21 May 2015
EMA/403340/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xultophy

International non-proprietary name: **INSULIN DEGLUDEC / LIRAGLUTIDE**

Procedure No. EMEA/H/C/002647/II/0002

Marketing authorisation holder (MAH): Novo Nordisk A/S

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
BMI	body mass index
DTSQs	Diabetes treatment satisfaction questionnaire status
ECG	electrocardiogram
EMA	European Medicines Agency
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
ICH	International Conference of Harmonisation
IDeg	insulin degludec
IDF	International Diabetes Federation
OAD	oral anti-diabetic drug
PYE	patient-year of exposure
RA	receptor agonist
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMPG	self-measured plasma glucose
SU	sulphonylurea
TRIM-D	Treatment related impact measure - diabetes
T2DM	type 2 diabetes mellitus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 9 December 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name**
Xultophy	INSULIN DEGLUDEC / LIRAGLUTIDE

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the transfer of patients from Glucagon-Like peptide-1 (GLP1) receptor agonist (RA) treatment to Xultophy. Consequently, sections 4.1, 4.2, 4.4, and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include the assigned ATC-code in section 5.1 of the SmPC and to make minor editorial changes in the SmPC. The application included a revised RMP (edition 2.0, version 1.0).

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/310/2011 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Robert James Hemmings

Timetable	Actual dates
Submission date	9 December 2014
Start of procedure	26 December 2014
CHMP Rapporteur Assessment Report	16 February 2015
CHMP CoRapporteur Assessment Report	16 February 2015
PRAC Rapporteur Assessment Report	23 February 2015
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur Updated Assessment Report	N/A
PRAC Teleconference	N/A
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 March 2015
CHMP comments	16 March 2015
CHMP Rapporteur Revised Assessment Report	20 March 2015
Request for Supplementary information (RSI)	26 March 2015
MAH's responses submitted to the CHMP	17 April 2015
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	4 May 2015
CHMP opinion	21 May 2015

2. Scientific discussion

2.1. Introduction

Xultophy is a combination of insulin degludec (basal insulin) and liraglutide (a GLP-1 agonist). It is currently approved for the treatment of adults with T2DM to improve glycaemic control in combination with oral glucose-lowering medicinal products, when these alone or combined with basal insulin do not provide adequate glycaemic control.

This variation application was submitted to extend the indication for Xultophy to include transfer of patients from Glucagon-Like peptide-1 (GLP-1) receptor agonist (RA) treatment to Xultophy. The application is based on trial NN9068-3851, which investigated the efficiency and safety of Xultophy versus unchanged GLP-1 RA therapy in insulin-naïve subjects with T2DM inadequately controlled on GLP-1 RA therapy in combination with metformin +/- pioglitazone +/- sulphonylurea (SU). The product Information and the Risk Management Plan has been updated with editorial changes and based on the results from trial NN9068-3851.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Xultophy (IDegLira) consists of two drug substances, insulin degludec and liraglutide, which are characterised as peptides. CHMP therefore considered it exempted from the requirement to perform an environmental risk assessment.

2.3. Clinical aspects

2.3.1. Introduction

Xultophy (IDegLira) is a combination of the long-acting basal insulin insulin degludec (IDeg, active substance of Tresiba) and the glucagon-like peptide-1 (GLP-1) analogue liraglutide (active substance of Victoza). IDegLira thus combines the active substances of two approved products that within their respective drug classes have shown desirable characteristics in the treatment of type 2 diabetes (T2DM):

- IDeg has a duration of action beyond 42 hours at clinically relevant doses, resulting in a flat and stable pharmacodynamic action profile and low day-to-day variability in glucose lowering effect.
- Liraglutide stimulates insulin secretion and inhibits glucagon secretion in a glucose dependent manner when plasma glucose levels are above normal and shows an effect on reducing body weight through mechanisms involving decreased hunger and lowered energy intake.

The complementary modes of action of these two compounds have been demonstrated to provide clinically relevant improvements in glycaemic control at a low risk of hypoglycaemia and weight gain in patients with T2DM when compared to insulin. In addition, IDegLira provides a treatment benefit to patients in terms of convenience by enabling the administration of both IDeg and liraglutide in one single injection.

IDegLira is initiated and titrated according to glycaemic control (fasting plasma glucose levels) as is current practice for basal insulin therapy. The combination product is provided in a pre-filled pen containing an IDeg/liraglutide ratio of 100 units/3.6 mg per mL. The pre-filled pen allows for dose adjustment in dose steps, with one dose step containing 1 unit of IDeg and 0.036 mg of liraglutide.

The dose range of the pre-filled pen is from 1 to 50 dose steps, with 50 dose steps corresponding to 50 units of IDeg and 1.8 mg of liraglutide.

Rationale for variation application

IDegLira is currently approved under the trade name Xultophy for the treatment of adults with T2DM to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control.

Given the progressive nature of T2DM, current anti-diabetic therapies, including treatment with GLP-1 receptor agonist (RA) (e.g., liraglutide and exenatide), often do not provide sustained glycaemic control, and insulin treatment is eventually indicated for many patients with T2DM. Accordingly, the addition of insulin therapy in T2DM patients inadequately controlled on GLP-1 RA treatment is consistent with current treatment guidelines.

This variation application was submitted to extend the indication for IDegLira to include transfer of patients from GLP-1 RA treatment to IDegLira. The application is based on Trial NN9068-3851 (in the following referred to as Trial 3851), which investigated the efficacy and safety of IDegLira versus unchanged GLP-1 RA therapy in insulin-naïve subjects with T2DM inadequately controlled on GLP-1 RA therapy in combination

with metformin ± pioglitazone ± sulphonylurea (SU).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- overview of clinical studies

The application is based on the single pivotal trial NN9068-3851 (in the following referred to as Trial 3851).

2.3.2. Clinical pharmacology

No new clinical pharmacology studies were submitted, which CHMP considered acceptable for this extension of indication application.

2.4. Clinical efficacy

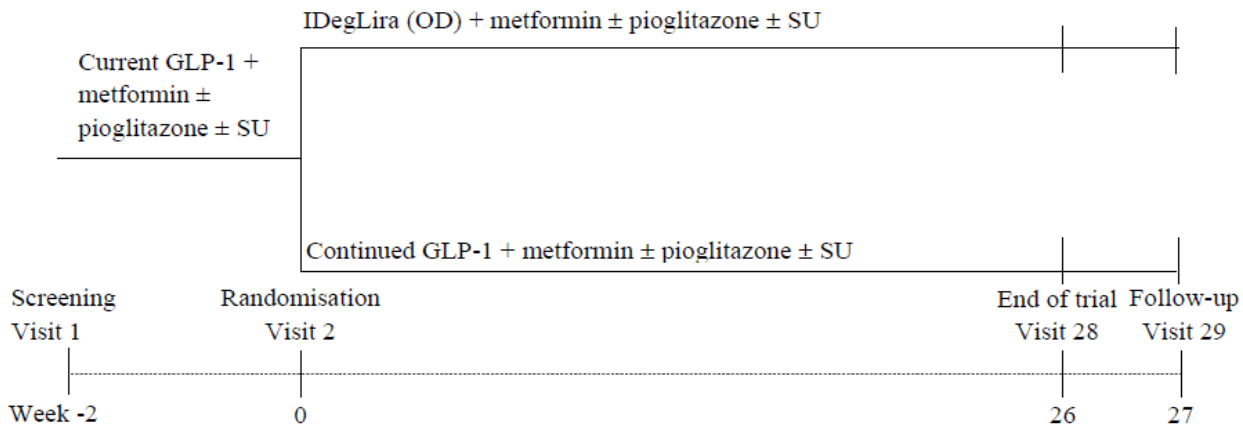
2.4.1. Main study (trial NN9068-3851)

Methods

Trial design

Trial 3851 was a 26-week, multi-centre, multinational, open-label, 2-arm parallel, randomised, treat-to-target trial in insulin-naïve subjects with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide]) and metformin ± pioglitazone ± SU. Inadequately controlled T2DM was defined as an HbA1c level of 7.0–9.0%, both inclusive. The trial design is shown in Figure 1.

Figure 1 Trial design – Trial 3851



GLP-1: glucagon-like peptide-1; OD: once daily; SU: sulphonylurea

Study participants

The subject population was chosen to represent patients with T2DM inadequately controlled (HbA1c ≥7%) on current therapy of GLP-1 RA and who are expected to benefit from intensified treatment. Paediatric or adolescent subjects (<18 years of age) were not enrolled in the trial, whereas subjects above 65 years were

included. Subjects with significant concomitant illnesses were excluded from the trial. Significant concomitant illnesses included: personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, acute cardiovascular disease, proliferative retinopathy or maculopathy requiring treatment, clinically significant active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for T2DM), neurological, genitourinary or haematological system and history of chronic pancreatitis or idiopathic acute pancreatitis. The key inclusion and exclusion criteria are shown in Table 1.

Table 1 Key inclusion and exclusion criteria – Trial 3851

Inclusion criteria
• Informed consent obtained before any trial-related activities • Subjects with T2DM • Males or females, ≥18 years of age • Baseline HbA_{1c} 7.0–9.0% (both inclusive) • Treatment with daily GLP-1 RA at maximum dose according to local label (i.e., 1.8 mg OD Victoza® [liraglutide] or 10 microgram BID Byetta® [exenatide]) or documented maximum tolerated dose (i.e., 1.2 mg OD Victoza® [liraglutide] or 5 microgram BID Byetta® [exenatide]) in combination with a stable daily dose of metformin (≥1500 mg or documented maximum tolerated dose) ± stable daily dose of pioglitazone (≥30 mg) ± stable dose of SU (≥ half of the maximum approved dose according to local label) for 90 days or more prior to screening visit. • BMI ≤40 kg/m^2
Exclusion criteria
• Use of any oral anti-diabetic drug (except for metformin, pioglitazone and SU) ≤90 days prior to screening visit. • Use of any drug (except metformin, pioglitazone, SU and GLP-1 RA) which in the investigators opinion could interfere with the blood glucose level (e.g., systemic corticosteroids). • Treatment with any insulin regimen (short term treatment due to intercurrent illness including gestational diabetes was allowed at the discretion of the investigator). • Screening calcitonin ≥50 ng/L

Withdrawal criteria

Subjects could choose to withdraw from the trial at any time or could be withdrawn at the discretion of the investigator due to safety concerns or if judged non-compliant with trial procedures. The key withdrawal criteria were set to ensure subject safety and to ensure that subjects were not exposed to ineffective therapy for an unacceptable period of time (Table 2).

Table 2 Key withdrawal criteria – Trial 3851

Trial 3948

• Initiation of any systemic treatment with products which in the investigator's opinion could interfere with glucose metabolism
• Pregnancy or intention of becoming pregnant
• If the fasting self-measured plasma glucose (SMPG) values taken on three consecutive days or if any of the fasting plasma glucose (FPG) samples analysed by the central laboratory exceeded the limit of:
  • 15.0 mmol/L (270 mg/dL) from baseline to Week 6
  • 13.3 mmol/L (240 mg/dL) from Week 7 to Week 12
  • 11.1 mmol/L (200 mg/dL) from Week 13 to Week 26
The subject was to be called for an unscheduled visit as soon as possible. A confirmatory FPG was to be obtained and analysed by the central laboratory. If this FPG exceeded the above described values, and no treatable intercurrent cause for the hyperglycaemia was diagnosed, the subject was to be withdrawn.
• Subjects diagnosed with acute pancreatitis

Treatments

Subjects were randomised to IDegLira or to continue their pre-trial GLP-1 RA therapy, both in combination with pre-trial doses of metformin ± pioglitazone ± SU.

The starting dose of IDegLira was 16 dose steps (16 units IDeg/0.6 mg liraglutide) followed by a treat-to-target approach with adjustment of doses to achieve the fasting plasma glucose (FPG) target of 4.0−5.0 mmol/L (72−90 mg/dL). The IDegLira dose was titrated twice weekly based on the mean of the three preceding fasting (pre-breakfast) self-measured plasma glucose (SMPG) values obtained prior to dose adjustment. The maximum dose of IDegLira was 50 dose steps (50 units IDeg/1.8 mg liraglutide).

For subjects in the GLP-1 RA arm, the pre-trial GLP-1 RA dose was to be continued.

Both arms continued with pre-trial doses of metformin ± pioglitazone ± SU unless there was a safety concern (see Table 1).

Choice of comparator

The reason for continuing unchanged pre-trial GLP-1 RA therapy in the arm not receiving IDegLira was to enable an evaluation of the distinct efficacy and safety associated with transfer of therapy from GLP-1 RA treatment to IDegLira in subjects in need of intensification.

Trial objectives

The primary objective of Trial 3851 was to confirm superiority of IDegLira versus unchanged GLP-1 RA therapy in controlling glycaemia in insulin-naïve subjects with T2DM inadequately controlled on GLP-1 RA therapy in combination with metformin ± pioglitazone ± sulphonylurea (SU).

The secondary objective was to compare general efficacy and safety of IDegLira versus unchanged GLP-1 RA therapy. This was done by assessment of various endpoints related to efficacy and safety.

Outcomes/endpoints

Primary endpoint

The primary endpoint was the change in HbA1c from baseline to 26 weeks of treatment

Secondary endpoints

The following secondary endpoints were investigated:

- Responders for HbA1c after 26 weeks of treatment
    - proportions of subjects achieving the target of HbA1c <7.0%
    - proportions of subjects achieving the target of HbA1c ≤6.5%
- Withdrawal due to ineffective therapy, defined as subjects withdrawing due to withdrawal criterion number 3 (fasting SMPG values taken on three consecutive days or any of the FPG samples exceeding the limits defined in Table 2).
- Change from baseline after 26 weeks in fasting plasma glucose
- Change from baseline after 26 weeks in SMPG – 9 point profile
    - Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time.
    - Postprandial plasma glucose increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals was derived as the mean of all available meal increments.
- Change from baseline after 26 weeks in body weight

- Change from baseline after 26 weeks in waist circumference
- Change from baseline after 26 weeks in blood pressure
- Diabetes-related assessments
    - insulin, C-peptide and glucagon
- Fasting lipid profile
- Change from baseline after 26 weeks in patient-reported outcomes based on TRIM-D and DTSQs

Sample size

The primary objective was to demonstrate superiority in the primary endpoint (change in HbA1c from baseline after 26 weeks of treatment) for IDegLira versus continued GLP-1 receptor agonist therapy.

The sample size was calculated using a two-sided t-test of 5%. Furthermore, the mean difference in the primary endpoint between IDegLira and continued GLP-1 receptor agonist therapy was assumed to be 0.4% with a standard deviation (SD) of 1.2%. From these assumptions the sample size was set to a total of 429 subjects, which is 286 in the IDegLira treatment group and 143 in the unchanged GLP-1 receptor agonist group, in order to obtain a power of 90% of meeting the primary objective.

Randomisation and blinding

Eligible subjects were randomised in a 2:1 manner to receive IDegLira or to continue their unchanged GLP-1 RA pre-trial medication. The randomisation was stratified according to prior type of GLP-1 RA, i.e., Victoza (liraglutide) or Byetta (exenatide). Both arms continued pre-trial doses of metformin ± pioglitazone ± SU.

An open-label design was chosen. It was not deemed feasible to include a placebo, as this would require a double dummy approach with two daily injections and would also restrict the GLP-1 RA studied in the trial to either liraglutide or exenatide (requiring a transfer of one of the pre-treatment GLP-1 RAs to the GLP-1 RA chosen to be administered masked in the control arm).

Statistical methods

Analysis sets

The following analysis sets were defined in accordance with ICH E9:5

- Full analysis set (FAS) – included all randomised subjects. In exceptional cases, subjects could be eliminated from the FAS. In such cases the elimination was justified and documented. The statistical evaluation of the FAS followed the intention-to-treat principle, and subjects contributed to the evaluation ‘as randomised’.
- Per Protocol (PP) Analysis Set – included all subjects in the FAS who fulfilled the following criteria:
    - had not violated any inclusion criteria
    - had not fulfilled any exclusion criteria
    - had a non-missing HbA1c measurement at screening and/or randomisation
    - had at least 12 actual treatment weeks of exposure
    - had at least one non-missing HbA1c measurement after 12 actual weeks of exposure

Subjects in the PP analysis set contributed to the evaluation “as treated”.

- Safety analysis set (SAS) – included all subjects receiving at least one dose of the trial product.

Subjects in the safety analysis set contributed to the evaluation ‘as treated’.

- Completer analysis set (CAS) – included all randomised subjects who completed the trial.

Subjects in the CAS contributed to the evaluation ‘as randomised’.

Descriptive statistics of all efficacy endpoints were based on the FAS. The robustness of the results for the primary endpoint was explored by sensitivity analyses including analysis on PP analysis set and CAS.

Missing data

Missing values (including intermittent missing values) were imputed using the last observation carried forward (LOCF) method. The sensitivity of the results of the primary analysis to this method was addressed by also applying mixed model for repeated measures (MMRM) for handling missing data.

Laboratory values below the lower limit of quantification were put to lower limit of quantification/2.

Statistical analyses

Change from baseline of continuous endpoints (for example HbA1c, FPG, 9-point SMPG, body weight and PRO endpoints) were analysed using an analysis of covariance model with treatment, pre-trial GLP-1 RA (Victoza or Byetta) and region as fixed factors and the relevant baseline value as covariate. Log-transformation was applied for a number of pre-specified endpoints. The analysis results were back-transformed and presented on the original scale.

The two responder endpoints (HbA1c <7.0% and ≤6.5%) were analysed using a logistic regression model with treatment, pre-trial GLP-1 RA (Victoza or Byetta) and region as fixed factors and baseline HbA1c value as covariate.

Number of treatment-emergent hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset. The model included treatment, pre-trial GLP-1 (Victoza and Byetta) and region as fixed factors.

Results

Participant flow

Subject disposition is shown in Table 3. A total of 704 subjects were screened, of which 266 subjects failed screening. The majority of screening failures (74.1%) was due to failure to meet inclusion criteria no. 4 (HbA1c 7.0–9.0% both inclusive).

A total of 10.3% of the subjects withdrew during the trial, but with a lower proportion of withdrawn subjects in the IDegLira group compared to the GLP-1 RA group. The proportion of subjects that completed the study was 94.5% in the IDegLira group and 80.1% in the GLP-1 RA group. The pattern of withdrawal was different between the two treatment groups; the primary reason for withdrawal in the IDegLira group was non-compliance with protocol (9 of 16 subjects), whereas in the GLP-1 RA group the primary reason was ineffective therapy (11 of 29 subjects). Three withdrawals were due to adverse events (1 subject in the IDegLira group and 2 subjects in the GLP-1 RA group).

Table 3 Subjects disposition – Trial 3851

	IDegLira N (%)	GLP-1 N (%)	Total N (%)
Screened			704
Screening Failures			266
Withdrawn before Randomisation			0
Randomised	292 (100.0)	146 (100.0)	438 (100.0)
Exposed	291 (99.7)	145 (99.3)	436 (99.5)
Withdrawn at/after Randomisation	16 (5.5)	29 (19.9)	45 (10.3)
Adverse Event	1 (0.3)	2 (1.4)	3 (0.7)
Non-Compliance With Protocol	9 (3.1)	3 (2.1)	12 (2.7)
Withdrawal Criteria	2 (0.7)	14 (9.6)	16 (3.7)
Other	4 (1.4)	10 (6.8)	14 (3.2)
Completed	276 (94.5)	117 (80.1)	393 (89.7)
Full analysis set	292 (100.0)	146 (100.0)	438 (100.0)
PP analysis set	279 (95.5)	135 (92.5)	414 (94.5)
Safety analysis set	291 (99.7)	145 (99.3)	436 (99.5)

N: Number of subjects, %: Percentage of subjects
1 screen failed subject (205005) from site 205 in Australia was by error allocated 2 ID numbers (205005 and 205006) resulting in 2 screen failures for 1 subject.

Recruitment

The trial was conducted at 81 sites in 5 countries as follows: Australia: 5 sites; France: 7 sites; Hungary: 4 sites; Slovakia 6 sites; United States: 59 sites.

The study was initiated on 29 August 2012 and completed on 11 March 2014.

Conduct of the study

There were 7 substantial amendments to the protocol, none of these are considered to have implications for the interpretation of the study data.

Protocol deviations

A total of 518 important PDs were reported for this trial. There was reported 1 PD at trial level, 1 PD at country level, 109 PDs at site level and 407 PDs at subject level. The majority of the PDs were related to the informed consent form (date field missing on all central ICFs in the US) and to assessments during the trial. None of the PDs had a major impact on the conduct of the trial, the safety of the subjects or the results of the analyses.

Baseline data

Demographics and diabetes characteristics

The two treatment groups were comparable with respect to baseline characteristics (Table 4). The mean age was 58.3 years, and the gender distribution was even.

Table 4 Demographic characteristics at baseline – Trial 3851

	IDegLira N (%)	GLP-1 N (%)	Total N (%)
Number of Subjects	292	146	438
Age (years)			
N	292	146	438
Mean (SD)	58.3 (9.9)	58.4 (8.8)	58.3 (9.5)
Median	59.8	58.8	59.6
Min ; Max	22.0 ; 77.9	37.8 ; 78.3	22.0 ; 78.3
Sex (%)			
N	292 (100.0)	146 (100.0)	438 (100.0)
Female	139 (47.6)	75 (51.4)	214 (48.9)
Male	153 (52.4)	71 (48.6)	224 (51.1)
Ethnicity (%)			
N	292 (100.0)	146 (100.0)	438 (100.0)
Hispanic or Latino	26 (8.9)	15 (10.3)	41 (9.4)
Not Hispanic or Latino	266 (91.1)	131 (89.7)	397 (90.6)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Race			
N	292 (100.0)	146 (100.0)	438 (100.0)
White	269 (92.1)	131 (89.7)	400 (91.3)
Black or African American	15 (5.1)	12 (8.2)	27 (6.2)
Asian	6 (2.1)	2 (1.4)	8 (1.8)
American Indian or Alaska Native	1 (0.3)	0 (0.0)	1 (0.2)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.3)	1 (0.7)	2 (0.5)
BMI (kg/m^2)			
N	292	146	438
Mean (SD)	32.9 (4.4)	33.0 (4.1)	32.9 (4.3)
Median	32.8	33.6	33.1
Min ; Max	21.6 ; 40.6	22.8 ; 40.7	21.6 ; 40.7

Baseline characteristics related to disease status were comparable for the two treatment groups (Table 5). Diabetic complications included nephropathy (7.5%), neuropathy (24.4%), macro-angiopathy (7.3%) and retinopathy (9.8%), with the proportion of subjects with nephropathy and macro-angiopathy being slightly higher in the IDegLira group compared to the GLP-1 RA group (nephropathy: 9.2% versus 4.1%; macro-angiopathy: 8.9% versus 4.1%). Overall, the occurrence of diabetes-related complications was as expected for the patient population.

Table 5 Key baseline characteristics – Trial 3851

	IDegLira	GLP-1	Total
Number of Subjects	292	146	438
HbA1c (%)			
N	292	146	438
Mean (SD)	7.8 (0.6)	7.7 (0.6)	7.8 (0.6)
Median	7.7	7.6	7.7
Min ; Max	6.7 ; 9.2	6.6 ; 9.7	6.6 ; 9.7
FPG (mmol/L)			
N	285	145	430
Mean (SD)	9.0 (2.1)	9.4 (2.3)	9.1 (2.2)
Median	8.7	8.8	8.8
Min ; Max	2.8 ; 15.9	4.8 ; 18.5	2.8 ; 18.5
Duration of Diabetes (years)			
N	292	146	438
Mean (SD)	10.36 (5.79)	10.39 (5.81)	10.37 (5.79)
Median	9.6	9.2	9.5
Min ; Max	0.02 ; 31.34	0.02 ; 31.89	0.02 ; 31.89
OAD at Screening; N (%)			
N	292	146	438
Metformin	217 (74.3)	108 (74.0)	325 (74.2)
Metformin + SU	61 (20.9)	32 (21.9)	93 (21.2)
Metformin + TZD	7 (2.4)	4 (2.7)	11 (2.5)
Metformin + SU + TZD	7 (2.4)	2 (1.4)	9 (2.1)

N: Number of subjects, SD: Standard deviation, FPG: Fasting plasma glucose, OAD: Oral anti-diabetic, SU: Sulphonylurea, TZD: Thiazolidinediones

Consistent with the subject inclusion criteria, all subjects were on metformin therapy at screening, with 21.2% of subjects receiving SU concomitantly, 2.5% of subjects receiving pioglitazone concomitantly and 2.1% of subjects receiving both SU and pioglitazone concomitantly. The distribution was similar for the two treatment groups. No clinically relevant differences in oral anti-diabetic treatment at screening were seen between the two treatment groups (Table 6).

Table 6 Daily oral anti-diabetic treatment doses (mg) at screening – Trial 3851

	IDegLira				GLP-1			
	N	%	Mean	SD	N	%	Mean	SD
Number of subjects	292				146			
Biguanide								
Metformin	292	100	1973.6	468.6	146	100	1944.5	476.3
Sulphonylurea								
Glibenclamide	5	1.7	13.4	4.2	2	1.4	8.0	2.8
Gliclazide	12	4.1	105.0	77.4	6	4.1	75.0	41.4
Glimepiride	37	12.7	6.2	9.4	21	14.4	5.2	2.2
Glipizide	14	4.8	17.1	4.7	5	3.4	12.0	4.5
Thiazolidinedione								
Pioglitazone	14	4.8	30.0	8.3	6	4.1	32.5	6.1

N: Number of subjects, %: Percentage of subjects, SD: Standard deviation

The subjects were stratified with respect to prior type of GLP-1 receptor agonist (79.5% liraglutide and 20.5% exenatide in each treatment group). Mean daily dose of liraglutide at screening was 1.7 mg in both treatment groups. Mean daily dose of exenatide at screening was close to 18.5 ìg in both treatment groups. The required minimum dose of liraglutide (1.2 mg/day) and exenatide (10 ìg/day) was met for all subjects;

however, 2 subjects had their dose of liraglutide and exenatide incorrectly reported in the database as 6 mg/day and 5 ìg/day, respectively.

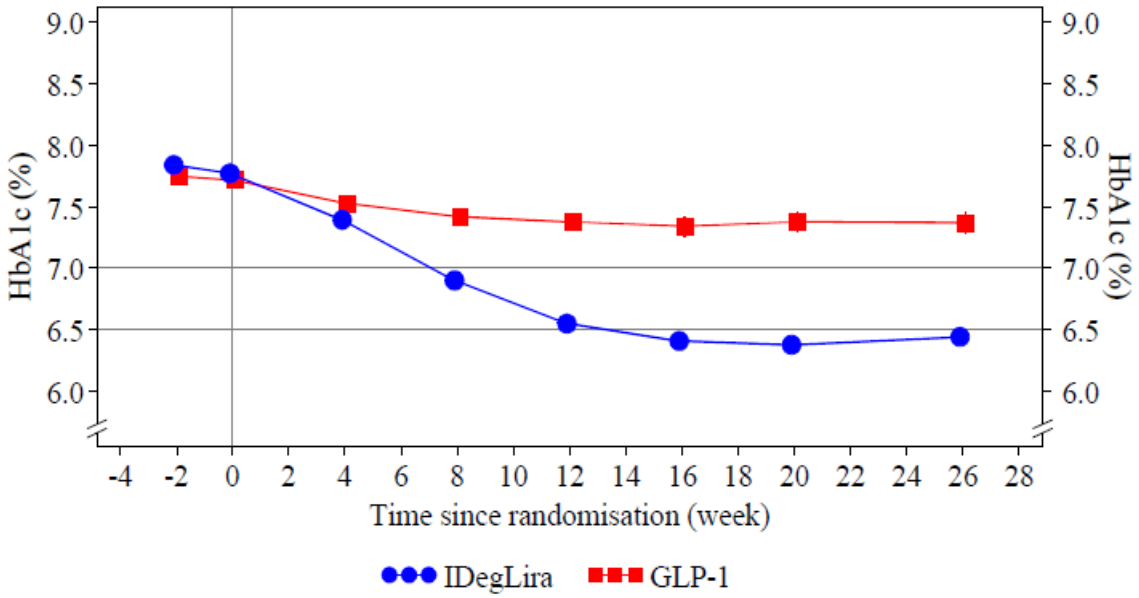
In general, the pattern of concomitant illnesses was representative for a population with T2DM. The most frequent disorders included 'hypertension' (79.5%) and 'hyperlipidaemia' (38.8%). There was a tendency towards a larger proportion of subjects in the IDegLira group reporting concomitant illnesses at screening compared to subjects in the GLP-1 RA group.

Outcomes and estimation

Change in HbA1c from baseline to 26 weeks of treatment (primary endpoint)

Mean HbA1c levels throughout the duration of the trial are depicted by treatment group in Figure 2. Mean HbA1c at baseline was 7.8% in the IDegLira group and 7.7% in the GLP-1 RA group. After 26 weeks of treatment, HbA1c had on average decreased by 1.3%-points to 6.4% in the IDegLira group and by 0.3%-points to 7.4% in the GLP-1 RA group. The reduction in HbA1c occurred primarily during the initial 3 months of treatment in both treatment groups.

Figure 2 HbA1c by treatment week – Trial 3851 – full analysis set



FAS; LOCF imputed data
Error bars: +- standard error (mean)
FAS: Full analysis set, LOCF: Last observation carried forward

The reduction in HbA1c was statistically significantly greater with IDegLira compared to GLP-1 RA (estimated treatment difference: -0.94 [-1.11; -0.78]95% CI; p<0.001), confirming superiority of IDegLira over unchanged GLP-1 RA therapy. The robustness of the primary analysis was confirmed by 3 sensitivity analyses, all of which showed high similarity to the primary analysis.

Secondary endpoints

Responders for HbA1c after 26 weeks of treatment

The proportion of subjects reaching the pre-defined HbA1c targets at the end of the 26-week treatment period was consistently greater with IDegLira than with GLP-1 RA. The ADA target of HbA1c <7.0% was reached by 75.3% of subjects receiving IDegLira versus 35.6% of subjects receiving GLP-1 RA. Similarly, the proportion of subjects reaching the IDF target of HbA1c ≤6.5% was 63.0% with IDegLira versus 22.6% with GLP-1 RA (Table 7).

Table 7 HbA1c target responders after 26 weeks of treatment – Trial 3851 – full analysis set

	IDegLira N (%)	GLP-1 N (%)	Total N (%)
Number of Subjects	292	146	438
HbA1c <7.0%			
Yes	220 (75.3)	52 (35.6)	272 (62.1)
No	72 (24.7)	94 (64.4)	166 (37.9)
HbA1c <=6.5%			
Yes	184 (63.0)	33 (22.6)	217 (49.5)
No	108 (37.0)	113 (77.4)	221 (50.5)

N: Number of subjects, %: Percentage of subjects

Logistic regression analysis showed that the estimated odds of achieving these HbA1c targets after 26 weeks of treatment were statistically significantly greater for subjects in the IDegLira group compared to the GLP-1 RA group. Estimated treatment difference of target responders to HbA1c <7.0% was 6.84 [4.28; 10.94]95% CI; p<0.001 and estimated treatment difference of target responders to HbA1c ≤6.5% was 7.53 [4.58; 12.38]95% CI; p<0.001.

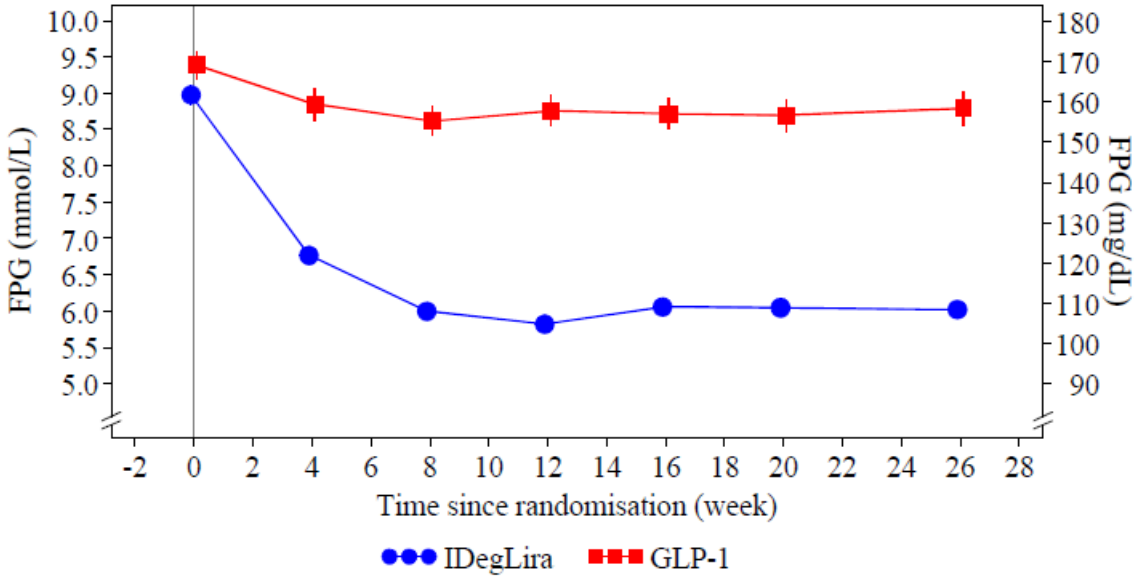
Withdrawal due to ineffective therapy

A total of 13 subjects were withdrawn due to ineffective therapy; 2 subjects in the IDegLira group and 11 subjects in the GLP-1 RA group. The odds ratio for withdrawal was statistically significantly lower for subjects treated with IDegLira compared to subjects treated with GLP-1 RA; odds ratio for IDegLira vs. GLP-1 RA was 0.08 [0.02; 0.38]95% CI; p=0.001.

Change from baseline after 26 weeks in fasting plasma glucose

Mean FPG levels throughout the duration of the trial are depicted by treatment group in Figure 3. Baseline FPG was 9.0 mmol/L (161.7 mg/dL) in the IDegLira group and 9.4 mmol/L (169.1 mg/dL) in the GLP-1 RA group. After 26 weeks of treatment, FPG had decreased by 3.0 mmol/L (53.6 mg/dL) to 6.0 mmol/L (108.5 mg/dL) in the IDegLira group and by 0.6 mmol/L (10.7 mg/dL) to 8.8 mmol/L (158.4 mg/dL) in the GLP-1 RA group. The greatest change in FPG occurred during the initial month of treatment in both treatment groups, and FPG had stabilised after approximately 8 weeks of treatment in both treatment groups (Figure 3).

Figure 3 Fasting plasma glucose by treatment week – Trial 3851 – full analysis set



FAS; LOCF imputed data
FPG: Fasting plasma glucose
Error bars: +- standard error (mean)
FAS: Full analysis set, LOCF: Last observation carried forward

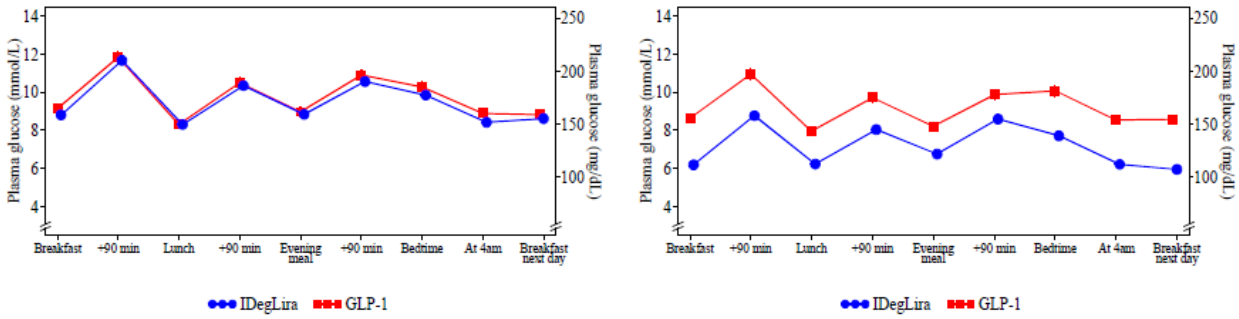
The reduction in FPG after 26 weeks of treatment was statistically significantly greater with IDegLira compared to GLP-1 RA (estimated treatment difference: -2.64 mmol/L [-3.03; -2.25]95% CI, p<0.001).

Change from baseline after 26 weeks in SMPG – 9 point profile

Mean 9-point plasma glucose profile

The 9-point SMPG profiles at baseline and after 26 weeks treatment are plotted in Figure 4. At baseline, the 9-point SMPG profiles appeared similar between treatments groups. After 26 weeks of treatment, plasma glucose concentrations had decreased for both treatments, however, the profile for the IDegLira group showed lower glucose concentrations compared to the GLP-1 RA group at all 9 time points.

Figure 4 9-point self-measured plasma glucose profile at baseline (left) and after 26 weeks of treatment (right) – Trial 3851 – full analysis set



FAS; LOCF imputed data
Error bars: +- standard error (mean)
FAS: Full analysis set, LOCF: Last observation carried forward

The estimated treatment difference in mean SMPG for IDegLira vs. GLP-1 RA was -1.78 mmol/L [-2.13;-1.43]95% CI, p <0.001. At all 9 time points, the SMPG values were lower in the IDegLira group compared to the GLP-1 RA group (p<0.001).

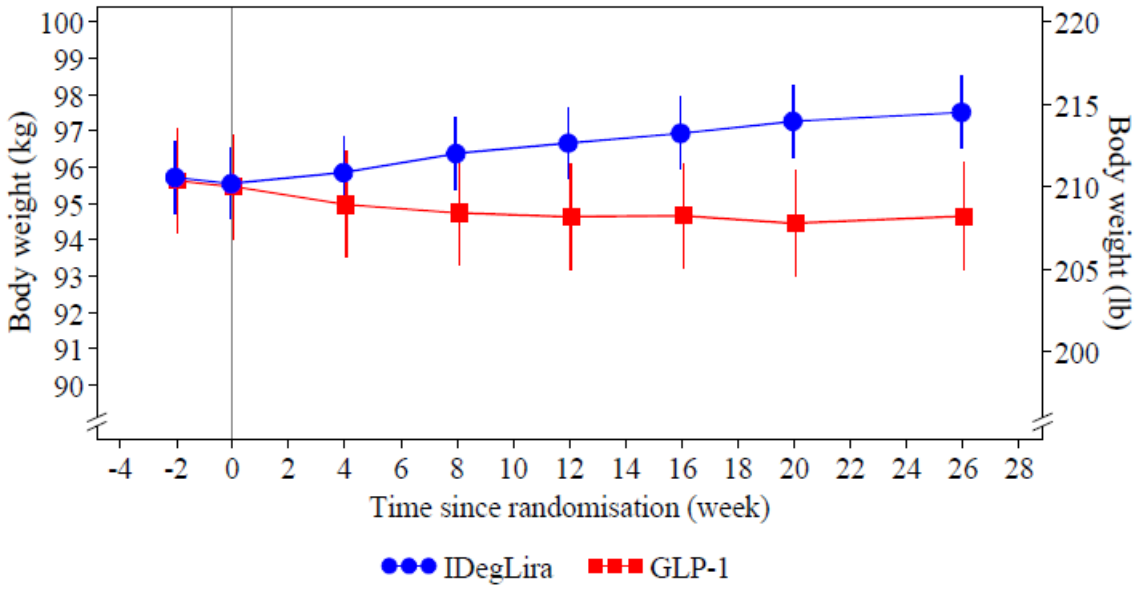
Prandial plasma glucose increments

The mean prandial increment across all meals was 2.1 mmol/L (37.0 mg/dL) in the IDegLira group and 1.9 mmol/L (34.3 mg/dL) in the GLP-1 RA group after 26 weeks of treatment. Consistent with the fact that both treatment groups received GLP-1 RA, there were no statistically significant differences in change from baseline in prandial increment between IDegLira and GLP-1 RA.

Change from baseline after 26 weeks in body weight and waist circumference

Mean body weight throughout the duration of the trial is depicted by treatment group in Figure 3–4. Mean body weight at baseline was 95.6 kg in the IDegLira group and 95.5 kg in the GLP-1 RA group. After 26 weeks of treatment, mean body weight had increased by 2.0 kg with IDegLira and decreased by 0.8 kg with GLP-1 RA.

Figure 5 Body weight by treatment week – Trial 3851 – full analysis set



FAS; LOCF imputed data
Error bars: +- standard error (mean)
FAS: Full analysis set, LOCF: Last observation carried forward

The estimated treatment difference between IDegLira and GLP-1 RA of 2.89 kg [2.17; 3.62]95% CI was statistically significant (p<0.001).

Waist circumference after 26 weeks of treatment was statistically higher in the IDegLira group compared to the GLP-1 RA group (estimated treatment difference: 2.14 cm [1.04; 3.25]95% CI, p<0.001).

Change from baseline after 26 weeks in blood pressure

Mean systolic and diastolic blood pressure at baseline were similar for the two treatment groups, and there was no statistically significant difference between treatment groups after 26 weeks of treatment.

Diabetes-related assessments

Fasting insulin and fasting C-peptide after 26 weeks of treatment were statistically significantly lower in the IDegLira group compared to the GLP-1 RA group, whereas no statistically significant difference was observed for fasting glucagon.

Fasting lipid profile

Total cholesterol and VLDL-cholesterol, triglycerides, free fatty acids and apolipoprotein B after 26 weeks of treatment were statistically significantly lower in the IDegLira group compared to the GLP-1 RA group. No

statistically significant differences were observed for HDL-cholesterol, LDL-cholesterol and apolipoprotein A-1.

Change from baseline after 26 weeks in patient-reported outcomes based on TRIM-D and DTSQs

Treatment related impact measure for diabetes

A higher score on the 1–5 point TRIM-D scale indicates a better health state (less negative impact). In both treatment groups, all sub-domain scores and total score increased throughout the trial, but the increase was more pronounced with IDegLira than with unchanged GLP-1 RA therapy.

After 26 weeks of treatment, the total score was statistically significantly higher for subjects in the IDegLira group compared to subjects in the GLP-1 RA group; estimated treatment difference was 5.0 units [2.9; 7.2]95% CI, p<0.001. Similarly, all sub-domains were statistically significantly higher for subjects in the IDegLira group compared to subjects in the GLP-1 RA group.

Diabetes treatment satisfaction questionnaire

After 26 weeks of treatment, the treatment satisfaction scale total was statistically significantly higher for subjects in the IDegLira group compared to subjects in the GLP-1 RA group; estimated treatment difference was 2.0 units [1.1; 2.8]95% CI, p<0.001. 'Hypoglycaemia' was scored statistically significantly higher by subjects in the IDegLira group compared to subjects in the GLP-1 RA group indicating that these events are perceived as occurring more frequently, whereas 'hyperglycaemia' was scored statistically significantly lower.

Comparison of results in sub-populations

The efficacy of IDegLira in sub-populations was assessed through statistical analysis by testing the null-hypothesis of equal treatment effect on HbA1c reduction after 26 weeks of treatment across the different sub-groups (age, diabetes duration, baseline HbA1c and oral anti-diabetic treatment) when comparing IDegLira vs. unchanged GLP-1 RA therapy. No statistically significant differences between estimated treatment effects across the sub-populations were observed.

Analysis of dose results

The starting dose of IDegLira was 16 dose steps (corresponding to 16 units insulin degludec and 0.6 mg liraglutide) followed by individual dose adjustments. This amount of liraglutide is similar to the recommended starting dose of 0.6 mg/day with Victoza. Transferring subjects from GLP-1 RA therapy to IDegLira was not associated with any deterioration in glycaemic control when using a starting dose of 16 dose steps and the pre-defined titration algorithm. This is illustrated in the plot of mean fasting plasma glucose levels in Figure 3.

Furthermore, an endpoint specifically assessed withdrawal due to ineffective therapy, defined as withdrawal due to withdrawal criteria no. 3 (continuous high SMPG values). Withdrawals due to ineffective therapy are summarised by treatment week in Table 8. Only 2 subjects in the IDegLira group were withdrawn due to ineffective therapy (with both of the withdrawals occurring during the last 4 weeks of the 26-week treatment period). In comparison, 11 subjects in the GLP-1 RA group were withdrawn due to ineffective therapy.

Table 8 Withdrawal due to ineffective therapy – summary – Trial 3851 – full analysis set

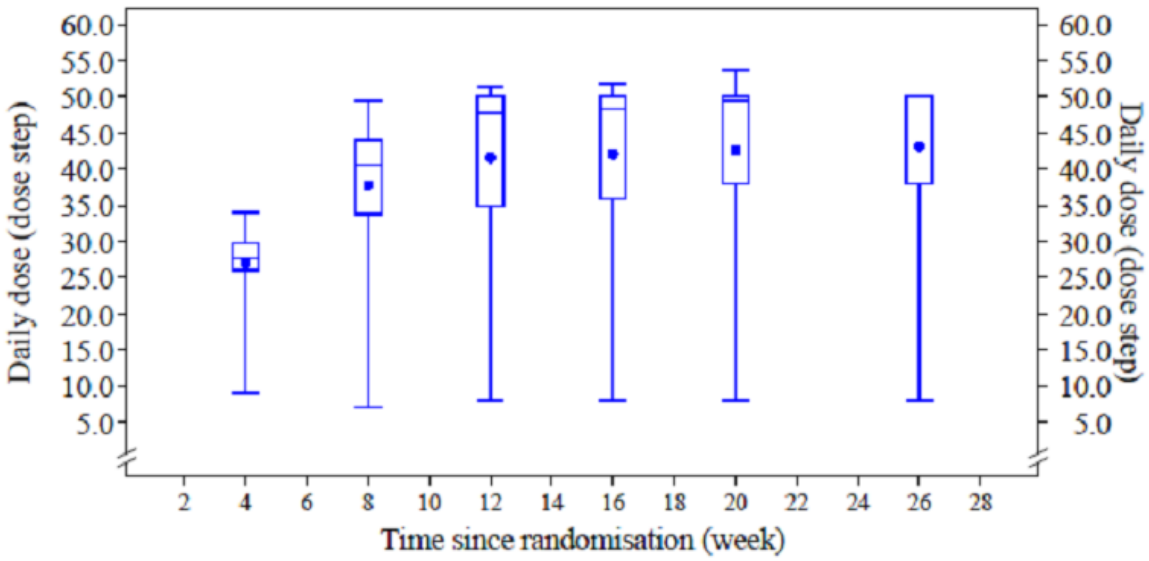
	IDegLira N (%)	GLP-1 N (%)	Total N (%)
Full analysis set	292	146	438
Withdrawal due to ineffective therapy			
Week 0-1			
Week 2-4			
Week 5-7			
Week 8-10			
Week 11-13		2 (1.37)	2 (0.46)
Week 14-16		2 (1.37)	2 (0.46)
Week 17-19		2 (1.37)	2 (0.46)
Week 20-22		2 (1.37)	2 (0.46)
Week 23-	2 (0.68)	3 (2.05)	5 (1.14)

N: Number of subjects, %: Percentage of subjects
x-y week: greater or equal to x weeks and less than or equal to y weeks plus 6 days.

The maximum dose of IDegLira was 50 dose steps. This corresponds to 50 units IDeg and 1.8 mg liraglutide, thereby not exceeding the maximum approved daily dose of liraglutide (Victoza).The actual daily IDegLira dose by week is presented in Figure 6, showing that after 10–12 weeks of treatment, the increase in mean daily IDegLira dose levelled off around approximately 43 dose steps. Approximately 50% of subjects reached a daily IDegLira dose of 50 dose steps (Figure 6). The maximum dose was exceeded in 8 subjects, no corresponding AEs were reported.

The mean HbA1c level was 6.5% in subjects who reached the maximum dose level of IDegLira. HbA1c after 26 weeks of treatment was, however, slightly lower for subjects receiving a daily IDegLira dose <50 dose steps versus those reaching 50 dose steps (6.3% vs. 6.5%), but the difference was relatively small and the statistical analyses confirmed highly significant changes in HbA1c after 26 weeks of treatment for both dosing groups compared to unchanged GLP-1 RA therapy. Corresponding results for HbA1c responders showed the same pattern, confirming that a substantial proportion of subjects who received the maximum dose level of IDegLira were within targets for overall glycaemic control.

Figure 6 Actual daily IDegLira dose by treatment week – box plot



LEGEND: Mean (dot), Median (centre line), 25 & 75 percentiles (box), Max & Min (top & bottom)
SAFETY; LOCF imputed data
SAFETY: Safety analysis set, LOCF: Last observation carried forward

2.4.2. Discussion on clinical efficacy

Trial 3851 was a 26-week, multi-centre, multinational, open-label, 2-arm parallel, randomised, treat-to-target trial in insulin-naïve subjects with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide]) and metformin ± pioglitazone ± SU. The overall design of the study, including the objectives and endpoints, is considered adequate.

The reasons for choosing an open-label design is understood and accepted although it should be kept in mind that the fact that this could introduce bias both with regards to the efficacy and safety assessment. Patients randomised to their usual treatment, known by the patient to be insufficient, may be less prone to intensify their background treatment whereas patients on the new treatment may be more motivated for lifestyle changes. The awareness for adverse events could also be affected by the open-label design.

The inclusion and exclusion criteria were adequate and reflect the proposed target population, although patients with a BMI>40 was not included. Patients with renal impairment (defined as serum-creatinine ≥133 µmol/L (1.5 mg/dL) for males and ≥125 µmol/L (1.4 mg/dL), or hepatic impairment (defined as alanine aminotransferase (ALAT) ≥ 2.5 times upper normal range) were also excluded. Exclusion of patients with significant concomitant illnesses was made either due to known safety concerns related to the investigational product or in order to minimise drop-out due to (unrelated) worsening of the concomitant disease. This is acceptable.

The choice of comparator is adequate considering the primary objective of the study which is to investigate the transfer from any GLP-1 RA to IDegLira. Liraglutide has been shown to exert a somewhat greater effect than exenatide (Buse et al, Lancet 2009), however, as patients were stratified with respect to pre-trial GLP-1 RA therapy this would not affect the overall interpretation of the data. No long-acting GLP-1 RAs were available at the time of the initiation of the study.

Withdrawal criteria, with regards to metabolic control, were specified which is of importance as patients in the control arm were to maintain their treatment in spite of inadequate metabolic control (HbA1c 7.0-9.0 %). Withdrawal rates were low, but higher in the GLP-1 treated group. Few patients in each group withdrew due to adverse events.

The study appears adequately conducted. One Slovakian site was inspected by the Slovakian authorities with no significant findings. The protocol deviations related to the informed consent forms were adequately handled.

The subject population included in the study was representative of subjects with T2DM who were not adequately controlled on GLP-1 RA therapy and thus qualifying for intensified therapy. The treatment groups were balanced with regards to demographic characteristics. Although mean diabetes duration did not differ between groups, it appears that the patients in the IDegLira groups had a somewhat more severe disease with more diabetes complications and concomitant illnesses reported at baseline than in the GLP-1 group.

The patients were stratified with respect to type of GLP-1 RA and the majority of patients were treated with liraglutide (79.5 %). The patients were adequately dosed with mean daily doses close to the maximal recommended dose for both liraglutide and exenatide and all patients were treated with at least liraglutide 1.2 mg/day or exenatide 10 µg/day at inclusion.

The study met its primary objective. The change in HbA1c was significantly greater in the IDegLira treated group compared to the group treated with GLP-1 RA (estimated treatment difference: -0.94 % [-1.11; -0.78]95% CI; p<0.001). It is noted that the HbA1c decreased on average by 0.3 % in the GLP-1 treated group in spite of the unchanged pharmacological treatment which is reassuring considering the open-label design of the study. It is also noted that the decrease in HbA1c was observed in the IDegLira treated group already after 4 weeks, thus it appears that the lower GLP-1 dose administered directly after the switch was

sufficiently compensated by the insulin component. Sensitivity analyses support the robustness of the results.

The secondary endpoints support the outcome of the primary endpoint. Significantly more patients reached both the 7.0% (75 % vs 36%) and the 6.5% (63% vs 23%) HbA1c target in the IDegLira treated group compared to the GLP-1 treated group. Withdrawals due to ineffective therapy was reported in 2 patients in the IDeg Lira group and in 11 patients in the GLP-1 treated group. This difference was statistically significant. All withdrawals occurred after week 11 in the study.

The FPG data support the primary endpoint. Switching from GLP-1 therapy to IDegLira did not change the overall pattern of the 9-point SMPG profile, thus prandial plasma glucose increments were not affected but the entire profile showed lower values after 26 weeks of treatment with IDegLira.

As expected, the reduction of HbA1c through the addition of insulin therapy resulted in a mean body weight increase by 2.0 kg, with a concomitant increase in waist circumference.

There were no differences observed with regards to blood pressure after 26 weeks of treatment. Fasting insulin and C-peptide decreased in the IDegLira treated group as could be expected when introducing insulin therapy. The changes in fasting lipid profile are in line with what is expected when metabolic glucose control is improved.

Statistically significant improvements in PROs were observed both with the TRIM-D and DTSQ in favour of IDegLira treatment, although the data did reflect the higher occurrence of hypoglycaemia in this group. Considering the open-label design of the study, these data should be interpreted with caution.

Subgroup analyses did not reveal any significant differences for the subgroups analysed. This is in line with previous data assessed with the original MAA.

The proposed posology when transferring from a GLP-1 RA is a starting dose of 16 Xultophy dose steps (16 units insulin degludec and 0.6 mg liraglutide). The data provided on FPG and HbA1c show that transfer from GLP-1 RA to IDegLira could be made at the recommended starting dose of 16 dose steps without any temporary loss in metabolic control. Thus the data support the proposed posology when switching from a short-acting GLP-1 RA. However, no data are available on subjects inadequately controlled on long-acting GLP-1 RAs, as no such medicinal products were available at the time of the initiation of the study. To address this issue, the applicant had provided during the procedure a conservative biomodelling analysis of a transfer from long-acting GLP-1 RA to IDegLira showing that patients are not expected to be subjected to a higher combined exposure and plasma concentration of the GLP-1 receptor agonist compared to the exposure prior to the transfer. In the SmPC section 4.2 wording has been added to consider the prolonged action of once weekly GLP-1 agonists when transferring patients from those products, which CHMP found to be adequate.

Although the mean IDegLira dose at the end of study was 43 dose steps, about 50 % of patients reached the maximal dose. On the other hand, the doses at the end of the study ranged between 8 and 50 dose steps, indicating that some patients had a significant response to the combination, taking into account that all patients included were treated with at least liraglutide 1.2 mg/day or exenatide 10 µg/day.

In patients receiving 50 dose steps of Xultophy at end study, around 27% did not reach the HbA1c target of <7%, and 42% did not reach the HbA1c target of ≤6.5%. This issue is not however unique to the proposed new indication, the most comparable study is trial 3912 in the MAA, where subjects uncontrolled on oral agents and basal insulin were switched to Xultophy - the mean daily IDegLira dose at 26 weeks was 45 dose steps, with 65% reaching 50 dose steps. Clearly, in practice patients needing more than 50 dose steps per day can be switched to liraglutide and insulin degludec separately, and the liraglutide and/or insulin dose titrated further, but the number of subjects reaching the maximum number of dose steps demonstrates that it is not a suitable option for all patients. In patients uncontrolled on oral agents plus a GLP-1 agonist, before

switching to Xultophy the prescriber should consider if the patient is likely to require more insulin in the short-term than Xultophy can provide. Principally, this would be in overweight patients with insulin resistance, and in patients with marked hyperglycaemia.

Xultophy provides a fixed dose ratio of liraglutide and insulin degludec, thus the doses of the separate components cannot be titrated separately. However, the submitted study shows a better proportion of patients reaching target in the IDegLira group, with only 1 case of severe hypoglycaemia in this arm.

2.4.3. Conclusions on the clinical efficacy

In conclusion, the data show that patients failing on GLP-1 RA treatment may achieve benefits by transfer to IDegLira. Although the open-label design of the study as well as the choice of comparator may have introduced some bias, the data were considered robust by CHMP.

2.5. Clinical safety

Methods

The safety evaluation of this variation is based on data from study Trial NN9068-3851. For this evaluation the safety analysis set was used except for supporting statistical analyses (pertinent for pulse and hypoglycemia), which are based on the full analysis set. The two analysis sets are defined below:

Safety analysis set (SAS): includes subjects receiving at least one dose of the investigational medicinal product or comparators. Subjects in the SAS will contribute to the evaluation 'as treated' (N=436).

Full analysis set (FAS): all randomized subjects in the trial. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised" (N=438).

Adverse events

All AEs described and discussed in this report are treatment-emergent, unless otherwise specified. A treatment-emergent AE (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day on randomised treatment.

Hypoglycaemic episodes were recorded on specific hypoglycaemic episode forms including additional information in order to be able to classify the episodes according to prespecified criteria (See further Section 0). In addition, episodes of severe hypoglycaemia during the trial were recorded as 'medical events of special interest' (MESI). Episodes of severe hypoglycaemia were reviewed by a blinded, external reviewer (endocrinologist).

Safety areas of interest were predefined based on the safety areas of interest known from the monocomponents. Events within these safety areas of interest were prespecified in the protocol as 'medical events of special interest' (MESI) as a tool to collect additional information to support the writing of comprehensive narratives for these events and a thorough evaluation of these safety areas. The evaluation included external adjudication of a subset of these events as specified in the table below (Table 9).

Furthermore, the following additional categories were considered safety areas of interest based on class effects for one or both of the monocomponents or due to special interest for all investigational products:

- Gastrointestinal adverse events
- Injection site reactions

- Hyperglycaemia
- Rare adverse events

Table 9 AEs classified as medical events of special interest

Type of event	Adjudication (Y/N)
Cardiovascular events	
1. Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Y
2. Cerebrovascular event (stroke or transient ischemic attack)	Y
3. Heart failure requiring hospital admission	Y
4. Revascularisation procedure	Y[a]
5. Cardiac arrhythmia	N
Pancreatitis or clinical suspicion of pancreatitis	Y
Elevated lipase and/or amylase >3xUNR	Y[b]
Neoplasms	Y
Thyroid disease	Y[c]
Any confirmed episode of calcitonin value ≥20 ng/L	N[d]
Altered renal function	N
Severe hypoglycaemic episodes	N
Lack of efficacy due to neutralising antibody formation (unscheduled measurement)	N
Allergic reactions	N
Immune complex disease	N
AEs leading to treatment discontinuation	N
Medication errors concerning trial products	N
Suspected transmission of an infectious agent *via* trial product	N

a) only coronary revascularisation procedures
b) only if suspicion of pancreatitis
c) only those requiring thyroidectomy and thyroid neoplasms
d) confirmed values of ≥20 ng/L were submitted to an independent calcitonin monitoring committee

Exposure to the drug

A total of 436 subjects were exposed to trial products (SAS); 291 subjects to IDegLira and 145 subjects to GLP-1 RA (liraglutide or exenatide), both added to metformin ± pioglitazone ± SU. The cumulative exposure in the IDegLira group and the GLP-1 RA group was 140.9 and 65.9 exposure years, respectively, consistent with the 2:1 randomisation ratio in the trial (Table 10). The majority of randomised subjects in both treatment groups (94.8% in the IDegLira group and 80.7% in the GLP- 1 RA group) were exposed for 25–28 weeks. The lower proportion of subjects with an exposure of 25−28 weeks in the GLP-1 RA group compared to the IDegLira group was caused by a higher withdrawal rate throughout the trial period in the GLP-1 RA group.

Table 10 Exposure - summery - safety analysis set

	IDegLira	GLP-1	Total
Number of Subjects	291	145	436
Total Exposure, yrs	140.9	65.9	206.8
Exposure (yrs)			
N	291	145	436
Mean (SD)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)
Median	0.5	0.5	0.5
Min ; Max	0.0 ; 0.6	0.0 ; 0.6	0.0 ; 0.6

N: Number of subjects, SD: Standard deviation
yrs: Years

Adverse events

Common adverse events

In Trial 3851, the percentage of subjects reporting AEs was 65.6% for IDegLira and 63.4% for GLP-1 RA. The rate per 100 PYE of AEs was 410.1 for IDegLira and 364.3 for GLP-1 RA (Table 11).

Table 11 Overview of adverse events – Trial 3851 - SAS

	IDegLira N	(%)	E	R	GLP-1 N	(%)	E	R
Number of Subjects	291				145			
Events	191	(65.6)	578	410.1	92	(63.4)	240	364.3
Serious								
Yes	9	(3.1)	12	8.5	3	(2.1)	3	4.6
No	190	(65.3)	566	401.6	91	(62.8)	237	359.7
Severity								
Severe	9	(3.1)	14	9.9	3	(2.1)	3	4.6
Moderate	68	(23.4)	114	80.9	24	(16.6)	29	44.0
Mild	162	(55.7)	450	319.3	82	(56.6)	208	315.7
Relationship to Investigational Product								
Probable	11	(3.8)	12	8.5	3	(2.1)	3	4.6
Possible	39	(13.4)	63	44.7	7	(4.8)	9	13.7
Unlikely	173	(59.5)	492	349.1	85	(58.6)	212	321.8
Missing	11	(3.8)	11	7.8	11	(7.6)	16	24.3
Unknown	0				0			
Related to Device								
Yes	0				0			
No	186	(63.9)	567	402.3	89	(61.4)	224	340.0
Missing	11	(3.8)	11	7.8	11	(7.6)	16	24.3
Outcome								
Recovered	174	(59.8)	470	333.5	77	(53.1)	194	294.4
Recovering	14	(4.8)	27	19.2	8	(5.5)	10	15.2
Recovered with Sequelae	1	(0.3)	1	0.7	1	(0.7)	1	1.5
Not Recovered	43	(14.8)	80	56.8	25	(17.2)	34	51.6
Fatal	0				0			
Unknown	0				1	(0.7)	1	1.5

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 exposure years
Relationship to trial product is based on investigator(s)'s assessment.

The most frequently reported AEs (≥ 5%) were 'nasopharyngitis', 'upper respiratory tract infection', 'lipase increased', 'headache' and 'diarrhoea' (Table 12). The rate of 'lipase increased' was higher in the IDegLira group compared to the GLP-1 RA group (22.0 vs. 12.1 events per 100 PYE, respectively) and the rate of 'nasopharyngitis' was lower in the IDegLira group compared to the GLP-1 RA group. For the remaining frequently reported events, no noticeable differences were observed between the two treatment groups (Table 12).

Table 12 Adverse events by system organ class and preferred term most frequent (>=5%) - treatment emergent - summery - Trial 3851 – SAS

	IDegLira N	(%)	E	R	GLP-1 N	(%)	E	R
Number of Subjects	291				145			
Events	88	(30.2)	129	91.5	39	(26.9)	60	91.1
Infections and infestations								
Nasopharyngitis	26	(8.9)	31	22.0	19	(13.1)	20	30.4
Upper respiratory tract infection	18	(6.2)	18	12.8	8	(5.5)	9	13.7
Investigations								
Lipase increased	29	(10.0)	31	22.0	7	(4.8)	8	12.1
Nervous system disorders								
Headache	27	(9.3)	31	22.0	9	(6.2)	14	21.2
Gastrointestinal disorders								
Diarrhoea	13	(4.5)	18	12.8	8	(5.5)	9	13.7

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 exposure years

Adverse events related to trial product

The majority of AEs were considered unlikely related to trial product by the investigator. The overall rate of AEs per 100 PYE considered possibly or probably related to trial product by the investigator was higher with IDegLira (44.7 and 8.5, respectively) than with GLP-1 RA (13.7 and 4.6, respectively) (Table 11).

At preferred term level, the most common AEs considered possibly or probably related to trial product were 'lipase increased', 'diarrhoea', 'nausea' and 'headache'. Of these, 'lipase increased', 'diarrhoea' and 'headache' occurred more frequently in the IDegLira group than in the GLP-1 RA group. 'Nausea" occurred more frequently in the GLP-1 RA group.

Adverse events by severity

The majority of the AEs in Trial 3851 were assessed as mild or moderate. Severe AEs were reported in 9 (3.1%) and 3 (2.1%) of the subjects in the IDegLira and GLP-1 RA groups, respectively. In total 17 severe reactions were reported within these subjects.

In the IDegLira group, the most common severe AE was 'headache' (4 events reported in 1 subject). The remaining severe AEs were single occurrences distributed across different SOCs. All severe AEs (n=17) except one (foot-fracture) had resolved or was resolving at end of study (Table 11).

Outcome of adverse events

There was no overall difference between the treatment groups with respect to outcome of AEs. At end of trial, approximately 86% of all AEs (703 of 818 AEs) had the outcome of 'recovered' (81.2%), 'recovering' (4.5%) or 'recovered with sequelae' (0.2%) (Table 11).

Serious adverse event and deaths

Serious adverse events

In total, there were 15 SAEs in Trial 3851; 12 in the IDegLira group (reported in 9 subjects) and 3 (reported in 3 subjects) in the GLP-1 RA group, corresponding to a rate of 8.5 and 4.6 events per 100 PYE. No clustering in type of SAEs was evident, and no SAEs were deemed possibly or probably related to trial product by the investigator. The overall number of the events was low, and therefore data should be interpreted with caution. Details of the individual SAEs are listed in Table 13 below.

The outcome of the 15 SAEs was reported as recovered for 12 SAEs, recovered with sequelae for one patient, not recovered for one and unknown for one patient (Table 13).

Table 13 Listing of SAEs - treatment emergent - Trial 3851 - SAS

Treatment	Subject ID	Age/sex	Preferred term	Study day	Severity	Causality	Outcome
IDegLira	108002	68/F	Atrial fibrillation	85	Moderate	Unlikely	Not recovered
IDegLira	108003	58/M/	Non-cardiac chest pain	18	Moderate	Unlikely	Recovered
IDegLira	130005	65/F	Peripheral artery thrombosis	73	Moderate	Unlikely	Recovered
			Thrombectomy	73	Moderate	Unlikely	Recovered
			Chronic obstructive pulmonary disease	165	Severe	Unlikely	Recovered
IDegLira	159003	57/F	Pituitary tumour	91	Moderate	Unlikely	Recovered with sequelae
			Adrenal insufficiency	107	Moderate	Unlikely	Recovered
IDegLira	168001	66/M	Cholecystitis acute	64	Severe	Unlikely	Recovered
IDegLira	205011	74/M	Lacunar infarction	124	Mild	Unlikely	Recovered
IDegLira	501003	49/M	Spinal pain	69	Moderate	Unlikely	Recovered
IDegLira	502001	65/F	Road traffic accident	7	Moderate	Unlikely	Recovered
IDegLira	604002	45/F	Transient ischaemic attack	78	Moderate	Unlikely	Recovered
GLP-1	121001	73/F	Foot fracture	7	Severe	Unlikely	Unknown
GLP-1	143005	65/M	Cholelithiasis	84	Moderate	Unlikely	Recovered
GLP-1	155006	74/M	Sciatica	133	Mild	Unlikely	Recovered

F = female; M = male; GLP-1 RA = glucagon-like peptide-1 receptor agonist

Deaths

There were no deaths reported in Trial 3851.

Adverse events of special interest

MAH considered that no clinically significant differences were observed between the IDegLira group and the GLP-1 RA group for the AEs of special interest including MESIs. MESIs are defined in Table 9 above.

Cardiovascular events

Cardiovascular events (including arrhythmias) were reported at a higher rate in the IDegLira group compared to the GLP-1 group (26 events in 14 subjects in the IDegLira group and 3 events in 3 subjects in the GLP-1 group corresponding to event rates of 18.4 and 4.6 events per 100 PYE for the IDegLira and the GLP-1 group, respectively). In the IDegLira group 2 subjects reported 9 and 4 CV events, respectively. This can partly explain the difference observed between treatment groups.

Two events ('lacunar infarction' and 'transient ischaemic attack; both in the IDegLira group) were confirmed as cardiovascular events by the external adjudication committee (EAC) and both events were identified as MACE.

Cardiac arrhythmia

Cardiac arrhythmia was to be reported as MESI in this trial. With the separate SMQ search made, 9 events potentially related to cardiac arrhythmia in 8 subjects were identified (2.1% in the IDegLira and 1.3% in the GLP 1 RA group); 7 events in the IDegLira group and 2 in the GLP-1 group. Except for 'atrial fibrillation', which was reported in 2 subjects (both in the IDegLira group), all events were single occurrences. All events were non-serious except for one event of 'atrial fibrillation' reported as SAE. Of the 9 potential cardiac arrhythmia events, 8 were considered unlikely related to trial product; the remaining 1 event ('sinus tachycardia') reported in the IDegLira group was considered possibly related to trial product. 5 of the events had resolved at the end of trial and 4 events had not resolved, all in the IDegLira group. No subjects with AEs potentially related to cardiac arrhythmia had an abnormal, clinically significant ECG during the trial.

Pancreatitis and thyroid events

No events of pancreatitis were reported and no thyroid-related AEs were sent for adjudication. Based on continuous calcitonin monitoring no safety issues were observed.

Neoplasms

3 events were confirmed as neoplasms by the EAC; 2 events in the IDegLira group and 1 event in the GLP-1 group. The rate of confirmed neoplasms was 1.4 and 1.5 events per 100 PYE in the IDegLira and GLP-1 groups, respectively. Of the 3 confirmed neoplasms, 1 ('lip squamous cell carcinoma') was classified as malignant (IDegLira group).

Allergic reactions

The rate of allergic reactions was higher in the GLP-1 group compared to the IDegLira group (10.6 and 6.4 and events per 100 PYE, respectively) (Table 14). All events were non-serious and considered unlikely related to the trial product except 'drug hypersensitivity' in the IDegLira group. This event was considered probably related to trial product and the subject was withdrawn from the trial.

Table 14 Allergic reaction (immunogenicity) by SOC and PT Treatment emergent - summery - SAS

	IDegLira				GLP-1			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	291				145			
Total Events	8	(2.7)	9	6.4	7	(4.8)	7	10.6
Skin and subcutaneous tissue disorders	3	(1.0)	3	2.1	5	(3.4)	5	7.6
Rash	1	(0.3)	1	0.7	2	(1.4)	2	3.0
Dermatitis	2	(0.7)	2	1.4				
Dermatitis allergic					1	(0.7)	1	1.5
Erythema nodosum					1	(0.7)	1	1.5
Urticaria					1	(0.7)	1	1.5
Respiratory, thoracic and mediastinal disorders	3	(1.0)	3	2.1	1	(0.7)	1	1.5
Rhinitis allergic	1	(0.3)	1	0.7	1	(0.7)	1	1.5
Allergic cough	1	(0.3)	1	0.7				
Bronchospasm	1	(0.3)	1	0.7				
Immune system disorders	2	(0.7)	3	2.1	1	(0.7)	1	1.5
Drug hypersensitivity	2	(0.7)	3	2.1				
Multiple allergies					1	(0.7)	1	1.5

Note: Only pre-selected preferred terms are included
N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years

The rate of AEs related to injection site reactions in the IDegLira group and the GLP-1 group was 7.1 and 1.5 events per 100 PYE, respectively. All injection site reactions were non-serious, mild in severity and had resolved by the end of the trial. The majority of the events were considered possible or probably related to trial product.

Gastrointestinal events

The proportion of subjects with GI AEs was similar between the two treatment groups (15.5% in the IDegLira group and 15.2% in the GLP-1 RA group). The corresponding rates were 44.7 (IDegLira) and 57.7 events per 100 PYE, respectively in the IDegLira group and the GLP-1 group. All events were non-serious, and the majority of the events were mild. The most frequent GI events are summarised in Table 15. The rate of diarrhoea was similar between treatment groups whereas the rates of “constipation” and “dyspepsia” were higher in the IDegLira group and “nausea” and “vomiting” were higher in the GLP-1RA group.

Table 15 Most frequent treatment-emergent GI event - SAS set

	IDegLira				GLP-1			
	N	(%)	E	R	N	(%)	E	R
Diarrhoea	13	(4.5)	18	12.8	8	(5.5)	9	13.7
Nausea	9	(3.1)	11	7.8	6	(4.1)	7	10.6
Vomiting	4	(1.4)	4	2.8	4	(2.8)	6	9.1
Constipation	7	(2.4)	7	5.0				
Dyspepsia	7	(2.4)	7	5.0				

N= Number of subjects
%= Percentage of subjects
E= Number of Events
R= Event Rate per 100 Exposure Years

Hypoglycaemic episodes

Methods

Episodes of hypoglycaemia were self-reported based on the subjects' self-monitored plasma glucose (SMPG) recordings, reflecting common clinical practice.

In addition, subjects had to measure plasma glucose upon suspicion of hypoglycaemia. All plasma glucose values ≤ 3.9 mmol/L (70 mg/dL), as well as values > 3.9 mmol/L (70 mg/dL) were recorded by the subjects in the diary, and the information was transferred to a separate form in the eCRF at the following site visit.

Definitions

Confirmed hypoglycemic episodes: a severe hypoglycaemic episodes (patient not able to self-treats; see below) **or** episodes of hypoglycaemia with plasma glucose < 3.1 mmol/L (56 mg/dL), regardless of symptoms.

Nocturnal hypoglyceamia: a hypoglycaemic episode with time of onset between 00:01 and 05:59 (both included).

Treatment-emergent hypoglycaemic episode: an episode with onset on or after the first day of exposure to randomised treatment and no later than 7 days after the last day on randomised treatment.

Hypoglycaemic episodes categorised according to the ADA criteria: definitions applying a plasma glucose cut-off level of 3.9 mmol/L (70 mg/dL).

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

Results

Confirmed hypoglycaemia

The proportion of subjects who experienced confirmed hypoglycaemic episodes in the IDegLira was 32% and in the GLP-1 group 2.8%. The corresponding rates were 281.7 and 12.1 episodes per 100 PYE, respectively. The estimated treatment ratio of IDegLira vs. GLP-1 was 25.36 [10.63; 60.51]95%CI, p<0.001, demonstrating a statistically significantly higher rate of confirmed hypoglycaemic episodes with IDegLira compared to GLP-1 (see Table 16 and Figure 7 below).

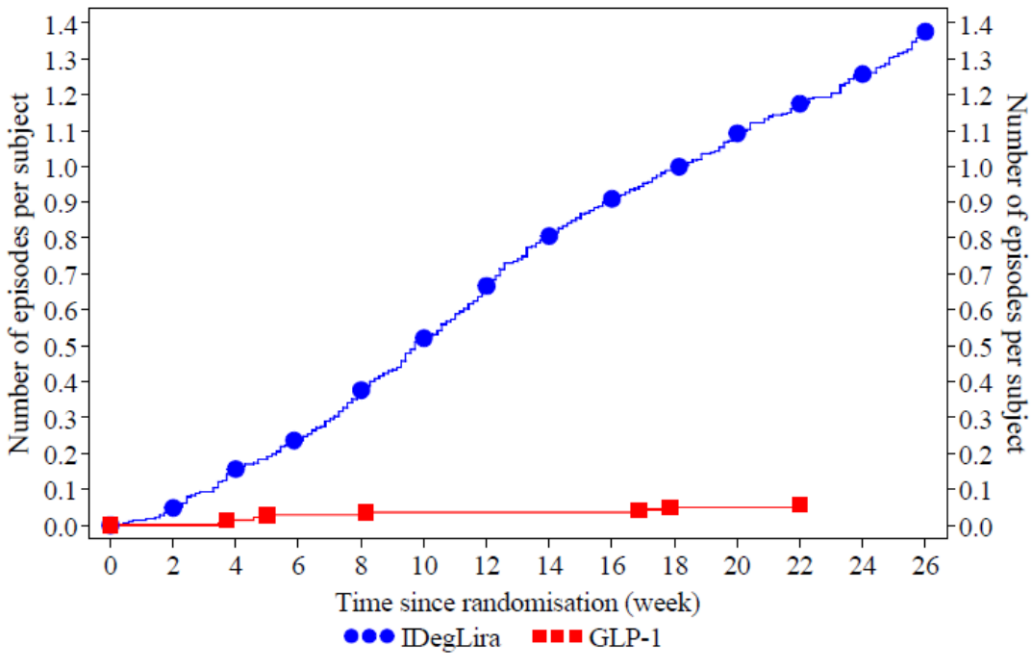
One episode of severe hypoglycaemia (non-serious) occurred during the trial. This occurred in a subject in the IDegLira group.

Table 16 Hypoglycaemic episodes by classification – treatment emeregent summary – safety analysis set.

	IDegLira				GLP-1			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	291				145			
Confirmed	93	(32.0)	397	281.7	4	(2.8)	8	12.1
Minor	92	(31.6)	396	281.0	4	(2.8)	8	12.1
ADA	201	(69.1)	2531	1795.8	23	(15.9)	71	107.8
Severe	1	(0.3)	1	0.7	0	(0.0)	0	0.0
Documented Sympt.	112	(38.5)	974	691.1	12	(8.3)	33	50.1
Asymptomatic	169	(58.1)	1484	1052.9	16	(11.0)	34	51.6
Probable Sympt.	15	(5.2)	18	12.8	0	(0.0)	0	0.0
Relative	24	(8.2)	54	38.3	3	(2.1)	4	6.1
ADA Unclassifiable	12	(4.1)	20	14.2	2	(1.4)	2	3.0

N: Number of Subjects
%: Percentage of Subjects with the Event
E: Number of Events
R: Event Rate per 100 Patient Year(s) of Exposure
ADA: American Diabetes Association
Confirmed hypoglycaemia: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL)
Minor: PG < 3.1 mmol/L (56mg/dL)

Figure 7 Confirmed hypoglycaemic episodes – treatment-emergent – mean cumulative function – safety analysis set



Hypoglycaemic episodes and SU use

Hypoglycaemic episodes were displayed according to SU treated subjects vs. non-SU treated subjects in the IDegLira and GLP-1 RA groups. The rate of confirmed hypoglycaemic episodes was higher in SU-treated subjects compared to non-SU treated subjects in both treatment groups. In the IDegLira group, the rate per

100 PYE of confirmed hypoglycaemic episodes was 634.4 in the SU treated subjects (n=68) compared to 174.8 in the non-SU treated subjects (n=223). In the GLP-1 group, the event rate per 100 PYE was 51.2 in SU treated subjects (n=34) and 0.0 in non-SU treated subjects (n=111) (Table 17).

Table 17 Confirmed hypoglycaemic episodes by OAD group – Trial 3851 – treatment emergent

	IDegLira					GLP-1				
	N	(%)	E	PYE	R	N	(%)	E	PYE	R
OAD group										
OAD = Met +- pio	62	(27.8)	189	1.082	174.8	0	(0.0)	0	0.503	0.0
OAD = Met +- pio + SU	31	(45.6)	208	0.328	634.4	4	(11.8)	8	0.156	51.2
All	93	(32.0)	397	1.409	281.7	4	(2.8)	8	0.659	12.1

N: Number of unique subjects with at least one event
%: Percentage of subjects within that group, with at least one event
E: Number of events, R: Event rate per 100 patient Year(s) of exposure
OAD: Oral antidiabetic drug, Met: Metformin, pio: Pioglitazone, SU: Sulfonylurea
Confirmed hypoglycaemia: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL)

Nocturnal confirmed hypoglycaemia

The proportion of subjects experiencing nocturnal confirmed hypoglycaemic episodes were higher for IDegLira (32 subject; 11%) than for GLP-1 RA (one subject; 0.7%). The estimated treatment ratio of IDegLira vs. GLP-1 RA was 32.82 [4.13; 261.04]95%CI; p < 0.001. None of the nocturnal hypoglycaemic episodes were classified as serious or severe.

Hypoglycaemic episodes (ADA classification)

For hypoglycaemic episodes as classified according to the ADA criteria (see definition above), the relative differences between treatment groups were similar to those observed for confirmed (69% and 16%, respectively) and nocturnal confirmed (37% and 3.4%, respectively) hypoglycaemia.

Discontinuation due to AES

Adverse events leading to withdrawal

A total of 3 subjects were withdrawn from Trial 3851 due to AEs: 1 subject (0.3%) in the IDegLira group with 'drug hypersensitivity' (a severe and non-serious event considered probably related to trial product) and 2 subjects in the GLP-1 RA group with 'abdominal discomfort' (a mild and non-serious event considered possibly related to trial product) and 'foot fracture' (a severe and serious event considered unlikely related to trial product), respectively. In addition, 1 subject in the IDegLira group was withdrawn due to other reasons. It was reported by the investigator that the subject skipped doses and then discontinued study drug due to hypoglycaemic episodes.

Adverse events leading to dose reduction in investigational product

In addition, three subjects had 3 AEs ('diarrhoea', 'vomiting' and 'skin induration') leading to dose reduction in the IDegLira group, whereas none was reported in the GLP-1 RA group. All three events were non-serious, and subjects recovered from the events.

Adverse events leading to temporary withdrawal of trial product

Six subjects had 9 AEs leading to temporary withdrawal of trial product in the IDegLira group ("nausea", "lacunar infarction", "migraine", "cholecystitis acute", "cholelithiasis", "wound infection", "pituitary tumour", "COPD" and "skin ulcer"), and 1 subject had 1 AE leading to temporary withdrawal of trial product in the GLP-1 group (vomiting). Four of the AEs were classified as serious. All AEs except one (nausea) were judged as unlikely related to study drug.

Clinically laboratory evaluation

Amylase

An increase in amylase activity was observed for IDegLira (mean change at Week 26 was 6.2 units/L), and a decrease was seen in the GLP-1 RA group (mean change at Week 26 was -1.0 units/L). Correspondingly, the proportion of subjects of the IDegLira group with amylase values above the reference range increased during the trial with the highest proportion at Week 12.

In the IDegLira group, the proportion of subjects that had a shift in amylase value within the reference range at screening to a value above reference range at end of trial was higher (7.6%) than the proportion of subjects (4.1%) that had a shift in the opposite direction (normalisation). In the GLP-1 RA group, the proportion of subjects that had abnormal amylase values did not appear to change significantly during the trial.

Lipase

A decrease in mean lipase activity during the trial was observed both in the IDegLira group (mean change at Week 26 was -1.0 units/L) and in the GLP-1 RA group (mean change at Week 26 was -1.8 units/L). The proportion of subjects that had abnormal lipase values did not appear to change significantly during the trial.

Lipase values >3xUNR, irrespective of symptoms from the gastrointestinal tract, were to be reported as a MESIs. A total of 15 subjects (13 in the IDegLira group and 2 in the GLP-1 RA group) had post-baseline lipase values >3xUNR and reported as MESIs. For the majority of these subjects, the increase was a single occurrence.

Of note, no subjects were withdrawn from the trial due to the withdrawal criterion related to suspicion of acute pancreatitis, and no subjects were withdrawn from the trial due to adverse events of increased lipase.

Calcitonin

Calcitonin was monitored as a biomarker of C-cell activity. A blood sample for calcitonin was drawn at screening, at randomization, and at Weeks 12 and 26. No clinically relevant differences were observed between the treatment groups in mean calcitonin levels during the trial.

Any confirmed episode of a calcitonin value ≥ 20 ng/L was to be reported as a MESI. In four subjects (1 in IDegLira and three in GLP-1 RA groups respectively) non-serious events of blood calcitonin increased was reported.

Other laboratory parameters (haematology, urinalysis and other biochemistry parameters)

The MAH concludes that no clinically relevant changes in haematology or urinalysis were observed from baseline to end of treatment in any of the two treatment groups

The proportion of subjects with abnormal biochemistry values did not either appears to change significantly during the trial or to differ between the treatment groups, except for sodium. However, the increased proportion of patients with a shift from normal to high levels of sodium in the IDegLira (from 7.6% to 14.1%) compared to no such change in the GLP-1RA (from 4.1%to 4.8%) was not considered as clinically significant.

Vital signs evaluation

Pulse

Pulse was measured at screening, at Weeks 12 and 26. At baseline there was no significant difference in pulse observed between the two groups. At Week 26 no increase in the pulse had occurred from baseline in any of the treatment groups (in IDegLira group the pulse was the same [77.2 beats/min] and in the GLP-1 group a reduction by 1.7 beats/min had occurred [75.5 beats/min]).

Other vital signs

According to the MAH "physical examination", ECG measurements and fundoscopy results did not demonstrated any clinically relevant changes between treatment groups.

There was no pregnancy reported during the study period.

Blood pressure is described in a previous section.

Safety in special populations

No clinically relevant differences or consistent patterns were observed for the overall distribution of adverse events or serious adverse events across age groups. However, it should be noted that subjects ≥75 years constituted a small sub-population of all trial subjects (n=9), and the results for this age subset should therefore be interpreted with caution.

In addition, patients with impaired renal or impaired liver function were excluded in Trial 3851. Therefore no safety data within these subgroups could be presented.

Post-marketing experience

No post-marketing data for IDegLira are available. Periodic safety update reports will be provided according to ICH and EMA requirements.

2.5.1. Discussion on clinical safety

In terms of safety, trial 3851 confirmed that IDegLira was generally well tolerated, with an adverse event profile reflecting previous experience from IDegLira clinical trials and the marketed mono-component products, IDeg and liraglutide. No clustering or unexpected patterns in the reported AEs and SAEs were observed, and IDegLira was not associated with any unexpected adverse reactions. The main safety finding is an expected difference in incidence and rate of confirmed hypoglycaemic episodes in the patients with a switch to IDegLira compared to those with a continued use of GLP-1RA. However, the presented frequencies and rates are in accordance with previous studies.

Besides "lipase increased" (higher among IDegLira subjects), there was no difference in frequency of the most common AEs of clinical interest between the two treatment groups. However, there was a larger difference in AEs pattern between the two groups when considering AEs judged as possibly or probably related to trial product. Of these, 'lipase increased', 'diarrhoea' and 'headache' occurred more frequently in the IDegLira group than in the GLP-1 RA group. 'Nausea" occurred more frequently in the GLP-1 RA group.

No consistent differences in the reporting of gastrointestinal side effects were observed between the IDegLira and GLP-1 groups in this trial. The frequency of GI events was lower compare to previous studies. This is expected since all patients in the present study already have been treated with GLP-1 RA before the study start.

In total, 4.8% in the IDegLira group and 3.9% in the GLP-1 RA group reported CV events including cardiac arrhythmic events. The difference observed between the two groups could possibly be explained by two

patients who experienced several reactions in the IDegLira group. The incidence of both CV events in general and cardiac arrhythmia specificity were low and in accordance with results in previous studies.

Allergic reactions were more frequent in the group that continued to be treated with a GLP1 agonist (4.8%) than in those randomized to IDegLira (2.7%). The frequency in both groups was also higher than previously reported in other studies (0.9% for IDegLira and 1.8% for liraglutide group in pooled data from study 3697 and 3912) . The discrepancy in the reporting rate for potential allergic/hypersensitivity reactions was linked to an expansion of the search criteria in trial 3851 compared to previous trials. Also, during the procedure, brief case reports for all the 15 events have been provided and all but one case were considered as unlikely related, thus alleviating any new safety concern.

An increase of frequency and rate of hypoglycaemic episodes is expected when initiating insulin with the aim to achieve a better metabolic control and lower HbA1c. In accordance with the efficacy results, with lower HbA1c in the IDegLira group, the present study demonstrated a higher proportion of subject in the IDegLira group that experienced confirmed hypoglycaemic episodes compared to the subjects in the GLP-1 RA group (32% versus 2.8%). The corresponding rates of confirmed hypoglycaemic episodes were also higher. Severe hypoglycaemic episodes were rare and occurred only once in one patient (IDegLira group). No serious or sever nocturnal hypoglycaemic episodes occurred in any or the two treatment groups.

Concomitant treatment of SU is known to increase the risk of hypoglycaemic episodes. In the IDegLira group the incidence and rate of hypoglycaemic episodes were, as expected, higher in the SU treated group. The frequency and rate of hypoglycaemic episodes of both non-SU and SU treated subject respectively on IDegLira are in accordance with findings in previous studies

In the present study there was a decrease in mean lipase activity during the trial observed both in the IDegLira group and in the GLP-1 RA group. Mean amylase was increased in the IDegLira group and decreased in the GLP-1 RA group. In previous studies both mean lipase and amylase have been increased in subjects that are treatment naïve to GLP-1 RA when initiating IDegLira. Since the increase of these biochemistry parameters are suggested to be driven by the use of GLP-1 RA it is logical that there has been an adaptation to this substance before study start, with further decrease during the study. The increase of lipase in 10% of the patients in the IDegLira group might reflect that the GLP-1 RA dose initially was lowered and later in the study increased.

Other safety findings in this study were in accordance with findings in previous studies and relevant issues and reactions sufficiently covered in the SmPC and RMP.

2.5.2. Conclusions on clinical safety

In summary, the safety profile of IDegLira as add-on to GLP-1 RA treated, insulin naïve patients on OAD is in line with findings from previous studies.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The PRAC considered that the risk management plan dated 24 November 2014 (Edition 2.0, version 1.0) is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

No updates to the summary of safety concerns have been proposed by the MAH.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been updated to include information on the transfer from GLP-1 RA to Xultophy. In addition, editorial changes have been made in sections 4.4, 4.6 and 5.1. The Package Leaflet has been updated accordingly.

Changes in Sections 4.1 and 4.2 of the SmPC:

Section 4.1

"Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or combined with basal insulin do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations)."

Section 4.2

"Transfer from GLP-1 receptor agonist

Therapy with GLP-1 receptor agonists should be discontinued prior to initiation of Xultophy. When transferring from a GLP-1 receptor agonist, the recommended starting dose of Xultophy is 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) (see section 5.1). The recommended starting dose should not be exceeded. If transferring from a long-acting GLP-1 receptor agonist (e.g. once weekly dosing), the prolonged action should be considered. Treatment with Xultophy should be initiated at the moment the next dose of the long-acting GLP-1 receptor agonist would have been taken. Close glucose monitoring is recommended during the transfer and in the following weeks."

Changes in the other Sections of the SmPC see Annex 1.

3. Benefit-Risk Balance

Xultophy (IDegLira) is a combination of insulin degludec (basal insulin) and liraglutide (GLP-1 agonist). It is currently approved for the treatment of adults with T2DM to improve glycaemic control in combination with oral glucose-lowering medicinal products, when these alone or combined with basal insulin do not provide adequate glycaemic control. The combination device means that only 1 daily injection is required rather than 2, and dose titration is simpler.

The aim of the current procedure is to extend the indication for Xultophy to include the transfer of patients inadequately controlled on GLP-1 receptor agonists to Xultophy. The use of GLP-1 agonists in patients not controlled on metformin (+/- other oral agents) in T2DM is not a new concept: it is reflected in SmPCs for multiple other products, and is accepted in the current practice guidance. Likewise, the addition of insulin in patients uncontrolled on GLP-1 agonists and ODAs is generally established. The proposed indication is agreed to be rational from a pharmacological point of view and fits into the current paradigm for the treatment of T2DM.

The application is supported by a single pivotal trial. Trial 3851 was a 26-week, multi-centre, multinational, open-label, 2-arm parallel, randomised, treat-to-target trial in insulin-naïve subjects with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide]) and metformin ± pioglitazone ± SU. The primary objective of Trial 3851 was to confirm superiority of IDegLira versus unchanged GLP-1 RA therapy. The study was well designed, conducted and analysed.

Benefits

Beneficial effects

The subject population included in the study was representative of subjects with T2DM who were not adequately controlled on GLP-1 RA therapy and thus qualifying for intensified therapy. The study met its primary objective. The change in HbA1c was significantly greater in the IDegLira treated group compared to the group treated with GLP-1 RA with an estimated treatment difference of -0.94 %([-1.11; -0.78]95 % CI; p<0.001). The HbA1c decreased on average with 0.3 % in the GLP-1 treated group in spite of the unchanged pharmacological treatment which is reassuring considering the open-label design of the study. It is noted that the decrease in HbA1c was observed in the IDegLira treated group already after 4 weeks, thus there was no indication of an initial loss of glycaemic control during the switch.

The secondary endpoints support the outcome of the primary endpoint. Significantly more patients reached both the 7.0 % (75% vs 36%) and the 6.5 % (63% vs 23%) HbA1c target in the IDegLira treated group than in the GLP-1 treated group. Withdrawals due to ineffective therapy was reported in 2 patients in the IDeg Lira group and in 11 patients in the GLP-1 treated group. This difference was statistically significant. As expected, body weight increased with the addition of insulin therapy with a concomitant increase in waist circumference.

Uncertainty in the knowledge about the beneficial effects

CHMP acknowledged the reasons for choosing an open-label design, although it should be kept in mind that this could introduce bias both with regards to the efficacy and safety assessment, as patients aware of being randomised to a new treatment might behave and might be motivated differently as otherwise e.g. with regard to life style choices.

The device does not provide adequate dosing for all patients. In the submitted pivotal trial around 50% of the subjects in the IDegLira group received the maximum dose 50 dose steps (50 units of insulin degludec/1.8 mg liraglutide). Whilst most patients at the top dose were effectively controlled, in patients receiving 50 dose steps of Xultophy at end study, around 27% did not reach the HbA1c target of <7%, and 42% did not reach the HbA1c target of ≤6.5%. This demonstrates that (as with the existing indications) Xultophy is not a suitable option for all patients, and as always in T2DM, management must be individualised.

The data support the proposed posology when switching from a short-acting GLP-1 RA. However, no data were available on subjects inadequately controlled on long-acting GLP-1 RAs, as no such medicinal products were available at the time of the initiation of the study. The MAH has provided modelled data supporting the switch from long-acting GLP-1 RAs based on the knowledge of the PK of these products. In the SmPC section 4.2 wording has been added to consider the prolonged action of long-acting GLP-1 agonists when transferring patients from those products.

Risks

Unfavourable effects

In terms of safety, trial 3851 confirmed that IDegLira was generally well tolerated, with an adverse event profile reflecting previous experience from IDegLira clinical trials and the marketed mono-component products, IDeg and liraglutide. No clustering or unexpected patterns in the reported AEs and SAEs were observed, and IDegLira was not associated with any unexpected adverse reactions.

The main safety finding is an expected difference in incidence and rate of confirmed hypoglycaemic episodes in the patients with a switch to IDegLira compared to those with a continued use of GLP-1RA. The proportion that experienced hypoglycaemic episode was 32% in the IDegLira group compared to 2.8% in those on continued use of GLP-1 RA. In both groups a higher rate of hypoglycaemia was observed in subjects on

concomitant sulphonylurea (SU) treatment. The presented frequencies and rates are in line with the observations in previous studies.

No consistent differences in the reporting of gastrointestinal (GI) side effects were observed between the IDegLira and GLP-1 groups in this trial (approximately 15% in both groups). In general the frequencies of GI events were lower compared to observations in previous studies. This is expected since all patients in the present study already have been on GLP-1 RA before the study start.

The incidence of allergic reactions was 2.7% and 4.8%in the IDegLira and GLP-1 RA group respectively. The frequency in both groups was higher than previously reported in other studies due to a change in search criteria between studies, thereby capturing more events in study 3851. The majority of events were unrelated to study treatment and no new safety concerns did arise from these data.

Uncertainty in the knowledge about the unfavourable effects

No new safety concerns did arise from the data presented.

Benefit-Risk Balance

In conclusion, the data show that patients failing on GLP-1 RA treatment may achieve benefits by transfer to IDegLira. Although the open-label design of the study as well as the choice of comparator may have introduced some bias, the data were considered robust by CHMP.

The safety profile of IDegLira as add-on to GLP-1 RA treated, insulin naïve patients on OAD is in line with findings from previous studies . All relevant safety issues are sufficiently covered in the SmPC and RMP.

Overall, the benefit-risk balance is considered positive in the proposed new indication. The newly submitted data do not adversely affect the benefit-risk balance of Xultophy, which remains positive.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the transfer of patients from Glucagon-Like peptide-1 (GLP1) receptor agonist (RA) treatment to Xultophy. Consequently, sections 4.1, 4.2, 4.4, and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include the assigned ATC-code in section 5.1 of the SmPC and to make minor editorial changes in the SmPC. The application included a revised RMP (edition 2.0, version 1.0).

The requested variation proposed amendments to the SmPC and Package Leaflet.