (N=556) n (%)	T2DM (N=611) n (%)
Age (years) [1]		
n	556	611
Mean	47.4	65.2
SD	15.70	9.59
Minimum	18	26
Q1	35.0	59.0
Median	47.0	66.0
Q3	59.0	71.0
Maximum	87	91
Age Group, n (%)		
n	556	611
<65 years	463 (83.3)	267 (43.7)
≥65 years	93 (16.7)	344 (56.3)
Sex, n (%)		
n	556	611
Male	310 (55.8)	364 (59.6)
Female	246 (44.2)	247 (40.4)
Ethnicity, n (%)		
n	556	611
Hispanic or Latino	82 (14.7)	164 (26.8)
Not Hispanic or Latino	474 (85.3)	447 (73.2)

Percentages were calculated using the number of patients with non-missing values as denominator.

[1] Age= (Date of Informed consent - Date of Birth)/365.25. If only year of birth recorded,

Age= (Year of Informed consent - Year of Birth).

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.1.4.1.2.1

Patient demographics for the FAS from Germany are summarised in Table 14.1.4.1.2.2.

Patient demographics for DPO outside Germany were generally similar to the FAS outside Germany (Table 14.1.4.1.1.1). In the T1DM group, the mean age at enrolment was 41.3 years and the majority of patients were younger than 65 years (46 [92.0%]). The majority of patients were male (26 [52.0%]) and not of Hispanic or Latino ethnicity (45 [90.0%]).

In the T2DM group, the mean age at enrolment was 66.4 years and the majority of patients were at least 65 years of age (28 [56.0%]). The majority of patients were male (36 [72.0%]) and not of Hispanic or Latino ethnicity (37 [74.0%]).

Patient demographics for DPO from Germany are summarised in Table 14.1.4.1.1.2.

Individual demographic data are shown in Annex 2, Listing 16.2.4.1.1.

10.2.2 Baseline characteristics

Patient baseline characteristics for the FAS outside Germany are summarised in Table 10–3.

In the T1DM group, the proportion of patients with glycaemic control at baseline was 19.2% according to a threshold of <7.0% HbA1c and 35.4% according to a threshold of <7.5% HbA1c. The mean HbA1c was 8.1% and mean FPG was 8.8 mmol/L. The mean body mass index (BMI) was 26.1 kg/m^2 and the BMI was most commonly in the normal (≥18.5 to <25 kg/m^2) and overweight (≥25 to <30 kg/m^2) range (46.0% and 35.3% of patients, respectively).

In the T2DM group, the proportion of patients with glycaemic control at baseline was 16.4% according to a threshold of <7.0% HbA1c and 29.7% according to a threshold of <7.5% HbA1c. The mean HbA1c was 8.2% and mean FPG was 9.0 mmol/L. The mean BMI was 31.1 kg/m^2 and the BMI was most commonly in the overweight (≥25 to <30 kg/m^2) and obese class I (≥30 to <35 kg/m^2) range (35.6% and 29.2% of patients, respectively).

Table 10–3 Baseline Characteristics (Full Analysis Set – excluding Germany)

	T1DM (N=556) n (%)	T2DM (N=611) n (%)
HbA1c (%)		
n	556	611
Mean	8.1	8.2
SD	1.30	1.37
Minimum	5	3
Q1	7.2	7.3
Median	7.9	8.0
Q3	8.7	8.9

	T1DM (N=556) n (%)	**T2DM (N=611) n (%)**
Maximum	14	16
HbA1c range, n (%)		
n	556	611
<7.0%	107 (19.2)	100 (16.4)
≥7.0 - <7.5%	90 (16.2)	81 (13.3)
≥7.5 - <8.5%	174 (31.3)	217 (35.5)
≥8.5 - <9.5%	111 (20.0)	120 (19.6)
≥9.5%	74 (13.3)	93 (15.2)
Fasting Plasma Glucose (mmol/L)		
n	392	526
Mean	8.8	9.0
SD	3.90	3.10
Minimum	2	3
Q1	6.0	6.9
Median	8.2	8.4
Q3	11.0	10.5
Maximum	26	23
Height (cm)		
n	502	567
Mean	171.1	167.7
SD	10.08	9.99
Minimum	140	141
Q1	164.0	160.0
Median	170.8	169.0
Q3	178.0	175.0
Maximum	200	212
Weight (kg)		
n	537	581
Mean	76.4	87.6
SD	15.62	19.58
Minimum	43	43
Q1	65.0	74.0
Median	75.0	85.5
Q3	85.5	99.0
Maximum	140	152
BMI (kg/m^2)		
n	498	559
Mean	26.1	31.1
SD	4.65	6.30
Minimum	17	19
Q1	22.8	26.8
Median	25.4	30.1

	T1DM (N=556) n (%)	**T2DM (N=611) n (%)**
Q3	28.6	34.2
Maximum	50	60
BMI (kg/m^2), n (%)		
n	498	559
Underweight (<18.5)	11 (2.2)	0
Normal (≥18.5 - <25)	229 (46.0)	75 (13.4)
Overweight (≥25 - <30)	176 (35.3)	199 (35.6)
Obese Class I (≥30 - <35)	54 (10.8)	163 (29.2)
Obese Class II (≥35 - <40)	23 (4.6)	71 (12.7)
Obese Class III (≥40)	5 (1.0)	51 (9.1)
Missing	58	52
SBP (mmHg)		
n	492	524
Mean	128.0	135.9
SD	16.47	15.01
Minimum	90	96
Q1	119.0	126.5
Median	127.0	135.0
Q3	139.0	144.0
Maximum	199	185
SBP (mmHg), n (%)	492	524
<140 mmHg	374 (76.0)	302 (57.6)
≥140 mmHg	118 (24.0)	222 (42.4)
Missing	64	87
DBP (mmHg)		
n	492	524
Mean	75.6	77.3
SD	8.95	9.45
Minimum	43	48
Q1	70.0	70.0
Median	76.0	80.0
Q3	80.0	80.5
Maximum	111	114
DBP (mmHg), n (%)	492	524
<90 mmHg	455 (92.5)	467 (89.1)
≥90 mmHg	37 (7.5)	57 (10.9)
Missing	64	87

	T1DM (N=556) n (%)	T2DM (N=611) n (%)

Baseline characteristics included the last value from visit 1 or visit 2 before initiating treatment with Tresiba®

Percentages were calculated using the number of patients with non-missing values as denominator.

BMI = body mass index; DBP = diastolic blood pressure; SD = standard deviation; SBP = systolic blood pressure; Q1 = first quartile; Q3 = third quartile; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.1.4.2.2.1

Baseline characteristics for the FAS from Germany are summarised in Table 14.1.4.2.2.2.

Baseline characteristics for DPO outside Germany were generally similar to the FAS outside Germany (Table 14.1.4.2.1.1). In the T1DM group, the proportion of patients with glycaemic control at baseline was 20.0% according to a threshold of <7.0% HbA1c and 30.0% according to a threshold of <7.5% HbA1c. The mean HbA1c was 9.8% and mean FPG was 9.1 mmol/L. The mean BMI was 25.9 kg/m^2 and the BMI was most commonly in the normal (≥18.5 to <25 kg/m^2) and overweight (≥25 to <30 kg/m^2) range (52.3% and 27.3% of patients, respectively).

In the T2DM group, the proportion of patients with glycaemic control at baseline was 16.0% according to a threshold of <7.0% HbA1c and 28.0% according to a threshold of <7.5% HbA1c. The mean HbA1c was 8.4% and mean FPG was 9.0 mmol/L. The mean BMI was 31.3 kg/m^2 and the BMI was most commonly in the overweight (≥25 to <30 kg/m^2) and obese class I (≥30 to <35 kg/m^2) range (22.2% and 33.3% of patients, respectively).

Baseline characteristics for DPO from Germany are summarised in Table 14.1.4.2.1.2.

A boxplot of SBP values for the FAS is displayed in Figure 14.1.4.4.1.1 and Figure 14.1.4.4.1.2 (for T1DM and T2DM, respectively, outside Germany); a boxplot of DBP values is displayed in Figure 14.1.4.4.2.1 and Figure 14.1.4.4.2.2 (for T1DM and T2DM, respectively, outside Germany).

Individual vital sign and body measurement data are shown in Annex 2, Listing 16.2.4.2.

10.2.3 Medical history

Medical history details of the FAS outside Germany by system organ class (SOC) and preferred term (PT) are summarised in Table 14.1.5.1.2.1.

The majority of patients in both groups reported at least one medical history condition (373 T1DM patients [67.1%] and 536 T2DM patients [87.7%]).

The most frequent medical history conditions by SOC (reported by >10% of patients) were:

- T1DM group: metabolism and nutrition disorders (161 patients [29.0%]), vascular disorders (145 patients [26.1%]), eye disorders (107 patients [19.2%]), endocrine disorders (94 patients [16.9%]), nervous system disorders (66 patients [11.9%]), musculoskeletal and connective tissue disorders (65 patients [11.7%])
- T2DM group: vascular disorders (408 patients [66.8%]), metabolism and nutrition disorders (307 patients [50.2%]), nervous system disorders (137 patients [22.4%]), and cardiac disorders (134 patients [21.9%]), eye disorders (93 patients [15.2%]), renal and urinary disorders (83 patients [13.6%]), musculoskeletal and connective tissue disorders (78 patients [12.8%]), endocrine disorders (69 patients [11.3%]), respiratory, thoracic and mediastinal disorders (66 patients [10.8%])

The most frequent medical history conditions by PT (reported by ≥10% of patients) were:

- T1DM group: hypertension (134 patients [24.1%]), diabetic retinopathy (73 patients [13.1%]), hypercholesterolaemia (59 patients [10.6%]), hypothyroidism (56 patients [10.1%]),
- T2DM group: hypertension (393 patients [64.3%]), dyslipidaemia (144 patients [23.6%]), hypercholesterolaemia (95 patients [15.5%]), and diabetic retinopathy (61 patients [10.0%]).

Medical history details of the FAS from Germany by SOC and PT are summarised in Table 14.1.5.1.2.2.

Medical history details of DPO outside Germany are summarised in Table 14.1.5.1.1.1.

Medical history details of DPO from Germany are summarised in Table 14.1.5.1.1.2.

Individual medical history details are shown in Annex 2, Listing 16.2.4.3.2.

10.2.4 Diabetic history

10.2.4.1 Diabetic history details

Diabetic history details are summarised for the FAS outside Germany in Table 14.1.5.2.2.1, based on eCRF data.

In the T1DM group, the mean duration of diabetes was 21.4 years; the mean total daily basal insulin dose was 24.7 U; the mean total daily bolus insulin dose was 26.8 U; 45 patients (8.1%) were high-dose insulin users and 379 patients (68.2%) were prone to hypoglycaemia (for definition see Section 9.4.1.1); the mean number of severe hypoglycaemic events in the previous 6 months was 2.4 based on recall data.

In the T2DM group, the mean duration of diabetes was 18.0 years; the mean total daily basal insulin dose was 36.3 U; the mean total daily bolus insulin dose was 37.4 U; 132 patients (21.6%) were

high-dose insulin users (>80 U daily) and 346 patients (56.6%) were prone to hypoglycaemia; the mean number of severe hypoglycaemic events in the previous 6 months was 1.6.

Diabetes history details are summarised for the FAS from Germany in Table 14.1.5.2.2.2.

Diabetic history details of DPO outside Germany are summarised in Table 14.1.5.2.1.1. Similar to FAS, the mean duration of diabetes in the DPO was 20.6 years for T1DM patients and 15.8 years for the T2DM patients.

Diabetic history details of DPO from Germany are summarised in Table 14.1.5.2.1.2.

A boxplot of basal insulin doses for the FAS is displayed in Figure 14.1.5.3.1.1 and Figure 14.1.5.3.1.2 (for T1DM and T2DM, respectively, outside Germany); a boxplot of bolus insulin doses is displayed in Figure 14.1.5.3.2.1 and Figure 14.1.5.3.2.2 (for T1DM and T2DM, respectively, outside Germany).

10.2.4.2 Anti-diabetic and insulin treatment during the baseline period

Anti-diabetic treatment taken during the baseline period is summarised for the FAS outside Germany in Table 10–4.

Based on available eCRF data, at least one insulin treatment was taken by 97.3% of T1DM patients and 93.6% of T2DM patients. On-site monitoring confirmed that all patients received at least one insulin treatment during the baseline period (see section 9.10). At least one anti-diabetic treatment, excluding insulin, was reported for 9.7% of T1DM patients and 62.0% of T2DM patients during the baseline period.

The most common anti-diabetic medications in the T2DM group, excluding insulin treatment (used by ≥10% of patients) were (by chemical subgroup anatomical therapeutic chemical [ATC] level 4) biguanides (50.2%), sodium-glucose co-transporter 2 (Sglt2) inhibitors (10.8%) and glucagon-like peptide-1 (Glp-1) analogues (10.5%). Less than 10% of T1DM patients used non-insulin treatment.

Table 10–4 Anti-diabetic treatment taken during the baseline period (Full Analysis Set – excluding Germany)

Therapeutic Subgroup (ATC Level 2) Chemical Subgroup (ATC Level 4)	T1DM (N=556) n (%)	T2DM (N=611) n (%)
Patients Taking At Least One Anti-Diabetic Treatment	545 (98.0)	603 (98.7)
Patients Taking At Least One Insulin Treatment	541 (97.3)	572 (93.6)
Patients Taking At Least One Anti-Diabetic Treatment - Excluding Insulin Treatment	54 (9.7)	379 (62.0)
Agents Acting On The Renin-Angiotensin System	0	1 (0.2)
Ace Inhibitors, Plain	0	1 (0.2)
Blood Substitutes And Perfusion Solutions	1 (0.2)	0
Solutions For Parenteral Nutrition	1 (0.2)	0
Diagnostic Agents	6 (1.1)	0
Tests For Diabetes	6 (1.1)	0
Drugs Used In Diabetes	545 (98.0)	603 (98.7)
Alpha Glucosidase Inhibitors	0	7 (1.1)
Biguanides	41 (7.4)	307 (50.2)
Combinations Of Oral Blood Glucose Lowering Drugs	0	31 (5.1)
Dipeptidyl Peptidase 4 (Dpp-4) Inhibitors	2 (0.4)	49 (8.0)
Glucagon-Like Peptide-1 (Glp-1) Analogues	4 (0.7)	64 (10.5)
Insulins And Analogues For Injection, Fast-Acting	501 (90.1)	363 (59.4)
Insulins And Analogues For Injection, Intermediate- Or Long-Acting Combined With Fast-Acting	9 (1.6)	32 (5.2)
Insulins And Analogues For Injection, Intermediate-Acting	19 (3.4)	25 (4.1)
Insulins And Analogues For Injection, Long-Acting	483 (86.9)	489 (80.0)
Other Blood Glucose Lowering Drugs, Excl. Insulins	0	15 (2.5)
Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	4 (0.7)	66 (10.8)
Sulfonylureas	0	41 (6.7)
Thiazolidinediones	1 (0.2)	8 (1.3)
Pancreatic Hormones	4 (0.7)	0
Glycogenolytic Hormones	4 (0.7)	0

Patients taking the same medication more than once were counted once. Insulin treatment were presented as entered by investigator/site on the anti-diabetic treatment page of case report form (CRF).
ATC = anatomical therapeutic chemical; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.1.6.1.1.1

Anti-diabetic treatment taken during the baseline period is summarised for the FAS from Germany in Table 14.1.6.1.1.2.

Insulin treatment taken during the baseline period is summarised for the FAS outside Germany in Table 10–5.

The most frequently used basal insulins during the baseline period were as follows: In the T1DM group, 22.7% of patients took detemir and 63.8% took glargine during the baseline period. In the T2DM group, 20.8 % of patients took detemir and 59.1% took glargine.

As shown in Table 10–5, 4 patients in the T1DM group and 4 patients in the T2DM group reported taking insulin degludec during the baseline period. Of note, two of these patients in each group (T1DM: patients [redacted] and [redacted]; T2DM patients [redacted] and [redacted] recorded partial rather than complete dates in the anti-diabetic treatment page that was used to categorize study periods as shown in Listing 16.2.4.4.3.1 and Listing 16.2.4.4.3.2. The other 4 patients were either open query with relation to the date of first study medication, or open query with comments of 'non-responsive site'.

Table 10–5 Insulin treatment taken during the baseline period (Full Analysis Set – excluding Germany)

Therapeutic Subgroup (ATC Level 2) Chemical Subgroup (ATC Level 4) Preferred Term	T1DM (N=556) n (%)	T2DM (N=611) n (%)
Patients Taking At Least One Insulin Treatment	541 (97.3)	572 (93.6)
Drugs Used In Diabetes	541 (97.3)	572 (93.6)
Insulins And Analogues For Injection, Fast-Acting	501 (90.1)	363 (59.4)
Insulin	1 (0.2)	0
Insulin Aspart	342 (61.5)	212 (34.7)
Insulin Glulisine	24 (4.3)	49 (8.0)
Insulin Human	2 (0.4)	2 (0.3)
Insulin Lispro	134 (24.1)	102 (16.7)
Insulins And Analogues For Injection, Intermediate- Or Long-Acting Combined With Fast-Acting	9 (1.6)	32 (5.2)
Humalog Mix	3 (0.5)	6 (1.0)
Human Mixtard	0	5 (0.8)
Insulin Human	0	1 (0.2)
Insulin Lispro	0	1 (0.2)
Novolog Mix	0	1 (0.2)
Novomix	6 (1.1)	18 (2.9)
Insulins And Analogues For Injection, Intermediate-Acting	19 (3.4)	25 (4.1)
Insulin Human	1 (0.2)	0
Insulin Human Injection, Isophane	14 (2.5)	17 (2.8)
Insulin Isophane Bovine	1 (0.2)	2 (0.3)
Insulin Lispro	2 (0.4)	0
Insulin Lispro Protamine Suspension	1 (0.2)	6 (1.0)
Insulins And Analogues For Injection, Long-Acting	483 (86.9)	489 (80.0)
Insulin Degludec	4 (0.7)	4 (0.7)
Insulin Detemir	126 (22.7)	127 (20.8)

Therapeutic Subgroup (ATC Level 2) Chemical Subgroup (ATC Level 4) Preferred Term	T1DM (N=556) n (%)	T2DM (N=611) n (%)
Insulin Glargine	355 (63.8)	361 (59.1)

Patients taking the same medication more than once were counted once. Insulin treatment were presented as entered by investigator/site on the anti-diabetic treatment page of case report form (CRF).
ATC = anatomical therapeutic chemical; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.1.6.1.1.3

Insulin treatment taken during the baseline period is summarised for patients from Germany in Table 14.1.6.1.1.4.

Individual baseline treatment data are shown in Annex 2, Listing 16.2.4.5.

10.2.4.3 Anti-diabetic and insulin treatment during the 12-month observation period

Anti-diabetic treatment taken during the 12-month observation period is summarised for the FAS outside Germany in Table 14.1.6.1.2.1.

Based on available eCRF data (see section 9.10), at least one insulin treatment was taken by 539 T1DM patients (96.9%) and 533 T2DM patients (87.2%); at least one anti-diabetic treatment, excluding insulin, was taken by 55 T1DM patients (9.9%) and 387 T2DM patients (63.3%).

The most common anti-diabetic medications (used by ≥10% of patients), were (by chemical subgroup):

- T1DM patients: fast-acting insulins and analogues for injection (501 patients [90.1%]) and long-acting insulins and analogues for injection (440 patients [79.1%])
- T2DM patients: long-acting insulins and analogues for injection (434 patients [71.0%]), fast-acting insulins and analogues for injection (378 patients [61.9%]), biguanides (314 patients [51.4%]), sodium-glucose co-transporter 2 (Sglt2) inhibitors (87 patients [14.2%]), glucagon-like peptide-1 (Glp-1) analogues (74 patients [12.1%])

Anti-diabetic treatment taken during the baseline period is summarised for the FAS from Germany in Table 14.1.6.1.2.2.

Insulin treatment taken during the 12-month observation period is summarised for the FAS outside Germany in Table 14.1.6.1.2.3. Insulin treatment taken during the 12-month observation period is summarised for the FAS from Germany in Table 14.1.6.1.2.4.

Individual diabetes history details are shown in Annex 2, Listing 16.2.4.3.1. Individual insulin treatment details are shown in Listing 16.2.4.4.4. Individual anti-diabetic treatment and anti-diabetic

treatment by diary period and by visit are shown in Listings 16.2.4.4.2, Listing 16.2.4.4.3.1 and Listing 16.2.4.4.3.2, respectively.

10.2.5 Concomitant medication

10.2.5.1 Concomitant medication during the baseline period

Concomitant medication taken during the baseline period is summarised for the FAS outside Germany in Table 14.1.6.2.1.1. At least one concomitant medication was taken by 342 T1DM patients (61.5%) and 487 T2DM patients (79.7%).

The most commonly used concomitant drugs (by therapeutic subgroup, taken by ≥10% of patients) were:

- T1DM group: lipid modifying agents (195 patients [35.1%]), agents acting on the renin-angiotensin system (164 patients [29.5%]), antithrombotic agents (76 patients [13.7%]), and thyroid therapy (73 patients [13.1%])
- T2DM group: lipid modifying agents (344 patients [56.3%]), agents acting on the renin-angiotensin system (326 patients [53.4%]), antithrombotic agents (242 patients [39.6%]), beta blocking agents (163 patients [26.7%]), diuretics (151 patients 24.7%]), calcium channel blockers (129 patients [21.1%]), and drugs for acid related disorders (103 patients [16.9%])

Concomitant medication taken during the baseline period is summarised for the FAS from Germany in Table 14.1.6.2.1.2.

10.2.5.2 Concomitant medication during the 12-month observation period

Concomitant medication taken during the 12-month observation period is summarised for the FAS outside Germany in Table 14.1.6.2.2.1. At least one concomitant medication was taken by 359 T1DM patients (64.6%) and 494 T2DM patients (80.9%).

The most commonly used concomitant drugs (by therapeutic subgroup, taken by ≥10% of patient) were:

- T1DM group: lipid modifying agents (208 patients [37.4%]), agents acting on the renin-angiotensin system (164 patients [29.5%]), antithrombotic agents (82 patients [14.7%]), thyroid therapy (74 patients [13.3%]), and drugs for acid related disorders (56 patients [10.1%])
- T2DM group: lipid modifying agents (349 patients [57.1%]), agents acting on the renin-angiotensin system (332 patients [54.3%]), antithrombotic agents (247 patients [40.4%]), beta blocking agents (164 patients [26.8%]), diuretics (157 patients [25.7%]), calcium channel blockers (138 patients [22.6%]), and drugs for acid related disorders (108 patients [17.7%])

Concomitant medications taken during the 12-month observation period in the FAS from Germany are summarised in Table 14.1.6.2.2.2.

Individual details for concomitant medications are shown in Annex 2, Listing 16.2.4.4.1.

10.3 Outcome data

All endpoints were analysed on the FAS, for patients outside Germany, by diabetes type (T1DM and T2DM). The FAS consisted of 556 T1DM patients and 611 T2DM patients (Table 10–1).

10.4 Main results

10.4.1 Primary observational endpoint

The primary observational endpoint was defined as 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) (Section 9.1.1).

10.4.1.1 Primary analysis of the primary observational endpoint

The mean change in the number of any hypoglycaemic events between the baseline period (i.e., 4 weeks before baseline) and the 12-month observation period with Tresiba® is summarised for the FAS outside Germany in Table 10–6.

The absolute mean change in any hypoglycaemic events rate was −17.47 events per patient year in the T1DM group and −7.84 events per patient year in the T2DM group.

Table 10–6 Observed and change from baseline in any hypoglycaemic event rate between 4 weeks before and 12 months after baseline (Full Analysis Set – excluding Germany)

	T1DM (N=556)			T2DM (N=611)		
Statistics	Baseline	12 Months After Baseline	Change from Baseline	Baseline	12 Months After Baseline	Change from Baseline
n	508	502	469	537	558	504
Mean	86.03	68.94	-17.47	17.12	8.47	-7.84
95% CI [1]	-	-	-23.24, -11.70	-	-	-10.25, -5.43
SD	87.489	76.199	63.582	36.733	21.513	27.557
Minimum	0.0	0.0	-290.2	0.0	0.0	-204.4
Q1	26.09	13.04	-43.48	0.00	0.00	-9.74
Median	65.22	47.83	-8.70	0.00	0.00	0.00
Q3	117.40	100.01	8.70	13.04	6.52	0.00
Maximum	482.7	476.1	243.5	247.8	230.5	191.3

Event rates were presented per patient year and were based on diary periods with 26-30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to what was recorded in the patient diary.

N is the total number of patients in each diabetes type group. The rate for '12 months after baseline' is the event rate calculated using the data from the diary periods for visit 3, visit 4, visit 5 and visit 6.

[1] 95% CIs of the mean were only presented for change from baseline values for post-baseline visits.

CI = confidence interval; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.1.1

The estimated annual incidence rate of any hypoglycaemic event during the 4-week baseline period and the 12-month observation period is summarised in Table 10–7.

For T1DM patients, 83.9% of patients reported 3305 hypoglycaemic events during the baseline period and 82.9% of patients reported 7297 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 85.8 (95% CI: 82.9, 88.8) during the baseline period to 69.8 (95% CI: 68.2, 71.4) during the 12-month observation period.

For T2DM patients, 34.8% of patients reported 699 hypoglycaemic events during the baseline period and 33.3% of patients reported 1030 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 17.1 (95% CI: 15.9, 18.5) during the baseline period to 8.7 (95% CI: 8.2, 9.2) during the 12-month observation period.

Table 10–7 Incidence of any hypoglycaemic event during the 12-month observation period (Full Analysis Set – excluding Germany)

Item	T1DM (N=556)	T2DM (N=611)
4 Week Baseline Period* [Pre-Baseline]		
n	508	537
Number of Patients Having a Hypoglycaemic Event [n (%)]	426 (83.9)	187 (34.8)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	80.4, 87.0	30.8, 39.0
Number of Hypoglycaemic Events [n]	3305	699
Total Follow-Up Time [patient years]	38.5	40.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	85.8 (82.9, 88.8)	17.1 (15.9, 18.5)
12 Month Observation Period* [Post-Baseline]		
n	502	558
Number of Patients Having a Hypoglycaemic Event [n (%)]	416 (82.9)	186 (33.3)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	79.3, 86.1	29.4, 37.4
Number of Hypoglycaemic Events [n]	7297	1030
Total Follow-Up Time [patient years]	104.5	118.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	69.8 (68.2, 71.4)	8.7 (8.2, 9.2)

* Based on diary periods with 26-30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to what was recorded in the patient diary.

[1] Clopper-Pearson 95% CIs are reported.

[2] Exact 95% CIs are reported.

[3] Estimated number of events per patient year.

CI = confidence interval; IR = incidence rate; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.1.2.3

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between baseline (i.e., period 4 weeks before baseline) and 12 months after baseline is shown in Table 10–8 for T1DM patients and Table 10–9 for T2DM patients.

According to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events was 0.80 (95% CI: 0.74, 0.88; p<0.001) in the T1DM group (Table 10–8) and 0.46 (95% CI: 0.38, 0.56; p<0.001) in the T2DM group (Table 10–9). These results indicate a statistically significant reduction of hypoglycaemic events for both types of diabetes after the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models.

Table 10–8 Negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between 4 weeks before and 12 months after baseline for T1DM (Full Analysis Set – excluding Germany)

Predictor Variables in Model	n	Incidence Rate Ratio of Period	95% Confidence Interval	p-value
Period [Crude]	541	0.80	(0.75, 0.87)	<0.001
Fully-Adjusted Model	481	0.80	(0.74, 0.88)	<0.001
Period [Crude] on Patients with Full Set of Covariates	481	0.81	(0.74, 0.87)	<0.001

Fully-adjusted model adjusted for Period, HbA1c (baseline), Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline and Country

Incidence Rate (IR) Ratio [IRR] of Period represents the change in the 12 month "Post-baseline" period IR compared to the 4 week "Baseline" period IR.

Based on diary periods with 26-30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to what was recorded in the patient diary.

The p-value tests the hypothesis that IRR=1. Robust standard errors used to adjust for potential dependence between repeated measures on individuals and site-level clustering.

BMI = body mass index; T1DM = type 1 diabetes mellitus.

Cross-reference: EOT Table 14.2.1.2.1

Table 10–9 Negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between 4 weeks before and 12 months after baseline for T2DM (Full Analysis Set – excluding Germany)

Predictor Variables in Model	n	Incidence Rate Ratio of Period	95% Confidence Interval	p-value
Period [Crude]	591	0.49	(0.41, 0.60)	<0.001
Fully-Adjusted Model	516	0.46	(0.38, 0.56)	<0.001
Period [Crude] on Patients with Full Set of Covariates	516	0.47	(0.39, 0.56)	<0.001

Fully-adjusted model adjusted for Period, HbA1c (baseline), Bolus insulin (Y/N, baseline), SU+Glinides (Y/N, baseline), Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline and Country.

Incidence Rate (IR) Ratio [IRR] of Period represents the change in the 12 month "Post-baseline" period IR compared to the 4 week "Baseline" period IR.

Based on diary periods with 26 30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to what was recorded in the patient diary.

The p-value tests the hypothesis that IRR=1. Robust standard errors used to adjust for potential dependence between repeated measures on individuals and site-level clustering.

BMI = body mass index; SU = sulphonylureas; T2DM = type 2 diabetes mellitus; Y/N = yes/no.

Cross-reference: EOT Table 14.2.1.2.2

A boxplot of any hypoglycaemic event rate per patient year for the FAS is displayed in Figure 14.2.1.1.1 and Figure 14.2.1.1.2 (for T1DM and T2DM, excluding Germany).

Individual details of hypoglycaemic episodes are shown in Annex 2, Listing 16.2.6.1.

10.4.1.2 Sensitivity analyses of the primary observational endpoint

Several sensitivity analyses were conducted to assess the robustness of the primary analysis. These analyses were conducted on the FAS outside Germany.

The primary analysis was based on diary data, which were to be collected by each patient for 28 days prior to each visit. Three sensitivity analyses were done to assess the impact of the difference in reporting in the patient diary. A fourth sensitivity analysis tested the impact of any missing data.

The primary analysis was based on diary periods of 26-30 days, where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly the diary data.

Sensitivity analysis 1 was based on diary periods of 26-30 days, where the dates of hypoglycaemic events recorded on the 'hypo page' of the diary fell within the diary period. Sensitivity analysis 2 was based on all diaries (except those with missing duration) where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly the diary data. Sensitivity analysis 3 was based on all diaries (except those with missing duration) where the dates of hypoglycaemic events recorded on the 'hypo page' fell within the diary period. According to these 3 analyses, the absolute mean change in the number of any hypoglycaemic events from the baseline period to the 12-month observation period with Tresiba® (Table 14.2.1.3.1.1, Table 14.2.1.3.2.1, Table 14.2.1.3.3.1), the estimated annual incidence rate during the baseline period and the 12-month observation period (Table 14.2.1.3.1.2.3, Table 14.2.1.3.2.2.3, Table 14.2.1.3.3.2.3) and the incidence rate ratio (Table 14.2.1.3.1.2.1, Table 14.2.1.3.1.2.2, Table 14.2.1.3.2.2.1, Table 14.2.1.3.2.2.2, Table 14.2.1.3.3.2.1, Table 14.2.1.3.3.2.2) were all similar to the results of the primary analysis (see Section 10.4.1.1).

Sensitivity analysis 4 was based on diary periods with 26-30 days, where the dates of hypoglycaemic events recorded on the 'hypo page' of the eCRF matched exactly the diary data for patients who completed the 12-month observation period, i.e., attended visit 6 and completed at least 23 diary days for each diary period during the 12-month observation period. For T1DM patients, the annual incidence rate during the baseline period was larger compared to the primary analysis (Table 14.2.1.3.4.2.3 and Table 10–7), which explains the larger mean decrease in the any hypoglycaemic event rate per patient year (−30.27; Table 14.2.1.3.4.1) and the smaller incidence rate ratio in favour of the treatment during the 12-month observation period (0.67 according to the fully-adjusted negative binomial model; Table 14.2.1.3.4.2.1) compared to the primary analysis (see Section 10.4.1.1). Nevertheless, the overlapping CIs indicate that these results were similar to those of the primary analysis. For T2DM patients, the absolute mean change in the number of any

hypoglycaemic events from the baseline period to the 12-month observation period with Tresiba® (Table 14.2.1.3.4.1) the estimated annual incidence rate during the baseline period and the 12-month observation period (Table 14.2.1.3.4.2.3) and the incidence rate ratio (Table 14.2.1.3.4.2.2) were all similar to the results of the primary analysis (see Section 10.4.1.1).

The results of these 4 sensitivity analyses confirm those of the primary analysis described in Section 10.4.1.1).

10.4.1.3 Subgroup analyses

Subgroup analyses were performed on the FAS outside Germany, on the 5 subgroups presented below.

Subgroup analysis by duration of diabetes mellitus

The subgroup analysis according to the quartiles of treatment duration in the FAS outside Germany is summarised in Table 14.2.1.4.1.1.

For T1DM patients, the observed mean rate of any hypoglycaemic events at baseline and month 12, and the absolute mean change between baseline period and 12 months after baseline according to quartiles of duration of diabetes, respectively, were as follows:

- Q1 (duration of ≤10.6 years): 59.83 and 52.19 events per patient year (baseline and month 12, respectively); change of −7.37 events per patient year
- Q2 (duration of >10.6 years and ≤19.8 years): 106.51 and 73.94 events per patient year (baseline and month 12, respectively); change of −35.20 events per patient year
- Q3 (duration of >19.8 years and ≤30.6 years): 90.52 and 77.51 events per patient year (baseline and month 12, respectively); change of −12.68 events per patient year
- Q4 (duration of >30.6 years): 88.24 and 72.69 events per patient year (baseline and month 12, respectively); change of −15.24 events per patient year

For T2DM patients, the observed mean rate of any hypoglycaemic events at baseline and month 12 and the absolute mean change between the baseline period and 12 months after baseline according to quartiles of duration of diabetes, respectively, were as follows:

- Q1 (duration of ≤10.9 years): 14.83 and 6.53 events per patient year (baseline and month 12, respectively); change of −9.21 events per patient year
- Q2 (duration of >10.9 years and ≤16.8 years): 13.71 and 6.23 events per patient year (baseline and month 12, respectively); change of –5.34 events per patient year
- Q3 (duration of >16.8 years and ≤22.8 years): 17.31 and 7.84 events per patient year (baseline and month 12, respectively); change of −7.23 events per patient year

- Q4 (duration of >22.8 years): 24.56 and 12.33 events per patient year (baseline and month 12, respectively); change of −11.67 events per patient year

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between the baseline period and 12 months after baseline by duration of DM is shown in Table 14.2.1.4.1.2.1 for T1DM patients and Table 14.2.1.4.1.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a reduction of events during the 12-month observation period compared to the baseline period, regardless of the quartile of DM duration analysed. This reduction was statistically significant for Q2 (0.67 [95% CI: 0.56, 0.79; p<0,001]) and Q4 (0.79 [95% CI: 0.67, 0.93; p=0.006]), but not for Q1 (0.92 [95% CI: 0.77, 1.10; p=0.342]) and Q3 (0.88 [95% CI: 0.75, 1.03; p=0.101]). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.1.2.1). Regardless of statistical significance, results across the categories moved in the same direction (a decrease).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a reduction of events during the 12-month observation period compared to the baseline period, regardless of the quartile of DM duration analysed. This reduction was statistically significant for each of the 4 quartiles analysed: Q1 (0.45 [95% CI: 0.31, 0.66; p<0.001]); Q2 (0.46 [95% CI: 0.33, 0.66; p<0.001]); Q3 (0.45 [95% CI: 0.27, 0.74; p=0.002]); Q4 (0.51 [95% CI: 0.36, 0.71; p<0.001]). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.1.2.2).

Individual subgroup data categories are shown in Annex 2, Listing 16.2.6.5.

Subgroup analysis by baseline bolus insulin

The subgroup analysis according to baseline bolus insulin in the FAS outside Germany is summarised in Table 14.2.1.4.2.1.

For patients who actively reported taking bolus insulin during the baseline period, the observed mean rate of any hypoglycaemic events was 89.59 events per patient year at baseline (464 patients) and 71.17 events per patient year at month 12 for T1DM patients (458 patients). For T2DM patients, observed mean rate was 21.86 events per patient year at baseline (339 patients) and 10.96 events per patient year at month 12 (347 patients). The absolute mean change in the rate of any hypoglycaemic events from baseline period to 12 months after baseline was −19.07 events per patient year for T1DM patients and −9.62 events per patient year for T2DM patients.

For patients who did not report taking bolus insulin during the baseline period, the observed mean rate of any hypoglycaemic events was 48.49 events per patient year at baseline and 46.25 events per patient year at month 12 for T1DM patients. For T2DM patients, observed mean rate was 9.00

events per patient year at baseline and 4.29 events per patient year at month 12. The absolute mean change in the rate of any hypoglycaemic events from the baseline period to 12 months after baseline was 0.15 events per patient year for T1DM patients and −4.89 events per patient year for T2DM patients. Of note, the number of T1DM patients who did not report taking bolus insulin during the baseline period was low in this analysis as all T1DM patients were expected to use bolus insulin during the baseline period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between baseline and 12 months after baseline by baseline bolus insulin is shown in Table 14.2.1.4.2.2.1 for T1DM patients and Table 14.2.1.4.2.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a reduction of events during the 12-month observation period compared to the baseline period, with or without baseline bolus insulin. This reduction was statistically significant for patients with baseline bolus insulin (0.81 [0.74, 0.88]; p<0.001), but not statistically significant for those without baseline bolus insulin (0.64 [0.39, 1.06]; p=0.084). Statistical significance of these results, or lack thereof, was consistent across the crude and fully-adjusted models (Table 14.2.1.4.2.2.1). Of note, the number of T1DM patients who did not report taking bolus insulin during the baseline period was low in this analysis as all T1DM patients were expected to use bolus insulin during the baseline period.

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a statistically significant reduction of events during the 12-month observation period compared to the baseline period, with or without baseline bolus insulin (0.43 [95% CI: 0.35, 0.54; p<0.001] and 0.56 [95% CI: 0.36, 0.86; p=0.009], respectively). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.2.2.2).

Individual details on the last dose of bolus insulin are shown in Annex 2, Listing 16.2.5.1.2. Individual subgroup data categories are shown in Annex 2, Listing 16.2.6.5.

Subgroup analysis by country of origin

The subgroup analysis according to the country of origin in the FAS outside Germany is summarised in Table 14.2.1.4.3.1.

By country, the observed mean rates of any hypoglycaemic event at baseline and month 12, respectively, and the absolute mean change between the baseline period and 12 months after baseline, respectively, were:

- Denmark: 62.55 and 65.54 events per patient year for T1DM patients; 13.08 and 6.65 events per patient year for T2DM patients; change of 2.67 (T1DM) and -6.33 (T2DM) events per patient year.

- Netherlands: 56.97 and 54.78 events per patient year for T1DM patients; 18.77 and 12.12 events per patient year for T2DM patients; change of -5.01 (T1DM) and -6.50 (T2DM) events per patient year.
- Spain: 110.92 and 97.07 events per patient year for T1DM patients; 26.92 and 6.82 events per patient year for T2DM patients; change of -13.94 (T1DM) and -20.36 (T2DM) events per patient year.
- Sweden: 97.71 and 85.77 events per patient year for T1DM patients; 19.31 and 10.24 events per patient year for T2DM patients; change of -9.84 (T1DM) and -11.94 (T2DM) events per patient year.
- Switzerland: 44.15 and 27.00 events per patient year for T1DM patients; 11.71 and 8.16 events per patient year for T2DM patients; change of -13.91 (T1DM) and -3.74 (T2DM) events per patient year.
- Italy: 69.56 and 50.31 events per patient year for T1DM patients; 14.70 and 6.04 events per patient year for T2DM patients; change of -19.49 (T1DM) and -7.97 (T2DM) events per patient year.
- United Kingdom: 110.31 and 81.16 events per patient year for T1DM patients; 32.71 and 27.00 events per patient year for T2DM patients; change of -30.60 (T1DM) and 2.49 (T2DM) events per patient year.

The absolute mean change in the rate of any hypoglycaemic events between the baseline period and 12 months after baseline varied across countries. A negative mean change indicating a decrease in the rate of any hypoglycaemic events was observed in all countries except Denmark in the T1DM group and United Kingdom in the T2DM group.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between the baseline period and 12 months after baseline by country is shown in Table 14.2.1.4.3.2.1 for T1DM patients and Table 14.2.1.4.3.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a statistically significant reduction of events during the 12-month observation period compared to the baseline period for patients in Switzerland, Italy and the United Kingdom (0.51 [95% CI: 0.31, 0.84; p=0.008], 0.69 [95% CI: 0.57, 0.82; p<0.001] and 0.76 [95% CI: 0.65, 0.90; p=0.001], respectively). For patients in Denmark and Netherlands there was a statistically non-significant increase in the rate (1.48 [95% CI: 0.80, 2.75; p=0.211] and 1.13 [95% CI: 0.80, 1.58; p=0.492], respectively). For patients in Spain and Sweden there was a statistically non-significant decrease (0.90 [95% CI: 0.76, 1.08; p=0.274] and 0.93 [95% CI: 0.76, 1.13; p=0.461], respectively). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.3.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a statistically significant reduction of events during the 12-month observation period compared to the baseline period for patients in the Netherlands, Spain, Sweden and Italy (0.66 [95% CI: 0.48, 0.90; p=0.010], 0.17 [95% CI: 0.09, 0.33; p<0.001], 0.38 [95% CI: 0.19, 0.75; p=0.006], and 0.40 [95% CI: 0.29, 0.55; p<0.001], respectively). For patients in Denmark, Switzerland and United Kingdom, there was a statistically non-significant reduction (0.59 [95% CI: 0.33, 1.06; p=0.076], 0.73 [95% CI: 0.46, 1.16; p=0.0178], and 0.91 [95% CI: 0.51, 1.61; p=0.741], respectively). Statistical significance of these results was consistent across the crude and fully-adjusted models, except for Denmark, Sweden and Switzerland (Table 14.2.1.4.3.2.2).

Individual subgroup data categories are shown in Annex 2, Listing 16.2.6.5.

Subgroup analysis by baseline HbA1c

The subgroup analysis according to baseline HbA1c in the FAS outside Germany is summarised in Table 14.2.1.4.4.1.

For T1DM patients, observed mean rate of any hypoglycaemic events at baseline and month 12, and the absolute mean change in the rate of any hypoglycaemic events between the baseline period and 12 months after baseline according to baseline HbA1c was as follows:

- Baseline HbA1c <7.5%: 103.63 and 80.09 events per patient year (baseline and month 12, respectively); change of −24.93 events per patient year
- Baseline HbA1c ≥7.5% and <8.5%: 89.13 and 75.50 events per patient year (baseline and month 12, respectively); change of −13.99 events per patient year
- Baseline HbA1c ≥8.5% and <9.5%: 67.71 and 50.95 events per patient year (baseline and month 12, respectively); change of −13.37 events per patient year
- Baseline HbA1c ≥9.5%: 57.26 and 48.72 events per patient year (baseline and month 12, respectively); change of −10.76 events per patient year

For T2DM patients, the absolute mean change in the rate of any hypoglycaemic events between baseline and 12 months after baseline according to baseline HbA1c was as follows:

- Baseline HbA1c <7.5%: 23.42 and 9.95 events per patient year (baseline and month 12, respectively); change of −12.11 events per patient year
- Baseline HbA1c ≥7.5% and <8.5%: 17.22 and 7.45 events per patient year (baseline and month 12, respectively); change of −8.89 events per patient year
- Baseline HbA1c ≥8.5% and <9.5%: 12.22 and 10.22 events per patient year (baseline and month 12, respectively); change of −1.85 events per patient year
- Baseline HbA1c ≥9.5%: 10.44 and 5.70 events per patient year (baseline and month 12, respectively); change of −4.62 events per patient year

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between the baseline period and 12 months after baseline by baseline HbA1c is shown in Table 14.2.1.4.4.2.1 for T1DM patients and Table 14.2.1.4.4.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a reduction of events during the 12-month observation period compared to the baseline period, regardless of the baseline HbA1c. This reduction was statistically significant for ranges HbA1c <7.5%, HbA1c ≥7.5% to <8.5%, and HbA1c ≥8.5% to <9.5% (0.77 [95% CI: 0.67, 0.87; p<0.001], 0.79 [95% CI: 0.67, 0.92; p=0.002] and 0.75 [95% CI: 0.59, 0.96; p=0.021], respectively). Results were statistically non-significant for HbA1c ≥9.5% (0.91 [95% CI: 0.67, 1.23; p=0.531]). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.4.2.1). Regardless of statistical significance, results across the categories moved in the same direction (a decrease) and were of similar magnitude.

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a reduction of events during the 12-month observation period compared to the baseline period, regardless of the baseline HbA1c. The reduction was statistically significant for ranges HbA1c <7.5%, HbA1c ≥7.5% to <8.5%, and HbA1c ≥9.5% (0.43 [95% CI: 0.32, 0.56; p<0.001], 0.43 [95% CI: 0.29, 0.62; p<0.001] and 0.46 [95% CI: 0.27, 0.79; p=0.005], respectively). Results were statistically non-significant for HbA1c ≥8.5% to <9.5% (0.73 [95% CI: 0.47, 1.14; p=0.164]). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.4.2.2). Regardless of statistical significance, results across the categories moved in the same direction (a decrease) and were of similar magnitude.

Individual subgroup data categories are shown in Annex 2, Listing 16.2.6.5.

Subgroup analysis by reason for switching to Tresiba®

The subgroup analysis according to the reason for switching to Tresiba® at baseline in the FAS outside Germany is summarised in Table 14.2.1.4.5.1.

For T1DM patients, the observed mean rate of any hypoglycaemic events was 108.34 events per patient year at baseline and 84.02 events per patient year at month 12 for patients who switched to Tresiba® due to hypoglycaemia. For patients who did not switch due to hypoglycaemia, observed mean rate was 47.09 events per patient year at baseline and 41.02 events per patient year at month 12. The absolute mean change in the rate of any hypoglycaemic events between the baseline period and 12 months after baseline according to reason for switching to Tresiba® was −24.61 events per patient year for patients who switched due to hypoglycaemia and −4.67 events per patient year for patients who did not switch due to hypoglycaemia.

For T2DM patients, the observed mean rate of any hypoglycaemic events was 30.94 events per patient year at baseline and 13.40 events per patient year at month 12 for patients who switched to

Tresiba® due to hypoglycaemia. For patients who did not switch due to hypoglycaemia, observed mean rate was 8.99 events per patient year at baseline and 5.74 events per patient year at month 12. The absolute mean change in the rate of any hypoglycaemic events between the baseline period and 12 months after baseline according to reason for switching to Tresiba® was −16.07 events per patient year for patients who switched due to hypoglycaemia and −3.19 events per patient year for patients who did not switch due to hypoglycaemia.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between the baseline period and 12 months after baseline by patients having switched to Tresiba® due to hypoglycaemia or not at baseline is shown in Table 14.2.1.4.5.2.1 for T1DM patients and Table 14.2.1.4.5.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a reduction of events during the 12-month observation period compared to the baseline period, regardless whether patients had switched to Tresiba® at baseline due to hypoglycaemia or not. This reduction was statistically significant for patients who had switched to Tresiba® due to hypoglycaemia (0.77 [95% CI: 0.70, 0.85; p<0.001]), but not for those who did not switch due to hypoglycaemia (0.90 [95% CI: 0.74, 1.09; p=0.269]). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.5.2.1). Regardless of statistical significance, results across the categories moved in the same direction (a decrease) and were of similar magnitude.

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio of any hypoglycaemic events showed a statistically significant reduction of events during the 12-month observation period compared to the baseline period, regardless of whether patients had switched to Tresiba® due to hypoglycaemia or not (0.40 [95% CI: 0.31, 0.51; p<0.001] and 0.60 [95% CI: 0.46, 0.80; p<0.001], respectively). Statistical significance of these results was consistent across the crude and fully-adjusted models (Table 14.2.1.4.5.2.2). Regardless of statistical significance, results across the categories moved in the same direction (a decrease) and were of similar magnitude.

Individual subgroup data categories are shown in Annex 2, Listing 16.2.6.5.

10.4.2 Secondary observational endpoints – Secondary observational effectiveness endpoints

Baseline was defined as visit 2 for the FPG and HbA1c endpoints (change from baseline) and as the 4-week diary period before baseline (visit 2) for the hypoglycaemia endpoints presented in this section. The most recent tests for the FPG and HbA1c were recorded at each visit.

10.4.2.1 Change from baseline (visit 2) in FPG by visit after 12 months of treatment

FPG values by visit and change from baseline are summarised for the FAS outside Germany in Table 14.2.2.1.1.

For T1DM patients, the mean FPG value was 8.82 mmol/L at baseline and 7.88 mmol/L at month 12. Mean FPG was decreased compared to baseline at each visit during the 12-month observation period, starting at month 3. At month 12, the mean absolute decrease in FPG was −0.59 mmol/L.

For T2DM patients, the mean FPG value was 8.96 mmol/L at baseline and 7.89 mmol/L at month 12. Mean FPG was decreased compared to baseline at each visit during the 12-month observation period, starting at month 3. At month 12, the mean absolute decrease in FPG −1.00 mmol/L.

MMRM analyses of change in FPG from baseline by visit using crude and adjusted estimates are presented in Table 10–10 for T1DM patients and Table 10–11 for T2DM patients.

In the T1DM group, according to the fully-adjusted MMRM model, the least squares (LS) mean decrease in FPG from baseline was statistically significant at all visits, except at month 3. At month 12, the LS mean decrease in FPG was −0.54 (95% CI: −0.95, −0.14; p=0.009). The statistically significant LS mean decrease in FPG at months 6, 9 and 12 was consistent across the crude and fully-adjusted models (Table 10–10).

In the T2DM group, according to the fully-adjusted MMRM model, the LS mean decrease in FPG from baseline was statistically significant at all visits. At month 12, the LS mean decrease in FPG was −0.84 (95% CI: −1.09, −0.60; p<0.001). The statistically significant LS mean decrease in FPG at all visits was consistent across the crude and fully-adjusted models (Table 10–11).

Table 10–10 Analysis of change from baseline in FPG by visit for T1DM (Full Analysis Set –– excluding Germany)

Model	Visit	n	LS Mean	95% CI	p-value
Crude [1]	Visit 3 (month 3)	262	-0.09	(-0.54, 0.37)	0.714
	Visit 4 (month 6)	240	-0.83	(-1.20, -0.46)	<0.001
	Visit 5 (month 9)	217	-0.54	(-0.96, -0.12)	0.013
	Visit 6 (month 12)	230	-0.64	(-1.02, -0.26)	0.001
Fully-Adjusted [2]	Visit 3 (month 3)	229	-0.04	(-0.52, 0.45)	0.885
	Visit 4 (month 6)	218	-0.75	(-1.14, -0.37)	<0.001
	Visit 5 (month 9)	191	-0.58	(-1.01, -0.15)	0.008
	Visit 6 (month 12)	209	-0.54	(-0.95, -0.14)	0.009
Crude on Patients with Full set of Covariates	Visit 3 (month 3)	229	-0.01	(-0.50, 0.48)	0.961
	Visit 4 (month 6)	218	-0.77	(-1.16, -0.38)	<0.001
	Visit 5 (month 9)	191	-0.54	(-0.97, -0.10)	0.015
	Visit 6 (month 12)	209	-0.57	(-0.97, -0.16)	0.006

[1] Crude model was based on an MMRM model with Baseline FPG and visit.

[2] Fully adjusted model was based on an MMRM model with Baseline FPG, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline and Country.

The OBSMARGINS option was applied whilst calculating the LSMEANS.

MMRM = mixed model for repeated measurements; CI = confidence interval; T1DM = type 1 diabetes mellitus; FPG = fasting plasma glucose; LS = least squares.

Cross-reference: EOT Table 14.2.2.1.2.1

Table 10–11 Analysis of change from baseline in FPG by visit for T2DM (Full Analysis Set – excluding Germany)

Model	Visit	n	LS Mean	95% CI	p-value
Crude [1]	Visit 3 (month 3)	373	-0.76	(-1.01, -0.51)	<0.001
	Visit 4 (month 6)	343	-0.94	(-1.18, -0.70)	<0.001
	Visit 5 (month 9)	321	-1.04	(-1.30, -0.79)	<0.001
	Visit 6 (month 12)	348	-0.95	(-1.18, -0.72)	<0.001
Fully-Adjusted [2]	Visit 3 (month 3)	341	-0.75	(-1.02, -0.49)	<0.001
	Visit 4 (month 6)	305	-0.92	(-1.17, -0.66)	<0.001
	Visit 5 (month 9)	294	-1.02	(-1.29, -0.75)	<0.001
	Visit 6 (month 12)	313	-0.84	(-1.09, -0.60)	<0.001
Crude on Patients with Full set of Covariates	Visit 3 (month 3)	341	-0.76	(-1.02, -0.49)	<0.001
	Visit 4 (month 6)	305	-0.91	(-1.17, -0.66)	<0.001
	Visit 5 (month 9)	294	-1.01	(-1.28, -0.73)	<0.001
	Visit 6 (month 12)	313	-0.85	(-1.10, -0.60)	<0.001
Fully Adjusted excluding time-varying covariates [3]	Visit 3 (month 3)	341	-0.76	(-1.03, -0.49)	<0.001
	Visit 4 (month 6)	305	-0.92	(-1.18, -0.67)	<0.001
	Visit 5 (month 9)	294	-1.01	(-1.28, -0.74)	<0.001
	Visit 6 (month 12)	313	-0.84	(-1.08, -0.59)	<0.001

Model	Visit	n	LS Mean	95% CI	p-value

[1] Crude model was based on an MMRM model with baseline FPG and visit.

[2] Fully adjusted model was based on an MMRM model with baseline FPG, Visit, Duration of DM at baseline, Gender, BMI at baseline, Age at baseline, Bolus insulin (Y/N, time-varying), SU+Glinides (Y/N, time-varying), GLP-1 (Y/N, time-varying), Other OADs (Y/N, time-varying) and Country

[3] Fully adjusted model excluding time-varying covariates is based on an MMRM model with Baseline FPG, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline, Baseline Bolus insulin (Y/N), Baseline SU+Glinides (Y/N), Baseline GLP-1 (Y/N), Baseline Other OADs (Y/N) and Country

The OBSMARGINS option was applied whilst calculating the LSMEANS.

MMRM = mixed model for repeated measurements; BMI = body mass index; CI = confidence interval; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; LS = least squares; OADs = oral anti-diabetic drugs; SU = sulphonylureas; T2DM = type 2 diabetes mellitus; Y/N = yes/no.

Cross-reference: EOT Table 14.2.2.1.2.2

A boxplot of FPG values for the FAS is displayed in Figure 14.2.2.1.1.2.1 and Figure 14.2.2.1.1.2.2 (for T1DM and T2DM, respectively, excluding Germany).

Individual details for FPG are shown in Annex 2, Listing 16.2.6.6.

10.4.2.2 HbA1c responder rates at the end of the study

HbA1c responder rates at the end of the study (i.e., at the last visit where HbA1c measurements were available in the observation period) are summarised for the FAS outside Germany in Table 14.2.2.2.1.

The proportions of T1DM and T2DM patients with HbA1c response at the end of the study were as follows:

- HbA1c <7%: 19.4% in T1DM patients and 24.2% in T2DM patients
- HbA1c <7.5%: 34.7% in T1DM patients and 44.2% in T2DM patients
- HbA1c <7% without severe hypoglycaemic events during the last 12 weeks of treatment: 19.4% in T1DM patients and 24.2% in T2DM patients
- HbA1c <7.5% without severe hypoglycaemic events during the last 12 weeks of treatment: 34.2% in T1DM patients and 44.2% in T2DM patients
- HbA1c lowered according to national guidelines: 18.7% in T1DM patients and 25.2% in T2DM patients
- For patients with a valid visit 6:
  - HbA1c <7%: 20.6% in T1DM patients and 23.6% in T2DM patients
  - HbA1c <7.5%: 35.9% in T1DM patients and 41.1% in T2DM patients

HbA1c responder rates for patients who completed the study (i.e., had a valid visit 6 in the observation period and within the visit 6 window) are summarised in Table 14.2.2.2.2. The results

for responders defined as having Hb1Ac <7% or <7.5% were similar to those observed for the overall FAS population (see Table 14.2.2.2.1).

10.4.2.3 Change from baseline (visit 2) in HbA1c after 3, 6, 9, and 12 months of treatment

HbA1c values by visit and change from baseline are summarised for the FAS outside Germany in Table 14.2.2.3.1.

For T1DM patients, the mean HbA1c value was 8.10% at baseline and 7.84% at month 12. Mean HbA1c was decreased compared to baseline at each visit during the 12-month observation period, starting at month 3. At month 12, the mean absolute decrease in HbA1c was −0.14%.

For T2DM patients, the mean HbA1c value was 8.18% at baseline and 7.75% at month 12. Mean HbA1c was decreased compared to baseline at each visit during the 12-month observation period, starting at month 3. At month 12, the mean absolute decrease in HbA1c was −0.36%.

MMRM analyses of change in HbA1c from baseline by visit using crude and adjusted estimates are presented in Table 10–12 for T1DM patients and Table 10–13 for T2DM patients.

In the T1DM group, according to the fully-adjusted MMRM model, the LS mean decrease in HbA1c from baseline was similar across the 12-month observation period and was statistically significant at all visits. At month 12, the LS mean decrease in HbA1c was -0.15 (95% CI: -0.23, -0.07; p<0.001). The statistically significant LS mean decrease in HbA1c at all visits was consistent across the crude and fully-adjusted models (Table 10–12).

In the T2DM group, according to the fully-adjusted MMRM model, the LS mean decrease in HbA1c from baseline was similar across the 12-month observation period and was statistically significant at all visits. At month 12, the LS mean decrease in HbA1c was -0.32 (95% CI: -0.42, -0.22; p<0.001). The statistically significant LS mean decrease in HbA1c at all visits was consistent across the crude and fully-adjusted models (Table 10–13).

Table 10–12 Analysis of change from baseline in HbA1c by visit for T1DM (Full Analysis Set – excluding Germany)

Model	Visit	n	LS Mean	95% CI	p-value
Crude [1]	Visit 3 (month 3)	387	-0.10	(-0.17, -0.03)	0.004
	Visit 4 (month 6)	357	-0.12	(-0.20, -0.05)	0.001
	Visit 5 (month 9)	308	-0.12	(-0.21, -0.04)	0.004
	Visit 6 (month 12)	355	-0.13	(-0.21, -0.05)	0.001
Fully-Adjusted [2]	Visit 3 (month 3)	345	-0.10	(-0.17, -0.03)	0.006
	Visit 4 (month 6)	319	-0.14	(-0.22, -0.06)	<0.001
	Visit 5 (month 9)	268	-0.14	(-0.23, -0.05)	0.003
	Visit 6 (month 12)	321	-0.15	(-0.23, -0.07)	<0.001
Crude on Patients with Full set of Covariates	Visit 3 (month 3)	345	-0.09	(-0.17, -0.02)	0.013
	Visit 4 (month 6)	319	-0.12	(-0.21, -0.04)	0.002
	Visit 5 (month 9)	268	-0.12	(-0.21, -0.03)	0.007
	Visit 6 (month 12)	321	-0.14	(-0.22, -0.05)	0.001

[1] Crude model was based on an MMRM model with baseline HbA1c and visit.

[2] Fully adjusted model was based on an MMRM model with baseline HbA1c, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline and Country.

The OBSMARGINS option was applied whilst calculating the LSMEANS.

MMRM = mixed model for repeated measurements; BMI = body mass index; CI = confidence interval; HbA1c = glycated haemoglobin A1c; T1DM = type 1 diabetes mellitus; LS = least squares.

Cross-reference: EOT Table 14.2.2.3.2.1

Table 10–13 Analysis of change from baseline in HbA1c by visit for T2DM (Full Analysis Set – excluding Germany)

Model	Visit	n	LS Mean	95% CI	p-value
Crude [1]	Visit 3 (month 3)	455	-0.31	(-0.39, -0.22)	<0.001
	Visit 4 (month 6)	409	-0.29	(-0.38, -0.19)	<0.001
	Visit 5 (month 9)	382	-0.39	(-0.48, -0.29)	<0.001
	Visit 6 (month 12)	423	-0.36	(-0.45, -0.26)	<0.001
Fully-Adjusted [2]	Visit 3 (month 3)	410	-0.29	(-0.37, -0.20)	<0.001
	Visit 4 (month 6)	361	-0.26	(-0.35, -0.16)	<0.001
	Visit 5 (month 9)	341	-0.37	(-0.46, -0.27)	<0.001
	Visit 6 (month 12)	377	-0.32	(-0.42, -0.22)	<0.001
Crude on Patients with Full set of Covariates	Visit 3 (month 3)	410	-0.28	(-0.37, -0.19)	<0.001
	Visit 4 (month 6)	361	-0.25	(-0.35, -0.16)	<0.001
	Visit 5 (month 9)	341	-0.36	(-0.46, -0.27)	<0.001
	Visit 6 (month 12)	377	-0.32	(-0.42, -0.22)	<0.001
Fully Adjusted excluding time-varying covariates [3]	Visit 3 (month 3)	410	-0.28	(-0.37, -0.20)	<0.001
	Visit 4 (month 6)	361	-0.26	(-0.35, -0.16)	<0.001
	Visit 5 (month 9)	341	-0.36	(-0.46, -0.27)	<0.001
	Visit 6 (month 12)	377	-0.32	(-0.42, -0.22)	<0.001

Model	Visit	n	LS Mean	95% CI	p-value

[1] Crude model was based on an MMRM model with baseline HbA1c and visit.

[2] Fully adjusted model was based on an MMRM model with baseline HbA1c, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline, Bolus insulin (Y/N, time-varying), SU+Glinides (Y/N, time-varying), GLP-1 (Y/N, time-varying), Other OADs (Y/N, time-varying) and Country

[3] Fully adjusted model excluding time-varying covariates is based on an MMRM model with Baseline HbA1c, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline, Baseline Bolus insulin (Y/N), Baseline SU+Glinides (Y/N), Baseline GLP-1 (Y/N), Baseline Other OADs (Y/N) and Country.

The OBSMARGINS option was applied whilst calculating the LSMEANS.

MMRM = mixed model for repeated measurements; BMI = body mass index; CI = confidence interval; GLP-1 = glucagon-like peptide-1; HbA1c = glycated haemoglobin A1c; OADs = oral anti-diabetic drugs; T2DM = diabetes mellitus; LS = least squares; SU = sulphonylureas; Y/N = yes/no.

Cross-reference: EOT Table 14.2.2.3.2.2

A boxplot of HbA1c values for the FAS is displayed in Figure 14.2.2.3.1.2.1 and Figure 14.2.2.3.1.2.2 (for T1DM and T2DM, respectively, excluding Germany).

Individual details for HbA1c are shown in Annex 2, Listing 16.2.6.7.

10.4.2.4 Change from baseline in the number of severe hypoglycaemic episodes according to the ADA definition of hypoglycaemia during and after 12 months of treatment

Severe hypoglycaemic events (according to ADA definition, see Section 9.4.2.1) during the baseline period and at 12 months after baseline and change from baseline are summarised for FAS patients outside Germany in Table 14.2.2.4.1.

For T1DM patients, the mean rate of severe hypoglycaemic events during the baseline period and 12 months after baseline was 0.81 and 0.32 events per patient year, respectively. The absolute mean change in the rate of severe hypoglycaemic events from the baseline period to 12 months after baseline was −0.53 events per patient year.

For T2DM patients, the mean rate of severe hypoglycaemic events during the baseline period and 12 months after baseline was 0.02 and 0.08 events per patient year, respectively. The absolute mean change in the rate of severe hypoglycaemic events from the baseline period to 12 months after baseline was 0.07 events per patient year.

The incidence of severe hypoglycaemic events (according to ADA definition) during the 12-month observation period is shown in Table 10–14.

For T1DM patients, 3.7% of patients reported 31 severe hypoglycaemic events during the baseline period and 2.8% of patients reported 35 events during the 12-month observation period. The

estimated annual incidence rate of any severe hypoglycaemic events decreased from 0.8 (95% CI: 0.5, 1.1) during the baseline period to 0.3 (95% CI: 0.2, 0.5) during the 12-month observation period.

For T2DM patients, 0.2% of patients reported 1 severe hypoglycaemic event during the baseline period and 0.9% of patients reported 7 events during the 12-month observation period. The estimated annual incidence rate of any severe hypoglycaemic events increased from 0.0 (95% CI: 0.0, 0.1) during the baseline period to 0.1 (95% CI: 0.0, 0.1) during the 12-month observation period. These results should be interpreted with caution due to the low number of events.

Table 10–14 Incidence of any ADA-defined severe hypoglycaemic event during the 12-month observation period (Full Analysis Set – excluding Germany)

Item	T1DM (N=556)	T2DM (N=611)
4 Week Baseline Period* [Pre-Baseline]		
n	508	537
Number of Patients Having a Hypoglycaemic Event [n (%)]	19 (3.7)	1 (0.2)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	2.3, 5.8	0.0, 1.0
Number of Hypoglycaemic Events [n]	31	1
Total Follow-Up Time [patient years]	38.5	40.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	0.8 (0.5, 1.1)	0.0 (0.0, 0.1)
12 Month Observation Period* [Post-Baseline]		
n	502	558
Number of Patients Having a Hypoglycaemic Event [n (%)]	14 (2.8)	5 (0.9)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	1.5, 4.6	0.3, 2.1
Number of Hypoglycaemic Events [n]	35	7
Total Follow-Up Time [patient years]	104.5	118.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	0.3 (0.2, 0.5)	0.1 (0.0, 0.1)

Based on diary periods with 26-30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' match exactly to what was recorded in the patient diary.

Severe hypoglycaemic event: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.

[1] Clopper-Pearson 95% CIs are reported.

[2] Exact 95% CIs are reported.

[3] Estimated number of events per patient year.

CI = confidence interval; IR = incidence rate; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.2.4.3

A negative binomial model examining the crude and fully-adjusted change in incidence rate of severe hypoglycaemic events (according to ADA definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.4.2.1 for T1DM patients and Table 14.2.2.4.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of severe hypoglycaemic events was 0.28 (95% CI: 0.14, 0.56; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.4.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of severe hypoglycaemic events was 2.87 (95% CI: 0.33, 24.65; p=0.337), indicating a statistically non-significant increase in events during the 12-month observation period. Lack of statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.4.2.2). These results should be interpreted with caution due to small sample size and low number of events.

A boxplot of any severe hypoglycaemic event rate per patient year for the FAS is displayed in Figure 14.2.2.4.1.1 and Figure 14.2.2.4.1.2 (for T1DM and T2DM, respectively, excluding Germany).

Individual patient details on hypoglycaemic episode categorisations and severe hypoglycaemic episodes according to the ADA definition are shown in Annex 2, Listing 16.2.6.3 and Listing 16.2.6.4.1, respectively.

10.4.2.5 Change from the baseline period in the number of asymptomatic hypoglycaemic episodes according to the ADA definition during and after 12 months of treatment

An asymptomatic hypoglycaemic event is defined as an episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL). Events during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.5.1.

For T1DM patients, the mean rate of asymptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 18.89 and 17.32 events per patient year, respectively. The absolute mean change in the rate of asymptomatic hypoglycaemic events from the baseline period to 12 months after baseline was −1.75 events per patient year.

For T2DM patients, the mean rate of asymptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 2.77 and 1.48 events per patient year, respectively. The

absolute mean change in the rate of asymptomatic hypoglycaemic events from the baseline period to 12 months after baseline was −0.96 events per patient year.

The incidence of any asymptomatic hypoglycaemic events (according to ADA definition) during the 12-month observation period is shown in Table 14.2.2.5.3.

For T1DM patients, 152 patients (29.9%) reported 729 asymptomatic hypoglycaemic events during the baseline period and 211 patients (42.0%) reported 1937 events during the 12-month observation period. The estimated annual incidence rate of asymptomatic hypoglycaemic events was 18.9 (95% CI: 17.6, 20.4) during the baseline period and 18.5 (95% CI: 17.7, 19.4) during the 12-month observation period.

For T2DM patients, 41 patients (7.6%) reported 113 any symptomatic hypoglycaemic events during the baseline period and 57 patients (10.2%) reported 172 events during the 12-month observation period. The estimated annual incidence rate of asymptomatic hypoglycaemic events decreased from 2.8 (95% CI: 2.3, 3.3) during the baseline period to 1.4 (95% CI: 1.2, 1.7) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of asymptomatic hypoglycaemic events (according to ADA definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.5.2.1 for T1DM patients and Table 14.2.2.5.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of asymptomatic hypoglycaemic events was 0.88 (95% CI: 0.71, 1.09; p=0.242), indicating a statistically non-significant decrease in events during the 12-month observation period. Lack of statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.5.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence ratio (12 months after baseline/4 weeks before baseline) of asymptomatic hypoglycaemic events was 0.48 (95% CI: 0.27, 0.87; p=0.016), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.5.2.2).

Individual patient details on asymptomatic hypoglycaemic episodes according to the ADA definition are shown in Annex 2, Listing 16.2.6.4.1.

10.4.2.6 Change from the baseline period in the number of documented symptomatic hypoglycaemic episodes according to the ADA definition during and after 12 months of treatment

A documented symptomatic hypoglycaemic event is defined as an episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL). Events during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.6.1.

For T1DM patients, the mean rate of documented symptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 55.55 and 45.22 events per patient year, respectively. The absolute mean change in the rate of documented symptomatic hypoglycaemic events from the baseline period to 12 months after baseline was −10.72 events per patient year.

For T2DM patients, the mean rate of documented symptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 10.23 and 5.43 events per patient year, respectively. The absolute mean change in the rate of documented symptomatic hypoglycaemic events from the baseline period to 12 months after baseline was −4.30 events per patient year.

The incidence of any documented symptomatic hypoglycaemic events (according to ADA definition) during the 12-month observation period is shown in Table 14.2.2.6.3.

For T1DM patients, 374 patients (73.6%) reported 2129 documented symptomatic hypoglycaemic events during the baseline period and 385 patients (76.7%) reported 4721 events during the 12-month observation period. The estimated annual incidence rate of documented symptomatic hypoglycaemic events decreased from 55.3 (95% CI: 53.0, 57.7) during the baseline period to 45.2 (95% CI: 43.9, 46.5) during the 12-month observation period.

For T2DM patients, 142 patients (26.4%) reported 418 documented symptomatic hypoglycaemic events during the baseline period and 146 patients (26.2%) reported 685 events during the 12-month observation period. The estimated annual incidence rate of documented symptomatic hypoglycaemic events decreased from 10.2 (95% CI: 9.3, 11.3) during the baseline period to 5.8 (95% CI: 5.3, 6.2) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of documented symptomatic hypoglycaemic events (according to ADA definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.6.2.1 for T1DM patients and Table 14.2.2.6.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of documented symptomatic hypoglycaemic events was 0.83 (95% CI: 0.76, 0.92; p<0.001), indicating a statistically significant decrease in events during

the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.6.2.1)

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of documented symptomatic hypoglycaemic events was 0.54 (95% CI: 0.44, 0.68; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.6.2.2).

Individual patient details on documented symptomatic hypoglycaemic episodes according to the ADA definition are shown in Annex 2, Listing 16.2.6.4.1.

10.4.2.7 Change from the baseline period in the number of pseudo-hypoglycaemic episodes according to the ADA definition during and after 12 months of treatment

A pseudo-hypoglycaemic event is an episode during which the person with diabetes reported any of the typical symptoms of hypoglycaemia with a measured PG concentration >3.9 mmol/L (70 mg/dL) but approaching that level. Events during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.7.1.

For T1DM patients, the mean rate of pseudo-hypoglycaemic events during the baseline period and 12 months after baseline was 4.30 and 2.04 events per patient year, respectively. The absolute mean change in the rate of pseudo-hypoglycaemic events from the baseline period to 12 months after baseline was −2.31 events per patient year.

For T2DM patients, the mean rate of pseudo-hypoglycaemic events during the baseline period and 12 months after baseline was 1.81 and 0.95 events per patient year, respectively. The absolute mean change in the rate of pseudo-hypoglycaemic events from the baseline period to 12 months after baseline was −0.91 events per patient year.

The incidence of any pseudo-hypoglycaemic events (according to ADA definition) during the 12-month observation period is shown in Table 14.2.2.7.3.

For T1DM patients, 68 patients (13.4%) reported 166 pseudo-hypoglycaemic events during the baseline period and 57 patients (11.4%) reported 193 events during the 12-month observation period. The estimated annual incidence rate of pseudo-hypoglycaemic event decreased from 4.3 (95% CI: 3.7, 5.0) during the baseline period to 1.8 (95% CI: 1.6, 2.1) during the 12-month observation period.

For T2DM patients, 36 patients (6.7%) reported 74 hypoglycaemic events during the baseline period and 42 patients (7.5%) reported 107 events during the 12-month observation period. The

estimated annual incidence rate of pseudo-hypoglycaemic event decreased from 1.8 (95% CI: 1.4, 2.3) during the baseline period to 0.9 (95% CI: 0.7, 1.1) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of pseudo-hypoglycaemic events (according to ADA definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.7.2.1 for T1DM patients and Table 14.2.2.7.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of pseudo-hypoglycaemic events was 0.44 (95% CI: 0.29, 0.67; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.7.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of pseudo-hypoglycaemic events was 0.42 (95% CI: 0.28, 0.63; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.7.2.2).

Individual patient details on pseudo-hypoglycaemic episodes according to the ADA definition are shown in Annex 2, Listing 16.2.6.4.1.

10.4.2.8 Change from the baseline period in the number of probable symptomatic hypoglycaemic episodes according to the ADA definition during and after 12 months of treatment

A probable symptomatic hypoglycaemic event is an episode during which symptoms of hypoglycaemia were not accompanied by a PG determination but that was presumably caused by a PG concentration ≤3.9 mmol/L (70 mg/dL). Events during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.8.1.

For T1DM patients, the mean rate of probable symptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 5.26 and 2.83 events per patient year, respectively. The absolute mean change in the rate of probable symptomatic events from the baseline period to 12 months after baseline was −2.25 events per patient year.

For T2DM patients, the mean rate of probable symptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 1.05 and 0.34 events per patient year, respectively. The absolute mean change in the rate of probable symptomatic events from the baseline period to 12 months after baseline was −0.67 events per patient year.

The incidence of any probable symptomatic hypoglycaemic events (according to ADA definition) during the 12-month observation period is shown in Table 14.2.2.8.3.

For T1DM patients, 74 patients (14.6%) reported 203 probable symptomatic hypoglycaemic events during the baseline period and 85 patients (16.9%) reported 286 events during the 12-month observation period. The estimated annual incidence rate of probable symptomatic hypoglycaemic events decreased from 5.3 (95% CI: 4.6, 6.0) during the baseline period to 2.7 (95% CI: 2.4, 3.1) during the 12-month period.

For T2DM patients, 23 patients (4.3%) reported 42 hypoglycaemic events during the baseline period and 24 patients (4.3%) reported 38 events during the 12-month observation period. The estimated annual incidence rate of probable symptomatic hypoglycaemic events decreased from 1.0 (95% CI: 0.7, 1.4) during the baseline period to 0.3 (95% CI: 0.2, 0.4) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of probable symptomatic hypoglycaemic events (according to ADA definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.8.2.1 for T1DM patients and Table 14.2.2.8.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of probable symptomatic hypoglycaemic events was 0.53 (95% CI: 0.36, 0.77; $p<0.001$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.8.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of probable symptomatic hypoglycaemic events was 0.36 (95% CI: 0.18, 0.70; $p=0.003$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.8.2.2).

Individual patient details on probable symptomatic hypoglycaemic episodes according to the ADA definition are shown in Annex 2, Listing 16.2.6.4.1.

10.4.2.9 Change from the baseline period in the number of severe or blood glucose confirmed hypoglycaemic episodes according to the Novo Nordisk definition during and after 12 months of treatment

Severe or blood glucose confirmed hypoglycaemic events according to the Novo Nordisk definition (see Section 9.4.2.1) during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.9.1.1.

For T1DM patients, the mean rate of severe or blood glucose confirmed hypoglycaemic events during the baseline period and 12 months after baseline was 33.00 and 25.83 events per patient year, respectively. The absolute mean change in the rate of severe or blood glucose confirmed hypoglycaemic events from the baseline period to 12 months after baseline was −7.25 events per patient year.

For T2DM patients, the mean rate of severe or blood glucose confirmed hypoglycaemic events during the baseline period and 12 months after baseline was 4.03 and 2.24 events per patient year, respectively. The absolute mean change in the rate of severe or blood glucose confirmed hypoglycaemic events from the baseline period to 12 months after baseline was −1.54 events per patient year.

The incidence of any severe or blood glucose confirmed hypoglycaemic events (according to the Novo Nordisk definition) during the 12-month observation period is shown in Table 14.2.2.9.1.3.

For T1DM patients, 324 patients (63.8%) reported 1265 severe or blood glucose confirmed hypoglycaemic events during the baseline period and 344 patients (68.5%) reported 2694 events during the 12-month observation period. The estimated annual incidence rate of severe or blood glucose confirmed hypoglycaemic events decreased from 32.8 (95% CI: 31.1, 34.7) during the baseline period to 25.8 (95% CI: 24.8, 26.8) during the 12-month observation period.

For T2DM patients, 81 patients (15.1%) reported 165 severe or blood glucose confirmed hypoglycaemic events during the baseline period and 85 patients (15.2%) reported 279 events during the 12-month observation period. The estimated annual incidence rate of severe or blood glucose confirmed hypoglycaemic events decreased from 4.0 (95% CI: 3.5, 4.7) during the baseline period to 2.3 (95% CI: 2.1, 2.6) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of severe or blood glucose confirmed hypoglycaemic events (according to the Novo Nordisk definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.9.1.2.1 for T1DM patients and Table 14.2.2.9.1.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of severe or blood glucose confirmed hypoglycaemic events was 0.79 (95% CI: 0.70, 0.90; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.9.1.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of severe or blood glucose confirmed hypoglycaemic events was 0.51 (95% CI: 0.38, 0.70; p<0.001), indicating a statistically significant decrease in events during

the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.9.1.2.2).

Individual patient details on severe or blood glucose confirmed hypoglycaemic episodes according to the Novo Nordisk definition are shown in Annex 2, Listing 16.2.6.3 and Listing 16.2.6.4.2.

10.4.2.10 Change from the baseline period in the number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes according to the Novo Nordisk definition during and after 12 months of treatment

Severe or blood glucose confirmed symptomatic hypoglycaemic events according to the Novo Nordisk definition (see Section 9.4.2.1) during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.9.2.1.

For T1DM patients, the mean rate of severe or blood glucose confirmed symptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 26.42 and 19.64 events per patient year, respectively. The absolute mean change in the rate of severe or blood glucose confirmed symptomatic hypoglycaemic events from the baseline period to 12 months after baseline was −6.64 events per patient year.

For T2DM patients, the mean rate of severe or blood glucose confirmed symptomatic hypoglycaemic events during the baseline period and 12 months after baseline was 3.28 and 1.91 events per patient year, respectively. The absolute mean change in the rate of severe or blood glucose confirmed symptomatic hypoglycaemic events from the baseline period to 12 months after baseline was −1.20 events per patient year.

The incidence of any severe or blood glucose confirmed symptomatic hypoglycaemic events (according to the Novo Nordisk definition) during the 12-month observation period is shown in Table 14.2.2.9.2.3.

For T1DM patients, 303 patients (59.6%) reported 1011 severe or blood glucose confirmed symptomatic hypoglycaemic events during the baseline period and 321 patients (63.9%) reported 1995 events during the 12-month observation period. The estimated annual incidence rate of severe or blood glucose confirmed symptomatic hypoglycaemic events decreased from 26.3 (95% CI: 24.7, 27.9) during the baseline period to 19.1 (95% CI: 18.3, 19.9) during the 12-month observation period.

For T2DM patients, 67 patients (12.5%) reported 134 severe or blood glucose confirmed symptomatic hypoglycaemic events during the baseline period and 77 patients (13.8%) reported 244 events during the 12-month observation period. The estimated annual incidence rate of severe or blood glucose confirmed symptomatic hypoglycaemic events decreased from 3.3 (95% CI: 2.8, 3.9) during the baseline period to 2.1 (95% CI: 1.8, 2.3) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of severe or blood glucose confirmed symptomatic hypoglycaemic events (according to the Novo Nordisk definition) between the baseline period and 12 months after baseline is shown in Table 14.2.2.9.2.2.1 for T1DM patients and Table 14.2.2.9.2.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of severe or blood glucose confirmed symptomatic hypoglycaemic events was 0.76 (95% CI: 0.67, 0.86; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.9.2.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of severe or blood glucose confirmed symptomatic hypoglycaemic events was 0.56 (95% CI: 0.40, 0.79; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.9.2.2.2).

Individual patient details on severe or blood glucose confirmed symptomatic hypoglycaemic episodes according to the Novo Nordisk definition are shown in Annex 2, Listing 16.2.6.4.2.

10.4.2.11 Change from the baseline period in the number of any hypoglycaemic episodes during the maintenance period

Any hypoglycaemic events during the baseline period and during the maintenance period (i.e., period after 16 weeks of treatment until the end of treatment [including diary data from visits 4, 5 and 6]) and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.10.1.

For T1DM patients, the mean rate of any hypoglycaemic events during the baseline period and during the maintenance period was 86.03 and 65.56 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events from the baseline period to the maintenance period was −21.59 events per patient year.

For T2DM patients, the mean rate of any hypoglycaemic events during the baseline period and during the maintenance period was 17.12 and 7.37 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events from the baseline period to the maintenance period was −9.41 events per patient year.

The incidence of any hypoglycaemic events during the maintenance period is shown in Table 14.2.2.10.3.

For T1DM patients, 426 patients (83.9%) reported 3305 hypoglycaemic events during the baseline period and 365 patients (79.3%) reported 4849 events during the 12-month observation period. The

estimated annual incidence rate of any hypoglycaemic events decreased from 85.8 (95% CI: 82.9, 88.8) during the baseline period to 64.6 (95% CI: 62.8, 66.4) during the maintenance period.

For T2DM patients, 187 patients (34.8%) reported 699 hypoglycaemic events during the baseline period and 145 patients (27.6%) reported 672 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 17.1 (95% CI: 15.9, 18.5) during the baseline period to 7.8 (95% CI: 7.3, 8.5) during the maintenance period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events between the baseline period and the maintenance period is shown in Table 14.2.2.10.2.1 for T1DM patients and Table 14.2.2.10.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (maintenance period/4 weeks before baseline) of any hypoglycaemic events was 0.76 (95% CI: 0.69, 0.84; p<0.001), indicating a statistically significant decrease in events during the maintenance period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.10.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (maintenance period/4 weeks before baseline) of any hypoglycaemic events was 0.40 (95% CI: 0.33, 0.49; p<0.001), indicating a statistically significant decrease in events during the maintenance period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.10.2.2).

Individual patient details on any hypoglycaemic episodes are shown in Annex 2, Listing 16.2.6.3.

10.4.2.12 Change from the baseline period in the number of any nocturnal hypoglycaemic episodes during the maintenance period

Any nocturnal (between 00:01 and 05:59 am) hypoglycaemic events during the baseline period and during the maintenance period (i.e., period after 16 weeks of treatment until the end of treatment) and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.11.1.

For T1DM patients, the mean rate of any nocturnal hypoglycaemic events during the baseline period and during the maintenance period was 8.90 and 5.35 events per patient year, respectively. The absolute mean change in the rate of any nocturnal hypoglycaemic events from the baseline period to the maintenance period was −3.98 events per patient year.

For T2DM patients, the mean rate of any nocturnal hypoglycaemic events during the baseline period and during the maintenance period was 1.32 and 0.49 events per patient year, respectively. The absolute mean change in the rate of any nocturnal hypoglycaemic events from the baseline period to the maintenance period was −0.76 events per patient year.

The incidence of any nocturnal hypoglycaemic events during the maintenance period is shown in Table 14.2.2.11.3.

For T1DM patients, 163 patients (32.1%) reported 342 nocturnal hypoglycaemic events during the baseline period and 157 patients (34.1%) reported 412 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 8.9 (95% CI: 8.0, 9.9) during the baseline period to 5.5 (95% CI: 5.0, 6.0) during the maintenance period.

For T2DM patients, 31 patients (5.8%) reported 54 nocturnal hypoglycaemic events during the baseline period and 21 patients (4.0%) reported 42 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 1.3 (95% CI: 1.0, 1.7) during the baseline period to 0.5 (95% CI: 0.4, 0.7) during the baseline period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any nocturnal hypoglycaemic events between the baseline period and the maintenance period is shown in Table 14.2.2.11.2.1 for T1DM patients and Table 14.2.2.11.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (maintenance period/4 weeks before baseline) of any nocturnal hypoglycaemic events was 0.61 (95% CI: 0.50, 0.74; $p<0.001$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.11.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (maintenance period/4 weeks before baseline) of any nocturnal hypoglycaemic events was 0.35 (95% CI: 0.19, 0.64; $p<0.001$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.11.2.2).

Individual patient details on any nocturnal hypoglycaemic episodes during the maintenance period are shown in Annex 2, Listing 16.2.6.3.

10.4.2.13 Change from the baseline period in the number of any nocturnal hypoglycaemic episodes during and after 12 months of treatment

Any nocturnal (between 00:01 and 05:59 am) hypoglycaemic events during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.12.1.

For T1DM patients, the mean rate of any nocturnal hypoglycaemic events during the baseline period and 12 months after baseline was 8.90 and 5.05 events per patient year, respectively. The absolute mean change in the rate of any nocturnal hypoglycaemic events from the baseline period to 12 months after baseline was −4.17 events per patient year.

For T2DM patients, the mean rate of any nocturnal hypoglycaemic events during the baseline period and 12 months after baseline was 1.32 and 0.47 events per patient year, respectively. The absolute mean change in the rate of any nocturnal hypoglycaemic events from during the baseline period to 12 months after baseline was −0.75 events per patient year.

The incidence of any nocturnal hypoglycaemic events during the 12-month observation period is shown in Table 10–15.

For T1DM patients, 32.1% of patients reported 342 nocturnal hypoglycaemic events during the baseline period and 39.0% of patients reported 561 events during the 12-month observation period. The estimated annual incidence rate of any nocturnal hypoglycaemic events decreased from 8.9 (95% CI: 8.0, 9.9) during the baseline period to 5.4 (95% CI: 4.9, 5.8) during the 12-month treatment period.

For T2DM patients, 5.8% of patients reported 54 nocturnal hypoglycaemic events during the baseline period and 5.4% of patients reported 57 events during the 12-month observation period. The estimated annual incidence rate of any nocturnal hypoglycaemic events decreased from 1.3 (95% CI: 1.0, 1.7) during the baseline period to 0.5 (95% CI: 0.4, 0.6) during the baseline period.

Table 10–15 Incidence of any nocturnal hypoglycaemic event during the 12-month observation period (Full Analysis Set – excluding Germany)

Item	T1DM (N=556)	T2DM (N=611)
4 Week Baseline Period* [Pre-Baseline]		
n	508	537
Number of Patients Having a Hypoglycaemic Event [n (%)]	163 (32.1)	31 (5.8)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	28.0, 36.3	4.0, 8.1
Number of Hypoglycaemic Events [n]	342	54
Total Follow-Up Time [patient years]	38.5	40.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	8.9 (8.0, 9.9)	1.3 (1.0, 1.7)
12 Month Observation Period* [Post-Baseline]		
n	502	558
Number of Patients Having a Hypoglycaemic Event [n (%)]	196 (39.0)	30 (5.4)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	34.8, 43.5	3.7, 7.6
Number of Hypoglycaemic Events [n]	561	57
Total Follow-Up Time [patient years]	104.5	118.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	5.4 (4.9, 5.8)	0.5 (0.4, 0.6)

Based on diary periods with 26-30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to what was recorded in the patient diary.

Nocturnal Events were identified as any event that occurred during (00:01-05:59), events with a missing time were not included in Nocturnal Events.

[1] Clopper-Pearson 95% CIs are reported.

[2] Exact 95% CIs are reported.

[3] Estimated number of events per patient year.

CI = confidence interval; IR = incidence rate; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.2.12.3

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any nocturnal hypoglycaemic events between the baseline period and 12 months after treatment is shown in Table 14.2.2.12.2.1 for T1DM patients and Table 14.2.2.12.2.2 for T2DM

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any nocturnal hypoglycaemic events was 0.61 (95% CI: 0.50, 0.73; $p<0.001$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.12.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any nocturnal hypoglycaemic events was 0.35 (95% CI: 0.20, 0.62; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.12.2.2).

A boxplot of any nocturnal hypoglycaemic event per patient year for the FAS is displayed in Figure 14.2.2.12.1.1 and Figure 14.2.2.12.1.2 (for T1DM and T2DM, respectively, excluding Germany).

Individual patient details on any nocturnal hypoglycaemic episodes during and after the 12-month observation period are shown in Annex 2, Listing 16.2.6.3.

10.4.2.14 Change from the baseline period in the number of any hypoglycaemic episodes occurring during sleep during and after 12 months of treatment

Any hypoglycaemic events occurring between 22:01 and 07:59 am during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.13.1.

For T1DM patients, the mean rate of any hypoglycaemic events during sleep during the baseline period and 12 months after baseline was 12.17 and 8.01 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events occurring during sleep from the baseline period to 12 months after baseline was −4.79 events per patient year.

For T2DM patients, the mean rate of any hypoglycaemic events during sleep during the baseline period and 12 months after baseline was 2.05 and 0.87 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events occurring during sleep from the baseline period to 12 months after baseline was −1.15 events per patient year.

The incidence of any hypoglycaemic events occurring during sleep during the 12-month observation period is shown in Table 14.2.2.13.3.

For T1DM patients, 193 patients (38.0%) reported 470 hypoglycaemic events during the baseline period and 245 patients (48.8%) reported 879 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 12.2 (95% CI: 11.1, 13.4) during the baseline period to 8.4 (95% CI: 7.9, 9.0) and during the 12-month observation period.

For T2DM patients, 41 patients (7.6%) reported 84 hypoglycaemic events during the baseline period and 39 patients (7.0%) reported 108 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events decreased from 2.1 (95% CI: 1.6, 2.6) during the baseline period to 0.9 (95% CI: 0.7, 1.1) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events occurring during sleep between the baseline period and 12 months after baseline is shown in Table 14.2.2.13.2.1 for T1DM patients and Table 14.2.2.13.2.2 for T2DM patients.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any hypoglycaemic events occurring during sleep was 0.70 (95% CI: 0.59, 0.83; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.13.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any hypoglycaemic events occurring during sleep was 0.56 (95% CI: 0.34, 0.90; p=0.017), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.13.2.2).

Individual patient details on any hypoglycaemic episodes occurring during sleep are shown in Annex 2, Listing 16.2.6.3.

10.4.2.15 Change from the baseline period in the number of non-severe hypoglycaemic episodes during and after 12 months of treatment

Non-severe hypoglycaemic events, defined as an event in which the patient was able to treat themselves, during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.14.1.

For T1DM patients, the mean rate of non-severe hypoglycaemic events during the baseline period and 12 months after baseline was 78.96 and 65.08 events per patient year, respectively. The absolute mean change in the rate of non-severe hypoglycaemic events from the baseline period to 12 months after baseline was −14.24 events per patient year.

For T2DM patients, the mean rate of non-severe hypoglycaemic events during the baseline period and 12 months after baseline was 14.02 and 7.18 events per patient year, respectively. The absolute mean change in the rate of non-severe hypoglycaemic events from the baseline period to 12 months after baseline was −5.97 events per patient year.

The incidence of non-severe hypoglycaemic events during the 12-month observation period is shown in Table 10–16.

For T1DM patients, 81.9% of patients reported 3033 non-severe hypoglycaemic events during the baseline period and 81.9% of patients reported 6911 events during the 12-month observation period. The estimated annual incidence rate of non-severe hypoglycaemic events decreased from 78.8 (95%

CI: 76.0, 81.6) during the baseline period to 66.1 (95% CI: 64.6, 67.7) during the 12-month observation period.

For T2DM patients, 31.7% of patients reported 572 non-severe hypoglycaemic events during baseline and 31.4% of patients reported 889 events during the 12-month observation period. The estimated annual incidence rate of non-severe hypoglycaemic events decreased from 14.0 (95% CI: 12.9, 15.2) during the baseline period to 7.5 (95% CI: 7.0, 8.0) during the 12-month observation period.

Table 10–16 Incidence of any non-severe hypoglycaemic event during the 12-month observation period (Full Analysis Set – excluding Germany)

Item	T1DM (N=556)	T2DM (N=611)
4 Week Baseline Period [Pre-Baseline]		
n	508	537
Number of Patients Having a Hypoglycaemic Event [n (%)]	416 (81.9)	170 (31.7)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	78.3, 85.1	27.7, 35.8
Number of Hypoglycaemic Events [n]	3033	572
Total Follow-Up Time [patient years]	38.5	40.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	78.8 (76.0, 81.6)	14.0 (12.9, 15.2)
12 Month Observation Period* [Post-Baseline]		
n	502	558
Number of Patients Having a Hypoglycaemic Event [n (%)]	411 (81.9)	175 (31.4)
95% CI for Percentage of Patients Having a Hypoglycaemic Event [1]	78.2, 85.1	27.5, 35.4
Number of Hypoglycaemic Events [n]	6911	889
Total Follow-Up Time [patient years]	104.5	118.8
Estimated Annual Incidence Rate [IR (95% CI)] [2] [3]	66.1 (64.6, 67.7)	7.5 (7.0, 8.0)

*Based on diary periods with 26-30 days - where the dates of hypoglycaemic events recorded on the 'hypo page' matched exactly to what was recorded in the patient diary.

Non-severe: an episode which does not require assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions and includes an event during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤3.9 mmol/L (70 mg/dL) or 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) or an event not accompanied by typical symptoms of hypoglycaemia but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL).

[1] Clopper-Pearson 95% CIs are reported.

[2] Exact 95% CIs are reported.

[3] Estimated number of events per patient year.

CI = confidence interval; IR = incidence rate; PG=plasma glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.2.14.3

A negative binomial model examining the crude and fully-adjusted change in incidence rate of non-severe hypoglycaemic events between the baseline period and 12 months after baseline is shown in Table 14.2.2.14.2.1 for T1DM patients and Table 14.2.2.14.2.2 for T2DM patients.

For T1DM patients, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of non-severe hypoglycaemic events was 0.83 (95% CI: 0.76, 0.91; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.14.2.1).

For T2DM patients, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of non-severe hypoglycaemic events was 0.53 (95% CI: 0.44, 0.64; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.14.2.2).

A boxplot of any non-severe hypoglycaemic event per patient year for the FAS is displayed in Figure 14.2.2.14.1.1 and Figure 14.2.2.14.1.2 (for T1DM and T2DM, respectively, excluding Germany).

Individual patient details on non-severe hypoglycaemic episodes are shown in Annex 2, Listing 16.2.6.3.

10.4.2.16 Change from the baseline period in the number of any hypoglycaemic episodes in high-dose insulin users during and after 12 months of treatment

Any hypoglycaemic events in high-dose insulin users (defined as patients using >80 U insulin daily) during the baseline period and at 12 months after baseline and change from during the baseline period are summarised for the FAS outside Germany in Table 14.2.2.15.1.

For T1DM patients, the mean rate any hypoglycaemic events in high-dose insulin users during the baseline period and 12 months after baseline was 63.61 and 54.41 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events in high-dose insulin users from the baseline period to 12 months after baseline was −11.40 events per patient year.

For T2DM patients, the mean rate any hypoglycaemic events in high-dose insulin users during the baseline period and 12 months after baseline was 10.76 and 8.04 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events in high-dose insulin users from the baseline period to 12 months after baseline was −2.67 events per patient year.

The incidence of any hypoglycaemic events in high-dose insulin users during the 12-month observation period is shown in Table 14.2.2.15.3.

For T1DM patients, 32 patients (78.0%) reported 199 hypoglycaemic events during the baseline period and 31 patients (75.6%) reported 512 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events in high-dose insulin users decreased from 63.8 (95% CI: 55.2, 73.3) during the baseline period to 59.2 (95% CI: 54.1, 64.5) during the 12-month observation period.

For T2DM patients, 39 patients (32.5%) reported 98 hypoglycaemic events during the baseline period and 39 patients (32.8%) reported 191 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events in high-dose insulin users decreased from 10.8 (95% CI: 8.7, 13.1) during the baseline period to 7.8 (95% CI: 6.7, 9.0) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events in high-dose insulin users between the baseline period and 12 months after baseline is shown in Table 14.2.2.15.2.1 for T1DM patients and Table 14.2.2.15.2.2 for T2DM patients.

For T1DM patients, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any hypoglycaemic events in high-dose insulin users was 0.98 (95% CI: 0.67, 1.42; p=0.906), indicating a statistically non-significant decrease in events during the 12-month observation period. Lack of statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.15.2.1).

For T2DM patients, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any hypoglycaemic events in high-dose insulin users was 0.75 (95% CI: 0.44, 1.27; p=0.281), indicating a statistically non-significant decrease in events during the 12-month observation period. Lack of statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.15.2.2).

Individual patient details on hypoglycaemic episodes in high-dose insulin users are shown in Annex 2, Listing 16.2.6.3.

10.4.2.17 Change from the baseline period in the number of any hypoglycaemic episodes in hypo-prone patients during and after 12 months of treatment

Any hypoglycaemic events in hypo-prone patients (see Section 9.4.1.1) during the baseline period and at 12 months after baseline and change from the baseline period are summarised for the FAS outside Germany in Table 14.2.2.16.1.

For T1DM patients, the mean rate any hypoglycaemic events in hypo-prone patients during the baseline period and 12 months after baseline was 97.70 and 75.21 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events in hypo-prone patients from the baseline period to 12 months after baseline was −22.19 events per patient year

For T2DM patients, the mean rate any hypoglycaemic events in hypo-prone patients during the baseline period and 12 months after baseline was 22.07 and 10.79 events per patient year, respectively. The absolute mean change in the rate of any hypoglycaemic events in hypo-prone patients from the baseline period to 12 months after baseline was −9.65 events per patient year.

The incidence of any hypoglycaemic events in hypo-prone patients during the 12-month observation period is shown in Table 14.2.2.16.3.

For T1DM patients, 306 patients (89.0%) reported 2534 hypoglycaemic events during the baseline period and 301 patients (87.2%) reported 5509 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events in hypo-prone patients decreased from 97.2 (95% CI: 93.4, 101.0) during the baseline period to 75.5 (95% CI: 73.5, 77.5) during the 12-month observation period.

For T2DM patients, 131 patients (42.1%) reported 522 hypoglycaemic events during the baseline period and 128 patients (40.5%) reported 717 events during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events in hypo-prone patients decreased from 22.2 (95% CI: 20.3, 24.2) during the baseline period to 10.4 (95% CI: 9.6, 11.2) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of any hypoglycaemic events in in hypo-prone patients between the baseline period and 12 months after baseline is shown in Table 14.2.2.16.2.1 for T1DM patients and Table 14.2.2.16.2.2 for T2DM patients.

For T1DM patients, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any hypoglycaemic events in hypo-prone patients was 0.78 (95% CI: 0.70, 0.86; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.16.2.1).

For T2DM patients, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/4 weeks before baseline) of any hypoglycaemic events in in hypo-prone patients was 0.46 (95% CI: 0.37, 0.56; p<0.001), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.2.2.16.2.2).

Individual patient details on hypoglycaemic episodes in hypo-prone patients are shown in Annex 2, Listing 16.2.6.3.

10.4.3 Secondary observational endpoints - Secondary observational safety endpoints

Select secondary observational endpoint results are described in Sections 10.4.3.1 and 10.4.3.2. Other secondary safety endpoints (as per SAP) are described in the sections indicated: SADRs Section 10.7.3, MESI (medication errors) Section 10.7.3, pregnancies Section 10.7.6, TEAEs and adverse drug reactions (ADR) Section 10.7.1.

10.4.3.1 Change from the baseline period in the number of severe hypoglycaemic episodes after 12 months of treatment

Baseline for this endpoint was defined as the 6-month recall period before visit 1, when patients were asked to recall any severe hypoglycaemic events over the previous 6 months. Any severe hypoglycaemic events during and after 12 months of treatment were taken from AE data recorded throughout the study.

Severe hypoglycaemic events during the 6-month recall period and 12 months after baseline and change from the 6-month baseline period are summarised for patients outside Germany in Table 14.3.2.1.1.

For T1DM patients, the mean rate of severe hypoglycaemic events during the 6-month recall period and after 12 months of treatment was 1.97 and 0.10 events per patient year, respectively. The absolute mean change in the rate of severe hypoglycaemic events from the 6-month recall period to 12 months after baseline was −1.87 events per patient year.

For T2DM patients, the mean rate of severe hypoglycaemic events during the 6-month recall period and after 12 months of treatment was 1.00 and 0.02 events per patient year, respectively. The absolute mean change in the rate of severe hypoglycaemic events from the 6-month recall period to 12 months after baseline was −0.99 events per patient year.

The incidence of severe hypoglycaemic events in patients outside Germany is summarised in Table 14.3.2.1.2.3.

For T1DM patients, 90 patients (16.2%) reported 548 severe hypoglycaemic events during the baseline period and 22 patients (4.0%) reported 52 events during the 12-month observation period. The estimated annual incidence rate of severe hypoglycaemic events decreased from 2.0 (95% CI: 1.8, 2.1) during the 6-month recall period to 0.1 (95% CI: 0.1, 0.1) and after 12 months of treatment.

For T2DM patients, 62 patients (10.1%) reported 307 severe hypoglycaemic events during the baseline period and 8 patients (1.3%) reported 10 events after 12 months of treatment. The estimated annual incidence rate of severe hypoglycaemic events decreased from 1.0 (95% CI: 0.9,

1.1) during the 6-month recall period to 0.0 (95% CI: 0.0, 0.0) during the 12-month observation period.

A negative binomial model examining the crude and fully-adjusted change in incidence rate of severe hypoglycaemic events between the 6-month recall period and 12 months after baseline is shown in Table 14.3.2.1.2.1 for T1DM patients and Table 14.3.2.1.2.2 for T2DM patients. Similar results were obtained with each of the models tested.

In the T1DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/6-month recall period) of severe hypoglycaemic events was 0.04 (95% CI: 0.02, 0.07; $p<0.001$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.3.2.1.2.1).

In the T2DM group, according to the fully-adjusted model, the incidence rate ratio (12 months after baseline/6-month recall period) of severe hypoglycaemic events was 0.02 (95% CI: 0.01, 0.04; $p<0.001$), indicating a statistically significant decrease in events during the 12-month observation period. Statistical significance of the results was consistent across the crude and fully-adjusted models (Table 14.3.2.1.2.2).

Data for severe hypoglycaemic events and their change between the 6-month recall period and the 12-month observation period for patients from Germany are provided in Table 14.3.2.2.1, Table 14.3.2.2.2.1, Table 14.3.2.2.2.2, and Table 14.3.2.2.2.3.

A boxplot of any severe hypoglycaemic event per patient year (based on baseline recall data and AE data) for the FAS is displayed in Figure 14.3.2.1.1.1 and Figure 14.3.2.1.1.2 (for T1DM and T2DM, respectively, outside Germany).

Individual data for severe hypoglycaemic events are provided in Annex 2, Listing 16.2.6.2.

10.4.3.2 Change from baseline (visit 2) in body weight after 12 months of treatment

The observed body weight by visit and change from baseline are summarised for the FAS outside Germany in Table 14.3.2.3.1.1.

For T1DM patients, the mean body weight was 76.20 kg at baseline and 77.46 kg at month 12. The mean body weight was higher at each visit, starting at month 3, during the 12-month observation period compared to baseline. At month 12, the absolute mean change in body weight was 0.63 kg.

For T2DM patients, the mean body weight was 87.42 kg at baseline and 87.32 kg at month 12. The mean body weight remained similar to baseline during the 12-month observation period. At month 12, the absolute mean change in body weight was 0.34 kg.

MMRM analyses of change in weight from baseline by visit using crude and adjusted estimates are presented in Table 10–17 for T1DM patients and Table 10–18 for T2DM patients.

In the T1DM group, the LS mean change from baseline at month 12 was 0.79 (95% CI: 0.38, 1.20; p<0.001) according to the fully-adjusted MMRM model, indicating a statistically significant weight increase during the 12-month observation period (Table 10–17).

In the T2DM group, the LS mean change from baseline at month 12 was 0.09 (95% CI: -0.39, 0.57; p=0.712) according to the fully-adjusted MMRM model, indicating a statistically non-significant weight increase during the 12-month observation period (Table 10–18).

Table 10–17 Analysis of change from baseline in weight by visit for T1DM (Full Analysis Set – excluding Germany)

Model	Visit	n	LS Mean	95% CI	p-value
Crude [1]	Visit 3 (month 3)	426	0.42	(0.20, 0.63)	<0.001
	Visit 4 (month 6)	381	0.67	(0.38, 0.96)	<0.001
	Visit 5 (month 9)	337	0.82	(0.46, 1.18)	<0.001
	Visit 6 (month 12)	365	0.71	(0.32, 1.09)	<0.001
Fully-Adjusted [2]	Visit 3 (month 3)	383	0.45	(0.24, 0.66)	<0.001
	Visit 4 (month 6)	347	0.76	(0.47, 1.04)	<0.001
	Visit 5 (month 9)	298	0.89	(0.51, 1.27)	<0.001
	Visit 6 (month 12)	334	0.79	(0.38, 1.20)	<0.001
Crude on Patients with Full set of Covariates	Visit 3 (month 3)	383	0.45	(0.24, 0.66)	<0.001
	Visit 4 (month 6)	347	0.77	(0.48, 1.06)	<0.001
	Visit 5 (month 9)	298	0.90	(0.52, 1.29)	<0.001
	Visit 6 (month 12)	334	0.80	(0.39, 1.21)	<0.001

Model	Visit	n	LS Mean	95% CI	p-value

[1] Crude model was based on an MMRM model with baseline Weight and visit.

[2] Fully adjusted model was based on an MMRM model with baseline Weight, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline and Country.

The OBSMARGINS option was applied whilst calculating the LSMEANS.

MMRM = mixed model for repeated measurements; BMI = body mass index; CI = confidence interval; T1DM = type 1 diabetes mellitus; LS = least squares.

Cross-reference: EOT Table 14.3.2.3.1.2.1

Table 10–18 Analysis of change from baseline in weight by visit for T2DM (Full Analysis Set – excluding Germany)

Model	Visit	n	LS Mean	95% CI	p-value
Crude [1]	Visit 3 (month 3)	485	0.13	(-0.15, 0.41)	0.369
	Visit 4 (month 6)	435	0.14	(-0.29, 0.56)	0.535
	Visit 5 (month 9)	395	0.16	(-0.28, 0.59)	0.479
	Visit 6 (month 12)	414	0.11	(-0.34, 0.57)	0.631
Fully-Adjusted [2]	Visit 3 (month 3)	443	0.08	(-0.22, 0.37)	0.607
	Visit 4 (month 6)	389	0.02	(-0.45, 0.48)	0.936
	Visit 5 (month 9)	360	0.03	(-0.43, 0.48)	0.914
	Visit 6 (month 12)	375	0.09	(-0.39, 0.57)	0.712
Crude on Patients with Full set of Covariates	Visit 3 (month 3)	443	0.08	(-0.22, 0.38)	0.606
	Visit 4 (month 6)	389	0.03	(-0.43, 0.50)	0.882
	Visit 5 (month 9)	360	0.04	(-0.41, 0.49)	0.866
	Visit 6 (month 12)	375	0.11	(-0.37, 0.58)	0.660
Fully Adjusted excluding time-varying covariates [3]	Visit 3 (month 3)	443	0.07	(-0.23, 0.36)	0.655
	Visit 4 (month 6)	389	0.02	(-0.45, 0.48)	0.943

Model	Visit	n	LS Mean	95% CI	p-value
	Visit 5 (month 9)	360	0.03	(-0.43, 0.48)	0.909
	Visit 6 (month 12)	375	0.09	(-0.38, 0.57)	0.704

[1] Crude model was based on an MMRM model with baseline Weight and visit.

[2] Fully adjusted model was based on an MMRM model with baseline Weight, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline, Bolus insulin (Y/N, time-varying), SU+Glinides (Y/N, time-varying), GLP-1 (Y/N, time-varying), Other OADs (Y/N, time-varying) and Country

[3] Fully adjusted model excluding time-varying covariates was based on an MMRM model with Baseline Weight, Visit, Duration of diabetes mellitus at baseline, Gender, BMI at baseline, Age at baseline, Baseline Bolus insulin (Y/N), Baseline SU+Glinides (Y/N), Baseline GLP-1 (Y/N), Baseline Other OADs (Y/N) and Country

The OBSMARGINS option was applied whilst calculating the LSMEANS.

MMRM = mixed model for repeated measurements; BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; GLP-1 = glucagon-like peptide-1; LS = least squares; OADs = oral anti-diabetic drugs; SU = sulphonylureas; Y/N = yes/no.

Cross-reference: EOT Table 14.3.2.3.1.2.2

10.4.4 Secondary observational endpoints - Secondary observational patient-reported outcome endpoints

10.4.4.1 Change from baseline in HR-QoL questionnaire (SF-36) scores after 12 months of treatment

SF-36 instrument scores by domain, by visit and change from baseline, are summarised for the FAS outside Germany in Table 14.2.3.1.1.

In the T1DM and T2DM groups, the scores for each domain of the SF-36 instrument remained similar after the 12-month observation period compared to baseline. The observed changes were not clinically relevant. At month 12, the absolute mean changes from baseline (and absolute mean values at baseline and month 12) in the SF-36 domains were as follows:

- Physical functioning: 0.42 points for T1DM patients (mean values at baseline and month 12: 50.94 points and 51.86 points, respectively) and 0.18 points for T2DM patients (mean values at baseline and month 12: 42.76 points and 43.46 points, respectively)
- Role-physical: –0.07 points for T1DM patients (mean values at baseline and month 12: 48.52 points and 49.17 points, respectively) and 0.40 points for T2DM patients (mean values at baseline and month 12: 42.08 points and 42.98 points, respectively)
- Bodily pain: –0.08 points for T1DM patients (mean values at baseline and month 12: 51.60 points and 52.25 points, respectively) and 1.20 points for T2DM patients (mean values at

baseline and month 12: 45.28 points and 46.80 points, respectively). The notable mean increase observed in the T2DM group was not clinically significant

- General health: 0.11 points for T1DM patients (mean values at baseline and month 12: 44.03 points and 44.78 points, respectively) and 0.60 points for T2DM patients (mean values at baseline and month 12: 40.51 points and 41.59 points, respectively)
- Vitality: –0.60 points for T1DM patients (mean values at baseline and month 12: 50.99 points and 51.20 points, respectively) and 0.04 points for T2DM patients (mean values at baseline and month 12: 48.70 points and 49.56 points, respectively)
- Social functioning: 0.03 points for T1DM patients (mean values at baseline and month 12: 48.64 points and 49.18 points, respectively) and 0.10 points for T2DM patients (mean values at baseline and month 12: 44.27 points and 44.84 points, respectively)
- Role-emotional: 0.13 points for T1DM patients (mean values at baseline and month 12: 47.55 points and 48.49 points, respectively) and –0.32 points for T2DM patients (mean values at baseline and month 12: 41.51 points and 41.91 points, respectively)
- Mental health: 0.41 points for T1DM patients (mean values at baseline and month 12: 48.68 points and 49.76 points, respectively) and 0.59 points for T2DM patients (mean values at baseline and month 12: 45.03 points and 46.41 points, respectively)

The combined physical component score (PCS) and mental component score (MCS) of the SF-36 instrument and change by visit for the FAS outside Germany are summarised in Table 14.2.3.1.2.

In the T1DM group and T2DM groups, the scores for the overall PCS and the overall MCS remained similar after the 12-month observation period compared to baseline. At month 12, the absolute mean change from baseline (and absolute mean values at baseline and month 12) in the SF-36 overall combined component scores were as follows:

- Overall PCS: 0.03 points for T1DM patients (mean values at baseline and month 12: 49.68 points and 50.25 points, respectively) and 0.47 points for T2DM patients (mean values at baseline and month 12: 42.97 points and 43.91 points, respectively)
- Overall MCS: 0.04 points for T1DM patients (mean values at baseline and month 12: 48.09 points and 48.84 points, respectively) and 0.04 points for T2DM patients (mean values at baseline and month 12: 45.42 points and 46.13 points, respectively)

Individual data of the SF-36 instrument are provided in Annex 2, Listing 16.2.6.14.

10.4.4.2 Change from baseline in DTSQs scores after 12 months of treatment

Total treatment satisfaction as per DTSQs by visit for the FAS outside Germany is summarised in Table 10–19.

At month 12, the absolute mean change from baseline in the total DTSQs score was 3.81 points for T1DM patients (mean values at baseline and month 12: 26.03 points and 29.91 points, respectively)

and 4.47 points for T2DM patients (mean values at baseline and month 12: 25.71 points and 29.96 points, respectively). This increase in the score reflected a clinically relevant increase in the patients' satisfaction with their treatment in both patient groups.

Table 10–19 Observed and change from baseline in total treatment satisfaction in DTSQs by visit (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline
Baseline				
n	546		595	
Mean	26.03		25.71	
95% CI [1]	-		-	
SD	6.719		7.652	
Minimum	1.0		3.0	
Q1	22.00		20.00	
Median	27.00		27.00	
Q3	31.00		32.00	
Maximum	36.0		36.0	
3 Months (± 45 days)				
n	458	454	499	488
Mean	29.04	2.80	29.37	3.76
95% CI [1]	-	2.20, 3.41	-	3.09, 4.42
SD	5.480	6.575	6.328	7.464
Minimum	0.0	-34.0	0.0	-36.0
Q1	26.00	-1.00	26.00	0.00
Median	30.00	2.00	31.00	3.00
Q3	33.00	6.00	34.00	7.00
Maximum	36.0	26.0	36.0	29.0
6 Months (± 45 days)				
n	396	391	466	457
Mean	29.88	3.84	29.36	3.51
95% CI [1]	-	3.15, 4.54	-	2.75, 4.28
SD	5.185	7.014	6.896	8.319
Minimum	0.0	-35.0	0.0	-34.0
Q1	27.50	0.00	26.00	0.00
Median	30.00	2.00	30.00	3.00
Q3	34.00	7.00	35.00	8.00
Maximum	36.0	26.0	36.0	28.0
9 Months (± 45 days)				
n	347	343	425	418
Mean	29.68	3.43	29.31	3.59

Visit Statistic	T1DM (N=556) Value	T1DM (N=556) Change from Baseline	T2DM (N=611) Value	T2DM (N=611) Change from Baseline
95% CI [1]	-	2.67, 4.18	-	2.88, 4.29
SD	5.843	7.135	6.095	7.326
Minimum	0.0	-36.0	0.0	-35.0
Q1	27.00	0.00	26.00	0.00
Median	30.00	2.00	30.00	3.00
Q3	34.00	7.00	34.00	6.00
Maximum	36.0	25.0	36.0	27.0
12 Months (± 45 days)				
n	380	376	448	439
Mean	29.91	3.81	29.96	4.47
95% CI [1]	-	3.07, 4.54	-	3.77, 5.18
SD	5.467	7.246	5.767	7.521
Minimum	2.0	-20.0	1.0	-29.0
Q1	27.00	0.00	27.80	0.00
Median	30.50	3.00	31.00	3.00
Q3	34.00	7.00	35.00	8.00
Maximum	36.0	25.0	36.0	30.0

DTSQs is the status version of DTSQ. N is the total number of patients in each diabetes type group.
[1] 95% CIs of the mean were only presented for change from baseline values for post-baseline visits.
CI = confidence interval; DTSQs = diabetes treatment satisfaction questionnaire -status; Q1 = first quartile; Q3 = third quartile; SD = standard deviation, T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.3.1.3

Individual treatment satisfaction scores as per DTSQs by visit for the FAS outside Germany are summarised in Table 14.2.3.1.4.

In the T1DM group and T2DM group, the scores of Items 1, 4, 5, 6, 7 and 8 were numerically larger at each timepoint over the 12-month observation period compared to baseline. This increase in scores was clinically relevant. At month 12, the absolute mean change from baseline in the DTSQs items scores were as follows:

- Item 1, 'How satisfied are you with your current treatment?': 0.67 points for T1DM patients (mean values at baseline and month 12: 4.29 points and 4.99 points, respectively) and 0.75 points for T2DM patients (mean values at baseline and month 12: 4.25 points and 4.97 points, respectively)
- Item 4, 'How convenient have you been finding your treatment to be recently?': 0.62 points for T1DM patients (mean values at baseline and month 12: 4.23 points and 4.84 points,

respectively) and 0.78 points for T2DM patients (mean values at baseline and month 12: 4.30 points and 5.02 points, respectively)

- Item 5 'How flexible have you been finding your treatment to be recently?': 0.62 points for T1DM patients (mean values at baseline and month 12: 4.22 points and 4.83 points, respectively) and 0.75 points for T2DM patients (mean values at baseline and month 12: 4.16 points and 4.90 points, respectively)
- Item 6, 'How satisfied are you with your understanding of your diabetes?': 0.26 points for T1DM patients (mean values at baseline and month 12: 4.70 points and 4.92 points, respectively) and 0.46 points for T2DM patients (mean values at baseline and month 12: 4.57 points and 5.03 points, respectively)
- Item 7, 'Would you recommend this form of treatment to someone else with your kind of diabetes?': 0.67 points for T1DM patients (mean values at baseline and month 12: 4.44 points and 5.13 points, respectively) and 0.79 points for T2DM patients (mean values at baseline and month 12: 4.27 points and 4.99 points, respectively)
- Item 8, 'How satisfied would you be to continue with your present form of treatment?': 0.99 points for T1DM patients (mean values at baseline and month 12: 4.14 points and 5.19 points, respectively) and 0.95 points for T2DM patients (mean values at baseline and month 12: 4.15 points and 5.06 points, respectively)

Perceived frequency of hypoglycaemia as per DTSQs (item 2 of the DTSQs) by visit for the FAS outside Germany is summarised in Table 10–20.

In both, T1DM and T2DM patients, the score was smaller at each timepoint over the 12-month observation period compared to baseline. At month 12, the absolute mean change from baseline in perceived frequency of hypoglycaemia was –0.58 points for T1DM patients (mean values at baseline and month 12: 2.56 points and 1.92 points, respectively) and –0.42 points for T2DM patients (mean values at baseline and month 12: 1.77 points and 1.33 points, respectively). This decrease in the patients' perception of hypoglycaemia frequency was not clinically relevant.

Table 10–20 Observed and change from baseline in perceived frequency of hypoglycaemia in DTSQs by visit (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline
Baseline				
n	546		598	
Mean	2.56		1.77	
95% CI [1]	-		-	
SD	1.578		1.593	
Minimum	0.0		0.0	
Q1	1.00		0.00	
Median	2.00		2.00	
Q3	4.00		3.00	
Maximum	6.0		6.0	
3 Months (± 45 days)				
n	459	456	499	490
Mean	2.24	-0.34	1.57	-0.20
95% CI [1]	-	-0.50, -0.17	-	-0.38, -0.02
SD	1.563	1.758	1.673	1.977
Minimum	0.0	-6.0	0.0	-6.0
Q1	1.00	-1.00	0.00	-1.00
Median	2.00	0.00	1.00	0.00
Q3	3.00	1.00	3.00	1.00
Maximum	6.0	5.0	6.0	6.0
6 Months (± 45 days)				
n	398	393	466	459
Mean	2.07	-0.48	1.62	-0.08
95% CI [1]	-	-0.65, -0.31	-	-0.26, -0.10
SD	1.480	1.702	1.722	1.915
Minimum	0.0	-6.0	0.0	-5.0
Q1	1.00	-1.00	0.00	-1.00
Median	2.00	0.00	1.00	0.00
Q3	3.00	1.00	3.00	1.00
Maximum	6.0	5.0	6.0	6.0
9 Months (± 45 days)				
n	346	343	426	421
Mean	2.05	-0.42	1.58	-0.08
95% CI [1]	-	-0.60, -0.24	-	-0.28, 0.11
SD	1.459	1.711	1.622	2.021
Minimum	0.0	-6.0	0.0	-6.0

Visit Statistic	T1DM (N=556) Value	T1DM (N=556) Change from Baseline	T2DM (N=611) Value	T2DM (N=611) Change from Baseline
Q1	1.00	-1.00	0.00	-1.00
Median	2.00	0.00	1.00	0.00
Q3	3.00	1.00	3.00	1.00
Maximum	6.0	4.0	6.0	6.0
12 Months (± 45 days)				
n	379	376	449	441
Mean	1.92	-0.58	1.33	-0.42
95% CI [1]	-	-0.76, -0.39	-	-0.59, -0.25
SD	1.494	1.830	1.551	1.849
Minimum	0.0	-6.0	0.0	-6.0
Q1	1.00	-2.00	0.00	-1.00
Median	2.00	0.00	1.00	0.00
Q3	3.00	0.00	2.00	0.00
Maximum	6.0	5.0	6.0	6.0

DTSQs is the status version of DTSQ. N is the total number of patients in each diabetes type group.

[1] 95% CIs of the mean were only presented for change from baseline values for post-baseline visits.

CI = confidence interval; DTSQs = diabetes treatment satisfaction questionnaire -status; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.3.1.5

Total treatment satisfaction as per DTSQc at month 12 for the FAS outside Germany is summarised in Table 14.2.3.1.6. The mean score at month 12 was 12.00 points in the T1DM group and 12.36 points in the T2DM group. This indicates an improvement in total treatment satisfaction.

Perceived frequency of hypoglycaemia as per DTSQc at month 12 for the FAS outside Germany is summarised in Table 14.2.3.1.7. The mean score at month 12 was –0.58 points for the T1DM patients and –0.78 points for T2DM patients. This indicates an improvement in the perceived frequency of hypoglycaemia.

Individual treatment satisfaction as per DTSQc at month 12 for the FAS outside Germany is summarised in Table 14.2.3.1.8.

The mean scores for T1DM and T2DM patients at month 12 were as follows:

- Item 1, ‘How satisfied are you with your current treatment?’: 2.16 points for T1DM patients and 2.10 points for T2DM patients
- Item 4, ‘How convenient have you been finding your treatment to be recently?’: 1.89 points for T1DM patients and 2.00 points for T2DM patients

- Item 5, 'How flexible have you been finding your treatment to be recently?': 1.84 points for T1DM patients and 1.97 points for T2DM patients
- Item 6, 'How satisfied are you with your understanding of your diabetes?': 1.89 points for T1DM patients and 2.07 points for T2DM patients
- Item 7, 'Would you recommend this form of treatment to someone else with your kind of diabetes?': 2.05 points for both T1DM and T2DM patients
- Item 8, 'How satisfied would you be to continue with your present form of treatment?': 2.18 points for T1DM patients and 2.17 points for T2DM patients

This indicates an improvement in individual treatment satisfaction.

Individual data for the DTSQ instrument are provided in Annex 2, Listing 16.26.12 and Listing 16.2.6.13.

10.4.5 Secondary observational endpoints - Health economic and dose-time flexibility observational endpoints

10.4.5.1 Physicians' primary reason for switching/not switching to treatment with Tresiba®

The physicians' reasons for switching/not switching to treatment with Tresiba® for DPO outside Germany are summarised in Table 10–21.

For DPO outside Germany and among those reporting if they had switch or not, 13 of 50 (26.0%) T1DM patients and 15 of 50 (30.0%) T2DM patients were switched to Tresiba®. The physicians switched patients early to Tresiba® for the following reasons:

- For T1DM: concern about hypoglycaemia (61.5%); to improve blood glucose control (53.8%); and current regimen too restrictive for daily dosing time (15.4%)
- For T2DM: to improve blood glucose control (80.0%); concern about hypoglycaemia (26.7%); and current regimen too restrictive for daily dosing time (6.7%)

Table 10–21 Summary for physicians' reason for switching/not switching to treatment with Tresiba® (Dropouts Prior to Observation Period – excluding Germany

Response	T1DM (N=50) n (%)	T2DM (N=50) n (%)
Physician Switched Treatment to Tresiba®		
Yes	13 (26.0)	15 (30.0)
No	6 (12.0)	5 (10.0)
Physicians reason for switching to treatment with Tresiba® [1][2]		
Concern about hypoglycaemia	8 (61.5)	4 (26.7)
Current regimen too restrictive for daily dosing time	2 (15.4)	1 (6.7)
Improve blood glucose control	7 (53.8)	12 (80.0)
Physicians Reason for Not Switching to Treatment with Tresiba® [3][4]		
Decided to leave treatment regimen unchanged	1 (16.7)	1 (20.0)
Other	2 (33.3)	2 (40.0)
Patient choice	2 (33.3)	2 (40.0)

[1] Multiple reasons for switching to Tresiba® were possible. Patients were included in counts for each reason recorded.

[2] Percentages based on the number of patients' physician switched treatment to Tresiba®.

[3] Multiple reasons for not switching to Tresiba® were possible. Patients were included in counts for each reason recorded.

[4] Percentages based on the number of patients' physician not switched treatment to Tresiba®.

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.4.1.1.1

The physicians' reasons for switching/not switching to treatment with Tresiba® for patients in Germany (DPO population) are summarised in Table 14.2.4.1.1.2.

10.4.5.2 Physicians' reasons for switching to treatment with Tresiba®

The physicians' reasons for switching to treatment with Tresiba® for the FAS outside Germany are summarised in Table 10–22.

Based on the FAS, the most common reasons for physicians to switch patients to Tresiba® were concern about hypoglycaemia (64.6%) and to improve blood glucose control (63.9%) for T1DM patients and to improve blood glucose control (73.3%) and concern about hypoglycaemia (36.2%) for T2DM patients.

Table 10–22 Summary for physicians' reason for switching to treatment with Tresiba® (Full Analysis Set – excluding Germany)

Response	T1DM (N=556) n (%)	T2DM (N=611) n (%)
Physician Switched Treatment to Tresiba®		
Yes	554 (99.6)	611 (100)
Physicians reason for switching to treatment with Tresiba® [1][2]		
Concern about hypoglycaemia	358 (64.6)	221 (36.2)
Current regimen too restrictive for daily dosing time	48 (8.7)	72 (11.8)
Improve blood glucose control	354 (63.9)	448 (73.3)
Other	23 (4.2)	21 (3.4)

[1] Multiple reasons for switching to Tresiba® were possible. Patients were included in counts for each reason recorded.

[2] Percentages based on the number of patients' physician switched treatment to Tresiba®.

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.4.1.2.1

The physicians' reasons for switching to treatment with Tresiba® for the FAS from Germany are summarised in Table 14.2.4.1.2.2.

Individual data for patients switching or not switching to Tresiba® are provided in Annex 2, Listing 16.2.6.8 and Listing 16.2.6.9, respectively. Individual subgroup data categories are shown in Annex 2, Listing 16.2.6.5.

10.4.5.3 Change from baseline in the number of times patient discussed hypoglycaemic event with physician or nurse

The estimated annual incidence rate of patients discussing any hypoglycaemic event with the physician or a nurse for the FAS outside Germany are summarised in Table 14.2.4.1.14.

For T1DM patients, 30 patients (5.9%) reported 53 hypoglycaemic events discussed with a physician or nurse during the baseline period and 38 patients (7.6%) reported 108 events discussed with a physician or nurse during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events discussed was 1.4 (95% CI: 1.0, 1.8) during the baseline period and 1.0 (95% CI: 0.8, 1.2) during the 12-month observation period.

For T2DM patients, 39 patients (7.3%) reported 99 hypoglycaemic events discussed with a physician or nurse during the baseline period and 24 patients (4.3%) reported 46 events discussed with a physician or nurse during the 12-month observation period. The estimated annual incidence rate of any hypoglycaemic events discussed was 2.4 (95% CI: 2.0, 3.0) during the baseline period and 0.4 (95% CI: 0.3, 0.5) during the 12-month observation period.

10.4.5.4 Change from baseline in the number of treatments by a paramedic at home

In both the T1DM and T2DM groups for the FAS outside Germany, the number of patients who had at least one treatment by a paramedic was low: 1 patient received 1 treatment, during the 4-week baseline period and 3 patients received 3 treatments at home during the 12-month observation period. In the T2DM group, no patient received treatment during the 4-week baseline period and 1 patient received 1 treatment at home during the 12-month observation period. (Table 14.2.4.1.3).

10.4.5.5 Change from baseline in the number of emergency room visits due to hypoglycaemia

In both the T1DM and T2DM groups for the FAS outside Germany, the number of patients who had at least one emergency room visit due to hypoglycaemia was low: No patient in the T1DM group visited the emergency room both during the 4-week baseline period and the 12-month observation period. In the T2DM group no patient visited the emergency room during the 4-week baseline period and 1 patient made 1 emergency visit during the 12-month observation period (Table 14.2.4.1.4).

10.4.5.6 Change from baseline in the number of hospitalisations due to hypoglycaemia, and duration of hospitalisation

In both the T1DM and T2DM groups for the FAS outside Germany, the number of patients who had at least hospitalisation due to hypoglycaemia was low: In the T1DM group, 1 patient was hospitalised once during the 4-week baseline period and no patient was hospitalised during the 12-month observation period. In the T2DM group, no patient was hospitalised during both the 4-week baseline period and the 12-month observation period (Table 14.2.4.1.5).

10.4.5.7 Absence from work due to hypoglycaemia

The absence of patients from work due to hypoglycaemia by visit, for the FAS outside Germany, is summarised in Table 14.2.4.1.6. The proportions of patients with at least one hypoglycaemic event that led to absence from work throughout the 12-month observation period ranged from 5.0% to 9.3% in the T1DM group (8.1% during baseline period) and from 3.3% to 9.4% in the T2DM group (6.1% during baseline period).

10.4.5.8 Change from baseline (visit 2) in the number of SMBG test strips used during the 12 months of treatment

The number of SMBG test strips by visit and change from baseline are summarised for the FAS outside Germany in Table 14.2.4.1.7.

For T1DM patients, the mean number of SMBG strips used was 4.33 strips/day during the baseline period and 4.69 strips/day at month 12. The absolute mean change in the number of strips used showed that the numbers remained similar to baseline throughout the 12-month observation period.

At month 12, the absolute mean change from baseline in the number of strips used was 0.18 strips/day.

For T2DM patients, the mean number of SMBG strips used was 2.69 strips/day during the baseline period and 3.02 strips/day at month 12. The absolute mean change in the number of strips used showed that the numbers increased from baseline throughout the 12-month observation period, with the greatest increase recorded at month 6 (0.62 strips/day). At month 12, the absolute mean change from baseline in the number of strips used was 0.29 strips/day.

10.4.5.9 Change from baseline (visit 2) in daily insulin dose (total, Tresiba®, bolus) after the observation period

Both basal and bolus insulin doses were recorded in this study. Daily basal insulin doses were recorded in a patient diary and bolus insulin doses were recorded at each visit as "Total daily dose of bolus insulin on day prior to visit".

Mean daily basal insulin doses by visit and change from baseline are summarised for the FAS outside Germany in Table 10–23.

For T1DM patients, the mean daily basal insulin dose was 25.02 IU at baseline and 22.81 IU at month 12. The absolute mean change in the daily insulin dose showed a decrease at each visit, starting at month 3, during the 12-month observation period compared to baseline. At month 12, the absolute mean change in the daily basal insulin dose was −2.21 IU.

For T2DM patients, the mean daily basal insulin dose was 37.45 IU at baseline and 35.90 IU at month 12. The absolute mean change in the daily insulin dose showed that the levels remained similar to baseline throughout the 12-month observation period. At month 12, the absolute mean change in the daily basal insulin dose was –0.14 IU.

Table 10–23 Observed and change from baseline in mean daily basal insulin dose by visit (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline
Baseline				
n	541		581	
Mean	25.02		37.45	
95% CI [1]	-		-	
SD	14.053		33.937	
Minimum	5.0		4.0	
Q1	16.00		18.00	
Median	22.00		26.86	
Q3	30.00		43.00	

	T1DM (N=556)		T2DM (N=611)	
Visit **Statistic**	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Maximum	140.0		300.0	
3 Months (± 45 days)				
n	449	440	492	478
Mean	22.11	-2.50	36.03	-1.24
95% CI [1]	-	-3.03, -1.98	-	-2.35, -0.14
SD	12.422	5.613	33.957	12.255
Minimum	3.5	-44.0	4.0	-72.0
Q1	14.82	-4.00	18.00	-3.93
Median	20.00	-1.36	26.00	0.00
Q3	26.00	0.00	40.00	0.89
Maximum	134.3	36.0	271.5	136.8
6 Months (± 45 days)				
n	394	387	448	436
Mean	22.11	-2.27	37.11	0.07
95% CI [1]	-	-2.85, -1.68	-	-1.34, 1.48
SD	12.666	5.850	35.697	14.955
Minimum	4.0	-47.0	4.0	-104.0
Q1	15.00	-4.00	18.02	-4.00
Median	20.00	-1.00	26.00	0.00
Q3	25.64	0.09	41.45	2.19
Maximum	150.0	16.0	300.0	116.8
9 Months (± 45 days)				
n	350	344	426	415
Mean	22.66	-2.28	36.48	0.52
95% CI [1]	-	-2.99, -1.57	-	-0.96, 2.00
SD	13.572	6.673	34.046	15.349
Minimum	4.0	-51.0	3.4	-116.4
Q1	15.00	-4.00	19.00	-3.80
Median	20.00	-1.00	26.00	0.00
Q3	26.18	1.00	42.00	3.14
Maximum	150.0	16.0	300.0	116.8
12 Months (± 45 days)				
n	360	355	433	423
Mean	22.81	-2.21	35.90	-0.14
95% CI [1]	-	-2.90, -1.53	-	-1.47, 1.19
SD	13.476	6.578	33.007	13.923
Minimum	4.0	-42.9	4.0	-94.6
Q1	15.00	-4.38	18.00	-4.00

	T1DM (N=556)		T2DM (N=611)	
Visit **Statistic**	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Median	20.00	-1.00	26.14	0.00
Q3	27.82	1.00	42.00	4.00
Maximum	150.0	17.0	300.0	100.0

N is the total number of patients in each diabetes type group.

[1] 95% CIs of the mean are only presented for change from baseline values for post-baseline visits.

CI = confidence interval; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.4.1.13.1

Daily bolus insulin doses by visit and change from baseline are summarised for the FAS outside Germany in Table 10–24.

For T1DM patients, the mean daily bolus insulin dose was 27.33 IU at baseline and 23.79 IU at month 12. The absolute mean change in the daily bolus insulin dose showed a decrease at each visit, starting at month 3, during the 12-month observation period compared to baseline. At month 12, the absolute mean change in the daily bolus insulin dose was −3.20 IU.

For T2DM patients, the mean daily bolus insulin dose was 38.91 IU at baseline and 38.33 IU at month 12. The absolute mean change in the daily bolus insulin dose showed that the levels remained similar to baseline throughout the 12-month observation period. At month 12, the absolute mean change in the daily insulin dose was 0.23 IU.

Table 10–24 Observed and change from baseline in bolus insulin dose by visit (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
Visit **Statistic**	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Baseline				
n	473		471	
Mean	27.33		38.91	
95% CI [1]	-		-	
SD	16.894		31.673	
Minimum	1.0		1.2	
Q1	17.00		20.00	
Median	24.00		30.00	
Q3	33.00		50.00	
Maximum	170.0		280.0	
3 Months (± 45 days)				

	T1DM (N=556)		T2DM (N=611)	
Visit **Statistic**	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
n	393	362	413	360
Mean	24.33	-1.97	37.67	-0.31
95% CI [1]	-	-2.98, -0.95	-	-2.12, 1.50
SD	14.787	9.827	30.942	17.486
Minimum	3.0	-75.0	2.0	-96.0
Q1	15.00	-4.00	18.00	-4.00
Median	22.00	0.00	28.00	0.00
Q3	30.00	2.00	47.00	2.00
Maximum	164.0	37.0	234.0	100.0
6 Months (± 45 days)				
n	351	324	368	317
Mean	23.34	-2.87	37.78	-1.17
95% CI [1]	-	-3.90, -1.85	-	-3.38, 1.05
SD	12.934	9.370	28.689	20.052
Minimum	3.0	-60.0	2.0	-122.0
Q1	14.00	-6.00	19.50	-6.00
Median	21.00	-1.00	28.00	0.00
Q3	30.00	1.00	48.00	4.00
Maximum	90.0	31.0	225.0	100.0
9 Months (± 45 days)				
n	320	289	327	290
Mean	23.90	-2.68	39.55	-0.24
95% CI [1]	-	-3.95, -1.41	-	-2.75, 2.26
SD	15.094	10.967	30.557	21.675
Minimum	2.0	-53.0	3.0	-90.0
Q1	15.00	-6.00	20.00	-6.00
Median	21.00	-1.00	30.00	0.00
Q3	30.00	3.00	50.00	4.00
Maximum	150.0	35.0	225.0	130.0
12 Months (± 45 days)				
n	346	318	361	311
Mean	23.79	-3.20	38.33	0.23
95% CI [1]	-	-4.68, -1.72	-	-1.85, 2.31
SD	13.853	13.401	30.561	18.649
Minimum	1.0	-70.0	2.0	-86.0
Q1	15.00	-8.00	19.00	-6.00
Median	20.50	-2.00	30.00	0.00
Q3	30.00	2.00	46.00	6.00
Maximum	107.0	85.0	210.0	120.0

Visit Statistic	T1DM (N=556) Value	 Change from Baseline	T2DM (N=611) Value	 Change from Baseline

N is the total number of patients in each diabetes type group.

[1] 95% CIs of the mean are only presented for change from baseline values for post-baseline visits.

Total daily dose of bolus insulin on the day prior to the visit (IU).

CI = confidence interval; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.4.1.13.2

Initial daily Tresiba® dose in patients outside Germany are summarised in Table 14.2.4.1.13.3. For T1DM patients, the mean initial daily basal insulin dose was 22.9 IU (range 5-150 IU). For T2DM patients, the mean initial daily basal insulin dose was 35.0 IU (range 4-300 IU).

Observed and change from baseline in total insulin dose by visit in patients outside Germany are summarised in Table 14.2.4.1.13.4. For T1DM patients, the mean total daily dose of bolus insulin was 51.12 IU at baseline and 46.83 IU at month 12. The absolute mean change in the total daily dose of bolus insulin was −5.12 IU. For T2DM patients, the mean total daily dose of bolus insulin was 72.35 IU at baseline and 69.26 IU at month 12. The absolute mean change in the total daily dose of bolus insulin was 0.46 IU.

10.4.5.10 Patient preference compared to previous treatment and FlexTouch® pen preference compared to previous injection at end of study

Patient preference compared to the previous treatment by visit for the FAS outside Germany is summarised in Table 10–25.

Throughout the study period, >90% of T1DM and T2DM patients preferred either Tresiba® over their previous treatment or the FlexTouch® pen over previous injections. At month 12, the proportion of patients who preferred Tresiba® over their previous treatment was 97.2% of T1DM patients and 99.2% of T2DM patients, and the proportion of patients who preferred the FlexTouch® pen over previous injections was 93.8% of T1DM patients and 97.5% of T2DM patients.

Table 10–25 Summary of patient preference compared to previous treatment by visit (Full Analysis Set – excluding Germany)

Visit	T1DM (N=556) n (%)	T2DM (N=611) n (%)
3 Months (± 45 Days)	438	498
Preference of Tresiba		
n	324	416
Yes	309 (95.4)	411 (98.8)

Visit	T1DM (N=556) n (%)	T2DM (N=611) n (%)
No	15 (4.6)	5 (1.2)
Missing	114	82
Preference of FlexTouch		
n	276	400
Yes	253 (91.7)	381 (95.3)
No	23 (8.3)	19 (4.8)
Missing	162	98
6 Months (± 45 Days)	379	436
Preference of Tresiba		
n	299	377
Yes	297 (99.3)	366 (97.1)
No	2 (0.7)	12 (3.2)
Missing	80	59
Preference of FlexTouch		
n	266	368
Yes	245 (92.1)	357 (97.0)
No	21 (7.9)	11 (3.0)
Missing	113	68
9 Months (± 45 Days)	346	410
Preference of Tresiba		
n	301	355
Yes	300 (99.7)	347 (97.7)
No	1 (0.3)	8 (2.3)
Missing	45	55
Preference of FlexTouch		
n	259	347
Yes	241 (93.1)	336 (96.8)
No	18 (6.9)	11 (3.2)
Missing	87	63
12 Months (± 45 Days)	373	451
Preference of Tresiba		
n	327	369
Yes	318 (97.2)	366 (99.2)
No	9 (2.8)	3 (0.8)
Missing	46	82
Preference of FlexTouch		
n	276	367
Yes	259 (93.8)	358 (97.5)
No	17 (6.2)	9 (2.5)
Missing	97	84

Note: Percentages are based on the number of patients with evaluable data.

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.2.4.1.8

10.4.5.11 Change from baseline in dose-time flexibility endpoints

Doses missed, reason for missed doses and action taken when dose missed

Missed doses by visit, including reason for missed doses and action taken when a dose was missed, for the FAS outside Germany are summarised in Table 14.2.4.1.9.

At each visit during the 12-month observation period, the proportion of patients with missed doses gradually decreased compared to baseline. At baseline, and months 3, 6, 9, and 12, the proportion of patients with missed doses were 14.6%, 9.1%, 4.8%, 2.9%, and 3.0% in the T1DM group and 14.9%, 6.9%, 6.0%, 5.4%, and 2.8% in the T2DM group, respectively.

Among those reporting a reason for missed doses the most common reasons in both patient groups were patient forgot and 'other'. These reasons were most commonly noted throughout the observation period. The number of patients in each group at month 9 and month 12 was too low to assess any trend.

The most common action taken for missed doses in both patient groups was that the patient did nothing. These reasons were most commonly noted throughout the observation period. The number of patients in each group at month 9 and month 12 was too low to assess any trend.

Changes in any social, leisure, and working activities due to insulin treatment

Shift tables for change in social, leisure, and working activities by visit in the FAS outside Germany are provided in Table 14.2.4.1.10.1 for the T1DM patients and Table 14.2.4.1.10.2 for T2DM patients.

Among the T1DM and T2DM patients who reported a change at baseline, the majority did not report a change at 3, 6, 9 months for all activities (ie., social, leisure and working activities).

Tresiba® flexibility option use

A summary of the Tresiba® flexibility option use by visit for the FAS outside Germany is shown in Table 14.2.4.1.11. The proportions of patients who used Tresiba® at a time different from their usual dosing time at least once throughout the 12-month observation period ranged from 21.8% to 32.7% in the T1DM group and from 13.7% to 27.2% in the T2DM group. The proportion of patients who used the dose-time flexibility option at least once throughout the 12-month observation period ranged from 20.9% to 22.9% in the T1DM group and from 14.0% to 22.0% in the T2DM group.

A summary of the dosing time by diary period for the FAS outside Germany is provided in Table 14.2.4.1.12. At baseline, the time of day during which the largest percentage of the total dosages was administered was between 06:00 and 08:59 (19.1% for T1DM patients and 13.9% for

T2DM patients) and between 21:00 and 23:59 (47.9% for T1DM patients and 60.2% for T2DM patients). At month 12, the time of day during which the largest percentage of the total dosages was administered was between 06:00 and 08:59 (20.3% for T1DM patients and 14.1% for T2DM patients) and between 21:00 and 23:59 (50.3% for T1DM patients and 60.4% for T2DM patients).

Individual patient details for dose-time flexibility are shown in Annex 2, Listing 16.2.6.10 and for patient diary dispensation in Listing 16.2.6.11.

10.4.6 Secondary observational endpoints - Secondary observational endpoints for external study registration

The following secondary observational endpoints were used in external registration of the study at clincialtrials.gov and the ENCePP register.

10.4.6.1 Change from baseline in HbA1c and FPG after 12 months

The change from baseline in HbA1c and FPG at month 12 is described in Section 10.4.2.3 and Section 10.4.2.1, respectively.

10.4.6.2 Change from the baseline period in the number of severe hypoglycaemic episodes after 12 months

The change from baseline in severe hypoglycaemia events at month 12 is described in Section 10.4.3.1.

10.4.6.3 Change from baseline in PRO scores (HR-QoL [SF-36] and DTSQ) after 12 months of treatment

The change from baseline in PRO scores (HR-QoL [SF-36] and DTSQs) at month 12 is described in Section 10.4.4.1 and 10.4.4.2.

10.4.7 Summary of main results

Only results for the FAS outside Germany are summarised below, unless otherwise indicated.

10.4.7.1 Summary of primary observational endpoint

The rate of any hypoglycaemic events decreased between the baseline period and 12 months after baseline in the T1DM and T2DM group. During the baseline and 12-month observation periods, the estimated annual incidence rate decreased from 85.8 to 69.8 events per patient year for T1DM patients and from 17.1 to 8.7 events per patient year for T2DM patients, compared to baseline. The incidence rate ratio of any hypoglycaemic events showed a statistically significant decrease in events for both the T1DM patient group (95% CI: 0.74, 0.88; $p<0.001$; fully adjusted negative binomial model) and the T2DM patient group (95% CI: 0.38, 0.56; $p<0.001$; fully-adjusted negative binomial model).

Sensitivity analyses which were conducted to assess the impact of the difference in reporting of hypoglycaemia events in the patient diary and the impact of any missing data confirmed the results of the primary analysis on the primary observational endpoint in the T1DM and T2DM group.

Subgroup analyses showed that, in the T1DM and T2DM group, the decrease in the rate of any hypoglycaemic events occurred across all ranges of duration of underlying DM, across all ranges of baseline HbA1c and regardless of whether patients had switched to Tresiba® at baseline due to hypoglycaemia or not. Analysis showed that the decrease in the rate of any hyperglycaemic events occurred in T1DM patients who took bolus insulin during the baseline period. The number of patients in the T1DM group who did not take bolus insulin was very small as expected and the decrease in the rate of any hyperglycaemic events was not statistically significant. For T2DM patients the rate of any hypoglycaemia decreased occurred regardless of whether they took bolus insulin at baseline or not. Analysis according to country showed a statistically significant decrease in the rate of any hypoglycaemic events for T1DM patients in Switzerland, Italy, and United Kingdom, and for T2DM patients in the Netherlands, Spain, Sweden and Italy. There were no statistically significant changes in the remaining countries. These variations across the subgroups are possibly a mix of inadequate power and false-positive results due to multiple testing.

10.4.7.2 Summary of secondary observational effectiveness endpoints

- FPG values decreased over the 12-month observation period compared to baseline. At month 12, the LS mean decrease in FPG compared to baseline was −0.54 mmol/L (95% CI: −0.95, −0.14; p=0.009) for T1DM patients and −0.84 mmol/L (95% CI: −1.09, −0.60; p<0.001) for T2DM patients.
- The proportions of T1DM patients with HbA1c <7% at baseline and end of study were 19.2% and 19.4%, respectively. The proportions of T1DM patients with HbA1c <7.5% at baseline and end of study were 35.4% and 34.7%, respectively. The proportions of T2DM patients with HbA1c <7% and at baseline and end of the study were 16.4% and 24.2%, respectively. The proportions of T2DM patients with HbA1c <7.5% at baseline and end of study were 29.7% and 44.2%, respectively.
- HbA1c values decreased over the 12-month observation period compared to baseline. At month 12, the LS mean decrease in HbA1c compared to baseline was -0.15 mmol/mol (95% CI: -0.23, -0.07; p<0.001) for T1DM patients and -0.32 mmol/mol (95% CI: -0.42, -0.22; p<0.001) for T2DM patients.
- The rate of severe hypoglycaemia events (according to the ADA definition) decreased during the baseline period and in the 12-month observation period for T1DM and T2DM patients. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was a statistically significant decrease in severe hypoglycaemic events for T1DM patients (0.28 [95% CI: 0.14, 0.56; p<0.001]) at 12 months after baseline compared to baseline, while there was no statistically significant change for T2DM patients.

- The rate of asymptomatic hypoglycaemia events (according to ADA definition) decreased between baseline and 12 months after baseline for both T1DM and T2DM patients. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was a statistically non-significant decrease in asymptomatic hypoglycaemia events for T1DM patients and a statistically significant decrease for T2DM patients (0.48 [95% CI: 0.27, 0.87; p=0.016]) at 12 months after baseline compared to baseline.
- The rate of documented symptomatic hypoglycaemic events (according to the ADA definition) decreased between baseline and 12 months after baseline for both T1DM and T2DM patients. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was a statistically significant decrease in documented symptomatic hypoglycaemic events for both T1DM (0.83 [95% CI: 0.76, 0.92; p<0.001]) and T2DM (0.54 [95% CI: 0.44, 0.68; p<0.001]) patients, at 12 months after baseline compared to baseline.
- The rate of pseudo-hypoglycaemic events (according to the ADA definition) decreased between baseline and 12 months after baseline in the T1DM and T2DM group. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was a statistically significant decrease in pseudo-hypoglycaemic events for both T1DM (0.44 [95% CI: 0.29, 0.67; p<0.001]) and T2DM (0.42 [95% CI: 0.28, 0.63; p<0.001]) patients, at 12 months after baseline compared to baseline.
- The rate of probable symptomatic hypoglycaemic events (according to the ADA definition) decreased between baseline and 12 months after baseline, for both T1DM and T2DM groups. According to the incidence rate ratio (12 months after base/4 weeks before baseline), there was a statistically significant decrease in probable symptomatic hypoglycaemic events for both T1DM (0.53 [95% CI: 0.36, 0.77; p<0.001]) and T2DM (0.36 [95% CI: 0.18, 0.70; p=0.003]) patients, at 12 months after baseline compared to baseline.
- The rate of confirmed hypoglycaemic events (according to the Novo Nordisk definition) decreased between baseline and 12 months after baseline. According to the incidence rate ratio (12 months after base/4 weeks before baseline), there was a statistically significant decrease in confirmed hypoglycaemic events for both T1DM (0.79 [95% CI: 0.70, 0.90; p<0.001]) and T2DM (0.51 [95% CI: 0.38, 0.70; p<0.001) patients, at 12 months after baseline compared to baseline.
- The rate of severe or blood glucose confirmed symptomatic hypoglycaemic events (according to the Novo Nordisk definition) decreased between baseline and 12 months after baseline. According to the incidence rate ratio (12 months after base/4 weeks before baseline), there was a statistically significant decrease in severe or blood glucose confirmed hypoglycaemic events for both T1DM (0.76 [95% CI: 0.67, 0.86; p<0.001]) and T2DM (0.56 [95% CI: 0.40, 0.79; p<0.001) patients, at 12 months after baseline compared to baseline.
- The rate of any hypoglycaemic events decreased between baseline and the maintenance period. According to the incidence rate ratio (maintenance period/4 weeks before baseline), there was a statistically significant decrease in any hypoglycaemic events for both T1DM (0.76 [95% CI:

0.69, 0.84; p<0.001]) and T2DM (0.40 [95% CI: 0.33, 0.49; p<0.001]) patients, during the maintenance period compared to baseline.

- The rate of nocturnal hypoglycaemic events decreased between baseline and the maintenance period. According to the incidence rate ratio (maintenance period/4 weeks before baseline), there was a statistically significant decrease in nocturnal hypoglycaemic events for both T1DM (0.61 [95% CI: 0.50, 0.74; p<0.001]) and T2DM (0.35 [95% CI: 0.19, 0.64; p<0.001]) patients, during the maintenance period compared to baseline.
- The rate of nocturnal hypoglycaemic events decreased between baseline and 12 months after treatment. According to the incidence rate ratio (12 months after base/4 weeks before baseline), there was a statistically significant decrease in events in the both the T1DM (0.61 [95% CI: 0.50, 0.73; p<0.001]) and T2DM (0.35 [95% CI: 0.20, 0.62; p<0.001]) group, at 12 months after baseline compared to baseline.
- The rate of any hypoglycaemic event occurring during sleep decreased between baseline and 12 months after treatment. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was a statistically significant decrease in any hypoglycaemic event occurring during sleep for both T1DM (0.70 [95% CI: 0.59, 0.83; p<0.001]) and T2DM (0.56 [95% CI: 0.34, 0.90; p=0.017]) patients, at 12 months after baseline compared to baseline.
- The rate of non-severe hypoglycaemic events decreased between baseline and 12 months after treatment. According to the incidence rate ratio (12 months after base/4 weeks before baseline), there was a statistically significant decrease in non-severe hypoglycaemic events for both T1DM (0.81 [95% CI: 0.74, 0.88; p<0.001]) and T2DM [0.46 (95% CI: 0.38, 0.56; p<0.001]) patients, at 12 months after baseline compared to baseline.
- The rate of any hypoglycaemic events in high-dose insulin users decreased between baseline and 12 months after treatment. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was no statistically significant decrease in any hypoglycaemic events in high-dose T1DM and T2DM insulin and users, at 12 months after baseline compared to baseline.
- The rate of hypoglycaemic events in hypo-prone patients decreased between baseline and 12 months after treatment. According to the incidence rate ratio (12 months after baseline/4 weeks before baseline), there was a statistically significant decrease in hypoglycaemic events in hypo-prone patients in both T1DM (0.78 [95% CI: 0.70, 0.86; p<0.001]) and T2DM (0.46 [95% CI: 0.37, 0.56; p<0.001]) groups, at 12 months after baseline compared to baseline.

10.4.7.3 Summary of secondary safety observational endpoints

- The rate of severe hypoglycaemia events was low during the 6-month recall period, and during and after 12 months of treatment for both T1DM and T2DM patients, based AE data.
- According to the fully-adjusted MMRM model, the LS mean change from baseline in body weight at month 12 indicated a statistically significant increase for T1DM patients (0.79 [95% CI: 0.38, 1.20; p<0.001]) but not for T2DM patients. The statistically significant changes in

body weight for T1DM patients were considered as not clinically relevant after the 12-month observation period.
- No new safety findings were identified based on the percentage of patients who experienced SADRs, MESIs, pregnancies, TEAEs or SAEs during the 12-month observation period.

10.4.7.4 Summary of secondary patient-reported outcome observational endpoints

There was no clinically significant change in the general health status as assessed with the HR-QoL instrument (SF-36). The scores for all 8 domains assessed (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and the combined scores, overall PCS and overall MCS, remained similar after the 12-month observation period compared to baseline in the T1DM and T2DM group.

At month 12, the absolute mean change from baseline in the total DTSQs score was 3.81 points for T1DM patients (mean values at baseline and month 12: 26.03 points and 29.91 points, respectively) and 4.47 points for T2DM patients (mean values at baseline and month 12: 25.71 points and 29.96 points, respectively). This increase in the score reflected a clinically relevant increase in the patients' satisfaction with their treatment in both patient groups, as assessed with the DTSQs, after the 12-month observation period.

10.4.7.5 Summary of health economic and dose-time flexibility observational endpoints

- Based on the FAS, the most common reasons for physicians to switch patients to Tresiba® were concern about hypoglycaemia (64.6%) and to improve blood glucose control (63.9%) for T1DM patients and to improve blood glucose control (73.3%) and concern about hypoglycaemia (36.2%) for T2DM patients.
- The estimated annual incidence rate of patients discussing any hypoglycaemia event with the physician or a nurse at baseline period was 1.4 and 2.4 for T1DM and T2DM patients, respectively, and 1.0 and 0.4, respectively, during the 12-month observation period.
- The numbers of patients who received treatment, by a paramedic at home, emergency room visits and hospitalisations due to hypoglycaemia were low (ie, ≤3 patients by any category).
- The proportions of patients with at least one hypoglycaemic event that led to absence from work throughout the 12-month observation period ranged from 5.0% to 8.1% in the T1DM group and from 3.3% to 9.4% in the T2DM group.
- The absolute mean change in the number of SMBG test strips used increased from baseline throughout the 12-month observation period. At month 12, the absolute mean change from baseline in the number of strips used by T1DM and T2DM patients were 0.18 and 0.29 strips, respectively.
- At month 12, most patients in both patient groups preferred Tresiba® (97.2% of T1DM patients and 99.2% of T2DM patients) and the FlexTouch® pen (93.8% of T1DM patients and 97.5% of T2DM patients) to their previous treatment.
- Dose-time flexibility endpoints:

- Throughout the 12-month observation period, the proportion of patients with missed doses decreased compared to baseline and ranged from 2.9% to 9.1% for T1DM patients and from 2.8 to 6.9% for T2DM patients (baseline value: 14.6% and 14.9% for T1DM and T2DM, respectively).
- The most common reasons for missed doses for both T1DM and T2DM patients throughout the observation period were patient forgot and 'other'.
- The most common action taken for missed doses for both T1DM and T2DM patients throughout the observation period was that the patient did nothing.
- The proportions of patients who reported changes in any social, leisure, and working activities due to insulin treatment were not clinically significant in either patient group.
- The proportions of patients who used Tresiba® at least once, at a time different from their usual dosing time throughout the 12-month observation period ranged from 21.8% to 32.7% in the T1DM group and from 13.7% to 27.2% in the T2DM group. The proportion of patients who used the dose-time flexibility option at least once throughout the 12-month observation period ranged from 20.9% to 22.9% in the T1DM group and from 14.0% to 22.0% in the T2DM group.
- At month 12, the time of day during which the largest percentage of the total dosages was administered was between 06:00 and 08:59 (20.3% for T1DM patients and 14.1% for T2DM patients) and between 21:00 and 23:59 (50.3% for T1DM patients and 60.4% for T2DM patients).

- The mean daily basal insulin dose decreased during the 12-month observation period in the T1DM group while it remained similar to baseline for T2DM patients. The absolute mean change in the daily basal insulin dose at month 12 was −2.21 IU for T1DM patients (baseline and month 12 values: 25.02 IU and 22.81 IU respectively) and −0.14 IU for T2DM patients (baseline and month 12 values: 37.45 IU and 35.90 IU, respectively).
- Likewise, the daily bolus insulin dose decreased during the 12-month observation period for T1DM patients while it remained similar to baseline for T2DM patients. The absolute mean change in the daily bolus insulin dose at month 12 was −3.20 IU for T1DM patients (baseline and month 12 values: 27.33 IU and 23.79 IU, respectively) and 0.23 IU for T2DM patients (baseline and month 12 values: 38.91 IU and 38.33 IU, respectively).
- The total daily bolus insulin dose decreased during the 12-month observation period for T1DM patients while it remained similar to baseline for T2DM patients. For T1DM patients, the absolute mean change in the total daily dose of bolus insulin was −5.12 IU. For T2DM patients, the absolute mean change in the total daily dose of bolus insulin was 0.46 IU.

10.5 Exposure to Tresiba®

Exposure to Tresiba® for the FAS outside Germany are summarised in Table 14.1.7.1.1, The mean exposure to Tresiba® was 351.8 days (11.6 months) for T1DM patients and 348.0 days (11.4 months) for T2DM patients. Exposure to Tresiba® beyond 13.5 months occurred in 13.7% of

T1DM patients and in 9.7% of T2DM patients. Results were similar for patients (excluding Germany) identified as completed per end of treatment form (Table 14.1.7.1.2).

Exposure to Tresiba® in patients from Germany is shown in Table 14.1.7.2.

Individual data on exposure to Tresiba® are shown in Annex 2, Listing 16.2.5.1.1.

10.6 Other analyses – Not applicable

10.7 Adverse events/adverse reactions

In this study, only the safety information listed in Section 10.1 of the protocol (Annex 1, Appendix 16.1.1) was required to be systematically reported. Voluntary reporting of any other AE information other than SADRs, MESI (medication errors) and pregnancies (including outcome) was at the physician's discretion. Severe hypoglycaemic events (regardless of the physician's evaluation of seriousness and causality) were also systematically collected and are described in Section 10.4.2.4 and Section 10.4.3.1.

10.7.1 Adverse events/adverse reactions

An overall summary of ADRs and TEAEs for the FAS outside Germany is provided in Table 10–26. As per protocol, ADRs and TEAE were not collected systematically.

Overall, 0.2% of T1DM patients and 0.5% of T2DM patients had at least 1 ADR leading to study treatment discontinuation.

Overall, 15.1% of T1DM patients and 8.5% of T2DM patients had at least 1 TEAE; 4.9% of T1DM patients and 3.3% of T2DM patients had at least 1 serious TEAE; 3.1% of T1DM patients and 2.1% of T2DM patients had at least 1 TEAE possibly/probably related to Tresiba®; and 0.5% of T1DM patients and 0.7% of T2DM patients had at least 1 TEAE leading to study treatment discontinuation. The most frequently reported TEAE by SOC was metabolism and nutrition disorders in both the T1DM group (81 events) and the T2DM group (17 events).

Table 10–26 Overall summary of adverse drug reactions and treatment-emergent adverse events (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
	#E	n (%)	#E	n (%)
Number of Patients with At Least One:				
Serious ADR	23	9 (1.6)	6	6 (1.0)
ADR Leading to Discontinuation	1	1 (0.2)	3	3 (0.5)
Number of Patients with At Least One:				
TEAE	183	84 (15.1)	96	52 (8.5)
Serious TEAE	61	27 (4.9)	25	20 (3.3)
TEAE possible/probably related to Tresiba®	36	17 (3.1)	14	13 (2.1)
TEAE Leading to Discontinuation	4	3 (0.5)	11	4 (0.7)

An ADR is an AE for which the causal relationship between the product and the AE is suspected; that is judged to be possible or probable by either Novo Nordisk or the reporter.

A TEAE is an adverse event with a start date on or after the date of the first dose of study drug, or with a start date prior to the date of first dose of study drug whose severity worsens on or after the date of first dose of study drug. A TEAE leading to discontinuation includes all TEAE which lead to the study drug being discontinued.

#E: Number of events; MedDRA Version 20.1

ADR = Adverse drug reaction; AE =Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.3.1.1.1.1 and EOT Table 14.3.1.1.2.1

An overall summary of ADRs and TEAEs for the FAS from Germany is provided in Table 14.3.1.1.2.2 and Table 14.3.1.1.1.2, respectively.

Summaries of ADRs by SOC and PT are provided in Table 14.3.1.2.2.1 for the FAS outside Germany and in Table 14.3.1.2.2.2 for the FAS from Germany. The most frequently reported PT for the FAS outside Germany was hypoglycaemia in both the T1DM group (28 events) and the T2DM group (7 events).

Summaries of TEAEs by SOC and PT are provided in Table 14.3.1.2.1.1 for the FAS outside Germany and in Table 14.3.1.2.1.2 for the FAS from Germany.

A summary of TEAEs by severity for the FAS outside Germany is provided in Table 14.3.1.3.1.1. The most frequently reported severity was ‘mild’ in both the T1DM group (70 events) and the T2DM group (42 events). Severe TEAEs were experienced by 22 (4.0%) T1DM patients and 12 (2.0%) T2DM patients.

A summary of TEAEs by severity for the FAS from Germany is provided in Table 14.3.1.3.1.2.

A summary of TEAEs by action taken to study product for the FAS outside Germany is provided in Table 14.3.1.3.2.1. The most frequently reported action taken to study product was 'dose not changed' in both the T1DM group (134 events) and the T2DM group (72 events). The study drug was discontinued as a result TEAEs in 3 (0.5%) T1DM patients and 4 (0.7%) T2DM patients (details provided in Section 10.7.4), interrupted in 3 (0.5 %) T2DM patients, reduced in 4 (0.7%) T1DM and T2DM patients each, and increased in 9 (1.6%) T1DM patients.

A summary of TEAEs by action taken to study product for the FAS from Germany is provided in Table 14.3.1.3.2.2.

A summary of TEAEs by causality for the FAS outside Germany is provided in Table 14.3.1.3.3.1. The most frequently reported causality was 'unlikely' (related) in both the T1DM group (114 events) and the T2DM group (79 events). A total of 8 (1.4%) T1DM patients and 8 (1.3%) T2DM patients had TEAEs assessed as probably related to Tresiba® (20 and 8 events, respectively) and 11 (2.0%) T1DM patients and 5 (0.8%) T2DM patients had TEAEs assessed as possibly related to Tresiba® (16 and 6 events, respectively).

A summary of TEAEs by causality for the FAS from Germany is provided in Table 14.3.1.3.3.2.

Patients who experienced AEs and event details are listed in Annex 2, Listing 16.2.7.1.

10.7.2 Deaths

Only deaths considered possibly/probably related to study product were collected systematically in the study. Eleven patients were reported to have died during this study (Annex 2, Listing 16.2.1.4.2.1 and CRFs Annex 3, Appendix 16.3.1). None of the deaths were reported as either possibly or probably related to the study product.

The following patient died prior to the observation period (included in the DPO population; Annex 2, Listing 16.2.3.1):

- Patient [redacted] (T2DM group) died from an unknown cause (Annex 2, Listing 16.2.1.4.2.1 and Listing 16.2.3.1).

The following patients, included in the FAS (Annex 2, Listing 16.2.1.2), died during the observation period:

- Patient [redacted] (T1DM group) died from a cause not reported (Annex 2, Listing 16.2.7.1 and Table 14.3.1.2.1.1)
- Patient [redacted] (T1DM group) died from pulmonary oedema (Annex 2, Listing 16.2.7.1 and CRF Annex 3, Appendix 16.3.1)

- Patient [redacted] (T1DM group) died from cardiac arrest (Annex 2, Listing 16.2.7.1 and CRF Annex 3, Appendix 16.3.1)
- Patient [redacted] (T2DM group) died from a cause not reported (Annex 2, Listing 16.2.1.4.2.1)
- Patient [redacted] (T2DM group) died from a cause not reported (Annex 2, Listing 16.2.1.4.2.1)
- Patient [redacted] (T2DM group) died due to stroke (Annex 2, Listing 16.2.1.4.2.1)
- Patient [redacted] (T2DM group) died due to respiratory insufficiency (Annex 2, Listing 16.2.1.4.2.1)
- Patient [redacted] (T2DM group) died from cardiac arrest (Annex 2, Listing 16.2.7.1 and CRF Annex 3, Appendix 16.3.1)
- Patient [redacted] (T2DM group) died from a cause not reported (Annex 2, Listing 16.2.7.1 and CRF Annex 3, Appendix 16.3.1)
- Patient [redacted] (T1DM group) died from cardiorespiratory arrest (CRF Annex 3, Appendix 16.3.1)

10.7.3 Other serious adverse events

SADRs by SOC and PT for the FAS outside Germany are summarised in Table 10–27. SADRs were reported for a total of 9 (1.6%) T1DM patients (23 events) and 6 (1.0%) T2DM patients (6 events) during the 12-month observation period. All of the SADRs were included in the SOCs metabolism and nutrition disorders and nervous system disorders. “Diabetic ketoacidosis” and “hypoglycaemia” were the only two PTs reported in at least 2 patients (2 [0.4%] patients in the T1DM group with [redacted]; 6 [1.1%] patients in the T1DM group and 5 [0.8%] patients in the T2DM group with hypoglycaemia). All SADRs were reported as recovered/resolved, except for 1 SADR ([redacted]) for patient [redacted]. [redacted].

Table 10–27 Summary of serious adverse drug reactions by system organ class and preferred term (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
	#E	n (%)	#E	n (%)
Number of Patients with At Least One SADR	23	9 (1.6)	6	6 (1.0)
Metabolism and nutrition disorders	22	8 (1.4)	5	5 (0.8)
Nervous system disorders	1	1 (0.2)	1	1 (0.2)
Diabetic ketoacidosis	3	2 (0.4)	0	0
Hypoglycaemia	19	6 (1.1)	5	5 (0.8)
Hypoglycaemic seizure	1	1 (0.2)	0	0
Hypoglycaemic unconsciousness	0	0	1	1 (0.2)

[1] SADRs are serious adverse events (AEs) for which the causal relationship between the product and the AE is suspected; that is judged to be possible or probable by either Novo Nordisk or the reporter.

#E: Number of events.

MedDRA Version 20.1

MedDRA = Medical Dictionary for Regulatory Activities; MESI = medication errors; SADRs = serious adverse drug reactions; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.3.1.2.2.3

A summary of SADRs by SOC and PT for the FAS in Germany is shown in Table 14.3.1.2.2.4.

Individual data for SADRs are provided in Annex 2, Listing 16.2.7.1.

10.7.4 Other significant adverse events

A summary of patients with at least 1 SADR, MESI or pregnancy, outside Germany (FAS), is provided in Table 10–28.

Table 10–28 Summary of SADRs, MESI and pregnancies during 12 months of treatment (Full Analysis Set – excluding Germany)

	T1DM (N=556)		T2DM (N=611)	
	#E	n (%)	#E	n (%)
Number of Patients with At Least One:				
Serious Adverse Drug Reactions [1]	23	9 (1.6)	6	6 (1.0)
MESI/Medication Error [2]	2	2 (0.4)	11	4 (0.7)
Pregnancies of patient [3]	4	4 (0.7)	0	0

[1] SADRs are serious adverse events (AEs) for which the causal relationship between the product and the AE is suspected; that is judged to be possible or probable by either Novo Nordisk or the reporter.

[2] MESI: Medical event of special interest. Following individual assessment, only 4 cases were identified as true medication errors.

[3] According to the protocol only pregnancies in female patients were to be reported.

#E: Number of events.

MedDRA Version 20.1

MedDRA = Medical Dictionary for Regulatory Activities; MESI = medication errors; SADRs = serious adverse drug reactions; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.3.2.4.1.1

A summary of SADRs for the FAS from Germany is shown in Table 14.3.2.4.1.2.

A summary of the FAS outside Germany with at least 1 MESI (medication error) is shown in Table 14.3.2.4.1.1. A total of 2 (0.4%) T1DM patients and 4 (0.7%) T2DM patients had MESIs during the 12-month observation period.

A summary of MESIs for the FAS from Germany is shown in Table 14.3.2.4.1.2.

MESIs by SOC and PT are summarised in Table 10–29.

Table 10–29 Summary of adverse events reported as medical events of special interest by system organ class and preferred term (Full Analysis Set – excluding Germany)

System Organ Class	T1DM (N=556)		T2DM (N=611)	
Preferred Term	#E	n (%)	#E	n (%)
Number of Patients with At Least One MESI:	2	2 (0.4)	11	4 (0.7)
Gastrointestinal disorders	0	0	2	1 (0.2)
Diarrhoea	0	0	1	1 (0.2)
Nausea	0	0	1	1 (0.2)
General disorders and administration site conditions	0	0	3	1 (0.2)
Asthenia	0	0	1	1 (0.2)
Fatigue	0	0	1	1 (0.2)
Non-cardiac chest pain	0	0	1	1 (0.2)
Infections and infestations	1	1 (0.2)	0	0
Erythema migrans	1	1 (0.2)	0	0
Injury, poisoning and procedural complications	0	0	1	1 (0.2)
Product name confusion	0	0	1	1 (0.2)
Metabolism and nutrition disorders	1	1 (0.2)	2	2 (0.3)
Hypoglycaemia	1	1 (0.2)	2	2 (0.3)
Nervous system disorders	0	0	1	1 (0.2)
Headache	0	0	1	1 (0.2)
Skin and subcutaneous tissue disorders	0	0	2	1 (0.2)
Rash generalised	0	0	1	1 (0.2)
Rash pruritic	0	0	1	1 (0.2)

MedDRA Version 20.1

#E: Number of events; MedDRA = Medical Dictionary for Regulatory Activities; MESI = medical event of special interest; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Cross-reference: EOT Table 14.3.1.2.2.5

A summary of SADRs by SOC and PT for patients in Germany is shown in Table 14.3.1.2.2.6 (there were no events).

Individual data for MESIs are provided in Annex 2, Listing 16.2.7.1.

Following individual case assessments, only 4 cases were identified as true medication errors:

- Patient [redacted] (T1DM group): Tresiba given intramuscularly (preferred term: ‘incorrect route of drug administered’), co-reported with ’hypoglycaemia’. Subject was subsequently reported as [redacted].

- Patient [redacted] (T2DM group): mix-up of [redacted] and [redacted] and self-administered the wrong drug (preferred terms: 'product selection error' and 'wrong drug administered'). No adverse event was co-reported.
- Patient [redacted] (T2DM group): problem in loading the insulin dose (preferred term: 'incorrect dose administered'). Co-reported with 'hypoglycaemic unconsciousness'. Subject was reported [redacted].
- Patient [redacted] (T2DM group): hypoglycaemia (preferred term: hypoglycaemia). Reported as [redacted].

A total of 3 patients in the T1DM group and 4 patients in the T2DM group discontinued treatment with study product due to TEAEs (Table 14.3.1.3.2.1 and Annex 2, Listing 16.2.7.1):

- Patient [redacted] (T1DM group) experienced dizziness and discomfort. These events were non-serious, of non-severe intensity and no MESI. Causal relationship to the study drug was not reported. [redacted].
- Patient [redacted] (T1DM group) experienced cardiorespiratory arrest. This event was serious because it was life-threatening and of severe intensity. The causal relationship to the study drug was reported as unlikely. The event was fatal.
- Patient [redacted] (T1DM group) experienced hyperglycaemia. This event was a non-serious ADR that was of non-severe intensity and no MESI. The causal relationship to the study drug was reported as probable. [redacted]
- Patient [redacted] (T2DM group) experienced hyperglycaemia. This event was a non-serious ADR that was of non-severe intensity and no MESI. The causal relationship to the study drug was reported as probable. [redacted].
- Patient [redacted] (T2DM group) experienced vertigo. This event was a non-serious ADR that was of non-severe intensity and no MESI. The causal relationship to the study drug was reported as probable. [redacted]
- Patient [redacted] (T2DM group) experienced hypoglycaemia. This event was a serious ADR of severe intensity and no MESI. The causal relationship to the study drug was reported as possible. [redacted]
- Patient [redacted] (T2DM group) experienced rash generalised, fatigue, rash pruritic, headache, asthenia, nausea, non-cardiac chest pain, and diarrhoea. All were non-serious, of non-severe intensity and non-MESI. The causal relationship to the study drug was reported as unlikely for each event. [redacted]. Note: The MESI status in Listing 16.2.7.1 is incorrect, due to an error in the clinical database.

10.7.5 Other observations related to safety

No safety information other than that described in Section 10.4.3.1 (severe hypoglycaemic events), Section 10.7.1 (AEs, ADRs), Section 10.7.2 (deaths), Section 10.7.3 (other SAEs), Section 10.7.4 (other significant adverse events), and Section 10.7.6 (pregnancy) was collected during the study.

10.7.6 Pregnancy

A summary of patients with at least one pregnancy outside Germany is shown in Table 14.3.2.4.1.1. A total of 4 (0.7%) T1DM patients and none of the T2DM patients had a pregnancy during the 12-month observation period.

A summary of pregnancies for patients in Germany is shown in Table 14.3.2.4.1.2.

Pregnancy narratives are provided in Section 14.3.3 and summarised below:

[redacted]

10.7.7 Technical complaints

Technical complaints were not systematically recorded in this study.

10.7.8 Summary of adverse events

Safety data are summarised for patients outside Germany only.

Overall, 17 T1DM patients and 13 T2DM patients had at least 1 ADR; 9 T1DM patients and 6 T2DM patients had at least 1 serious ADR; and 1 T1DM patient and 3 T2DM patients had at least 1 ADR leading to study treatment discontinuation.

Overall, 84 T1DM patients and 52 T2DM patients had at least 1 TEAE; 27 T1DM patients and 20 T2DM patients had at least 1 serious TEAE; 17 T1DM patients and 13 T2DM patients had at least 1 TEAE possibly/probably related to Tresiba®; and 3 T1DM patients and 4 T2DM patients had at least 1 TEAE leading to study drug discontinuation.

Severe TEAEs were experienced by 22 T1DM patients and 12 T2DM patients.

Deaths were not systematically recorded in this study. However, 4 patients in the T1DM and 6 patients in the T2DM groups were reported to have died during the observation period of the study, and 1 patient died prior to the observation period.

During the 12-month observation period, a total of 9 T1DM patients and 6 T2DM patients had SADRs, and a total of 2 T1DM patients and 4 T2DM patients had MESIs (medication errors). By manual assessment, 1 T1DM and 3 T2DM patients were found to have had true medication errors. A total of 4 T1DM patients or their partners and none of the T2DM patients (or their partners) had a pregnancy during the 12-month observation period.

Overall, treatment with Tresiba® was well tolerated throughout the 12-month observation period and no new safety concerns were identified, in relation to the use of Tresiba®.

11 Discussion

11.1 Key results

This was a 12-month, multi-centre, prospective, non-interventional study to assess the safety and effectiveness of Tresiba® in patients with type 1 and type 2 DM, in a real-world clinical setting. The primary objective of this study was to assess the safety of Tresiba®, used with any other anti-diabetic treatment and according to label, by analysing whether treatment with Tresiba® OD was 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 continued the prior basal insulin as part of their anti-diabetic treatment regimen.

Switching to degludec from other basal insulins was associated with significantly reduced rates of hypoglycaemia. The observed decrease in the rate of hypoglycaemic episodes occurred across all analysed ranges of duration of the underlying DM, all ranges of patient baseline HbA1c, regardless of whether patients had taken bolus insulin medication during the baseline period and regardless of whether the patient's reason for switching to Tresiba® had been reported as "due to hypoglycaemia" or "not due to hypoglycaemia". Generally, rates were higher for T1DM patients than T2DM patients, while reductions in the rates were larger for T2DM patients than T1DM patients.

The observed decrease in the rate of any hypoglycaemic episodes was also observed in all populations for both the Novo Nordisk and ADA definitions of hypoglycaemia that are described in Section 9.4.2.1, and was accompanied by simultaneous improvement in glycaemic control as evidenced by the levels of HbA1c and FPG, and in treatment satisfaction, at the end of the 12 month observation period.

11.2 Limitations

While no causal relationships can be concluded based on a non-interventional single-arm study design, the aim was to explore the association between Tresiba® and other anti-diabetic treatment regimens with regard to any hypoglycaemia episodes.

Because patients acted as their own control, the baseline period prior to planned initiation of Tresiba® was used to obtain reference data for the enrolled patients. The absence of a comparator group resulted in a number of threats to internal and external validity of the study design, the most critical of which was that the design did not provide the ability to rule out many alternative explanations for changes from baseline.

As for other observational studies, this study exhibited several potential factors of limitation such as being subject to bias and confounding. Although these limiting factors could be mitigated by ensuring an unselected enrolment of both site and patients, as well as proper adjustment of known confounders in the statistical analysis, they cannot be fully excluded.

Because the use of diaries and questionnaires in this study could bias data towards those patients, either through socio-economic or educational reasons, who were better able to monitor and maintain a diary and thus maintain improved blood glucose, the broad inclusion criteria from a wide demographic were implemented to minimise the potential impact of this bias.

Further details on bias is provided in Section 9.6 and relevant sections in the protocol (see Annex 1, Appendix 16.1.7).

11.3 Interpretation

The selection of sites from seven European countries aimed to include a heterogeneous sample of the source population. Demographics and baseline characteristics were similar between the DPO and FAS, however, due to competitive recruitment, Italy was overrepresented among the T2DM patients, accounting for 51% of the data collected.

This study adds to the body of evidence related to the treatment of T1DM and T2DM with Tresiba® in routine clinical practice. The prospective collected hypoglycaemia data from dedicated patient diaries in this study demonstrates higher rates of hypoglycaemia providing an additional level of detail and a more in-depth view of the hypoglycaemic burden experienced by patients that is not possible with retrospective chart reviews like the EU-TREAT study.[6] In addition, this study provides novel insights from the patients regarding treatment satisfaction and patient reported outcomes. This study demonstrated that switching to Tresiba® from other basal insulins is associated with significantly reduced rates of hypoglycaemia and at significantly lower or similar insulin doses in patients with T1DM or T2DM under routine clinical practice. A substantial proportion of the subjects exhibited adequate glycaemic control at study initiation. As Tresiba® succeeded in reducing the rates of hypoglycaemia, improvement in glycaemic control was also achieved even though physicians were not necessarily trying to adjust dose to achieve better overall glycaemic control. In addition, treatment satisfaction was also improved.

The observed decreases among all hypoglycaemia definitions and subgroups agree with the data obtained from the clinical development programme of Tresiba®, which has consistently shown a lowered risk of hypoglycaemia in patients treated with Tresiba® against comparators with similar efficacy. The hypoglycaemic event rate ratios from ReFLeCT showed larger relative reductions than in the degludec SWITCH randomized clinical trials.[7,8] However, overall the benefits obtained with degludec were similar across the different study and trial designs.

The study showed a moderate decrease in patient HbA1c. This decrease was accompanied by a higher rate of responders to treatment with Tresiba® in patients who had HbA1c values of <7.5% at the end of the study (against those with HbA1c values of <7.0%).

11.4 Generalisability

This was a non-interventional study without highly restrictive inclusion-exclusion criteria and was conducted at multiple geographical sites. Our results apply to a heterogeneous real-world population of patients with T1DM or T2DM. In addition, the substantial observation period of 12-months allowed for a relatively long-term evaluation of safety and effectiveness.

12 Other information

Not applicable.

13 Conclusion

- There was a statistically significant reduction of any hypoglycaemic events for both types of diabetes after the 12-month observation period, based on the incidence rate ratio: 0.80 (95% CI: 0.74, 0.88; p<0.001) for T1DM patients and 0.46 (95% CI: 0.38, 0.56; p<0.001) for T2DM patients.
- The observed decrease occurred across all analysed ranges of duration of the underlying DM, all ranges of patient baseline HbA1c, regardless of whether patients had recorded taking bolus insulin medication during the baseline period and regardless of whether the patient's reason for switching to Tresiba® had been reported as "due to hypoglycaemia" or "not due to hypoglycaemia".
- Generally, rates of any hypoglycaemic events were higher for T1DM patients than T2DM patients, while reductions in the rates were larger for T2DM patients than T1DM patients. The decrease in the rate of any hypoglycaemic episodes was observed in all populations regardless of which definition of hypoglycaemia (Novo Nordisk or ADA) was applied.
- The decrease in the rate of any hypoglycaemic episodes was accompanied by simultaneous improvement in glycaemic control and in treatment satisfaction.
- Overall, treatment with Tresiba® was well tolerated throughout the 12-month observation period and no new safety concerns were identified, in relation to the use of Tresiba®.

14 Tables, figures and listings

14.1 Demographic data

14.2 Efficacy data

14.3 Safety data

15 References

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16 Annexes

16.1 Annex 1 – Study information

Number	Title	Comment
16.1.1	Protocol and protocol amendments	Applicable
16.1.2	Sample case report form	Applicable
16.1.3	List of Independent Ethics Committees and/or Institutional Review Boards	Applicable
16.1.4	List and description of physicians in the study	Applicable
16.1.5	Signatures of principal or coordinating physician and sponsor	Applicable
16.1.6	Audit certificates	N/A
16.1.7	Documentation of statistical methods	Applicable
16.1.8	Documentation of inter-laboratory standardisation methods and quality assurance	N/A
16.1.9	Publications based on the study	N/A
16.1.10	Important publications referenced in the report	Available upon request

Abbreviation: N/A = not applicable

16.2 Annex 2 – Subject data listings

Number	Title	Comment
16.2.1	Discontinued subjects	Applicable
16.2.2	Important protocol deviations	Applicable
16.2.3	Subjects excluded from the effectiveness analysis	Applicable
16.2.4	Demographic data	Applicable
16.2.5	Compliance and/or drug concentration data	Applicable
16.2.6	Individual effectiveness response data	Applicable
16.2.7	Adverse event listings (by subject)	Applicable
16.2.8	Listing of individual laboratory measurements by subject	N/A

Abbreviation: N/A = not applicable

16.3 Annex 3 – Case report forms

Number	Title	Comment

Number	Title	Comment
16.3.1	CRFs for deaths, other serious adverse events and adverse event withdrawals	Available upon request
16.3.2	Other CRFs submitted	N/A

Abbreviation: CRF = case report form; N/A = not applicable