20 March 2014
EMA/CHMP/805141/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tresiba

International non-proprietary name: insulin degludec

Procedure No. EMEA/H/C/002498/II/0006

Note

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

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1. Background information on the procedure

1.1. Requested 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 8 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**Tresiba:**	**Presentations:**
Tresiba	insulin degludec	See Annex A

The following variation was requested:

Variation(s) requested		**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

The MAH proposed the update of sections 4.2 and 5.1 of the SmPC in order to include guidance for prescribers on the use of Tresiba in combination with GLP-1 receptor agonists. The Package Leaflet was proposed to be updated accordingly.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9 and to include some editorial changes.

This variation application contains an updated RMP.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Rapporteur: Kristina Dunder

1.2. Steps taken for the assessment

Submission date:	8 August 2013
Start of procedure:	25 October 2013
Rapporteur's preliminary assessment report circulated on:	16 December 2013
PRAC Rapporteur assessment report circulated on:	19 December 2013
Rapporteur's updated assessment report on the RMP circulated on:	17 January 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 January 2014
MAH's responses submitted to the CHMP on:	13 February 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 February 2014
CHMP opinion:	20 March 2014

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/44/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/44/2010 was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

This variation application evaluates the efficacy and safety of Tresiba (insulin degludec [IDeg,]) in combination with GLP-1 receptor agonists in subjects with T2DM, inadequately controlled on either OADs ± basal insulin or OADs ± GLP-1 receptor agonists.

The Marketing Authorisation Holder (MAH) also proposed to update the Risk Management Plan (RMP) to remove co-administration of IDeg and GLP-1 receptor agonist as missing information and proposed to update the product information accordingly.

Tresiba (IDeg) is basal insulin developed to cover basal insulin requirements in patients with diabetes mellitus from early to late stages of the disease. On 21 January 2013, the European Commission approved Tresiba 100 units (U)/mL and 200 U/mL for treatment of adult patients with diabetes mellitus (T1DM or T2DM) by once-daily (OD) subcutaneous (s.c.) administration. IDeg has a duration of action beyond 42 hours and is characterised by a flat pharmacodynamic action profile. In patients with T2DM, IDeg can be administered alone, or in combination with prandial insulin and/or OADs according to the approved label. Until now, information on the use of IDeg in combination with GLP-1 receptor agonists has been missing.

Victoza (liraglutide) is a GLP-1 receptor agonist, approved in 2009 for treatment of adults with T2DM by OD s.c. administration at doses up to 1.8 mg/day. Like other GLP-1 receptor agonists, liraglutide stimulates insulin secretion in a glucose-dependent manner and inhibits glucagon secretion when plasma glucose (PG) levels are above normal. Liraglutide also reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake. Treatment with liraglutide has been shown to be at least as effective as other marketed GLP-1 receptor agonists.

IDegLira is a new fixed dose combination (FDC) product containing IDeg and liraglutide in a fixed ratio of 100 U/3.6 mg per mL administered in increments of 1 dose step containing 1 unit of insulin degludec and 0.036 mg of liraglutide. IDegLira combines the properties of IDeg and liraglutide and is intended for improvement of glycaemic control in adults with T2DM via OD s.c. injection. The marketing authorisation application (MAA) for IDegLira is currently under assessment. Data from the clinical development programme for IDegLira are used as supportive data in this variation application.

No specific scientific advice has been provided for this submission.

Data is submitted in order to support a labelling update for the use of Tresiba in combination with GLP-1 receptor agonists, as well as a parallel labelling update for the use of Victoza in combination with basal insulin (EMEA/H/C/1026/II/23). This data consists in a pharmacokinetic (PK) interaction study, between degludec and liragutide and 4 phase 3 randomised controlled clinical trials.

2.2. Clinical Pharmacology aspects

2.2.1. Methods – analysis of data submitted

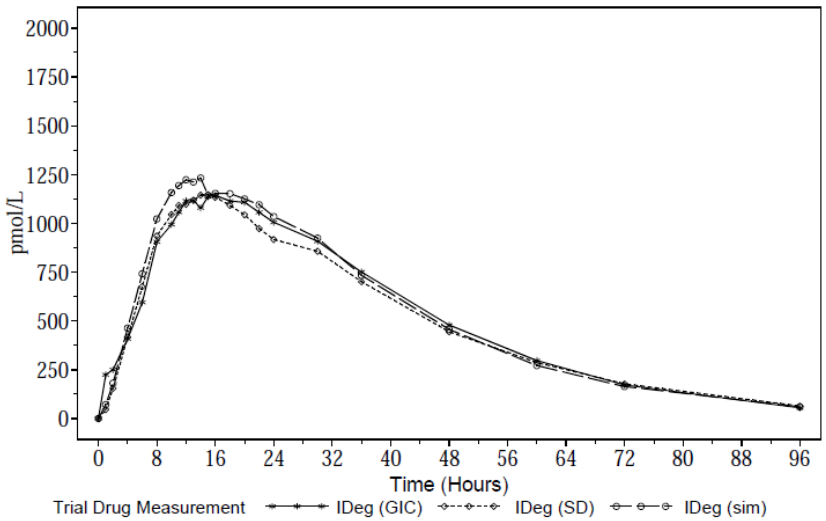
A pharmacokinetic phase 1 interaction study, between degludec (IDeg) and liragutide (Lira), has been performed (NN9068-3632). The study was included in the MAA of IDegLira. It was a 4-way randomized single-dose cross-over trial in healthy men, comparing the PK of both IDeg and Lira following administration of IDeg and Lira separately, simultaneous administration of IDeg and Lira as well as administration of IDegLira. The dose tested was 17 U and 0.6 mg for IDeg and Lira, respectively. All doses were administered s.c. in the thigh. A 24 hour euglycaemic clamp was applied, and blood sampling for PK assessment was performed for 72h for Lira and 96H for IDeg.

The study included 24 healthy male volunteers aged 22-55 years, who all completed the trial and were included in the PK analysis.

2.2.2. Results

Figure 1 shows the plasma concentration-time profiles of IDeg following s.c. administration of just IDeg, of simultaneous administration of IDeg and Lira and administration of IDegLira.

Figure 1 Mean plasma concentration of IDeg versus time following s.c. administration of 17 U as just IDeg, as simultaneous administration of IDeg and Lira (17U+0.6 mg) and as IDegLira (17U/0.6 mg)



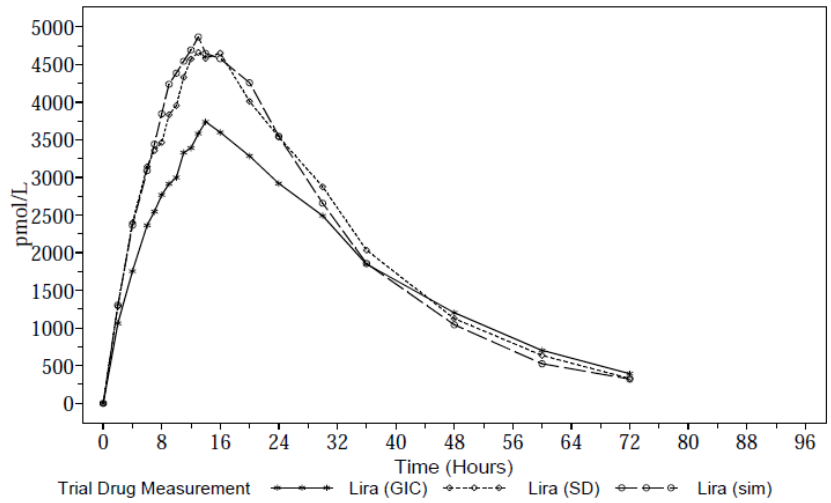
IDeg (GIC): insulin degludec/liraglutide, IDeg (SD): insulin degludec plus placebo, IDeg (sim): insulin degludec plus liraglutide

The relative bioavailability for IDeg following simultaneous administration of IDeg+Lira compared to administration of just IDeg was 1.05 (90% CI 1.01-1.09) with respect to AUC and 1.08 (90% CI 0.95-1.22) for C_{max}.

Figure 2 shows the plasma concentration-time profiles of Lira following s.c. administration of just Lira, of simultaneous administration of IDeg and Lira and administration of IDegLira

The relative bioavailability for Lira following simultaneous administration of IDeg+Lira compared to administration of just Lira was 0.99 (90% CI 0.92-1.07) with respect to AUC and 1.03 (90% CI 0.91-1.16) (Figure 2).

Figure 2 Mean plasma concentration of Lira versus time following s.c. administration of 0.6 mg as just Lira, as simultaneous administration of IDeg and Lira (17U+0.6 mg) and as IDegLira (17U/0.6 mg)



Lira (GIC): insulin degludec/liraglutide, Lira (SD): liraglutide plus placebo, Lira (sim): liraglutide plus insulin degludec

2.2.3. Discussion

The study was included in the MAA of IDegLira and has been assessed in the evaluation of IDeg/Lira. It was designed as a 4-way, randomized, single-dose, cross-over study. The design and conduct of the study are considered adequate.

The focus of the current Type II variation is generated in three of the study arms, by running a comparison of the exposure following simultaneous injection of the two components with the exposure following injection of each of the components administered separately.

No differences were seen in the systemic exposure of IDeg or of Lira if administered as simultaneous injections of the two components compared to standalone s.c. injections of the drugs. The 90% confidence intervals (CIs) for the ratios, simultaneous injection/standalone injection, of total exposure as well as of maximum plasma concentrations, for both IDeg and Lira, were within the intervals defined for bioequivalence 0.80-1.25.

2.3. Clinical Efficacy aspects

2.3.1. Introduction

Data from 4 phase 3 randomised controlled clinical trials, conducted according to Good Clinical Practice, are included with this variation application (

Table **1**). Trial 3948 (pivotal trial) is from the IDeg phase 3b programme, Trials 3697 and 3912 are from the IDegLira phase 3a programme, and Trial 1842 is from the liraglutide phase 3b programme.

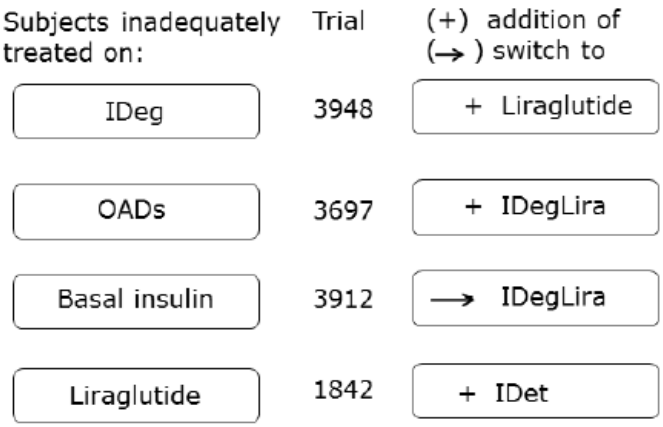
Table 1 Overview of relevant clinical trials

Trial ID	Treatment	Trial duration	Anti-diabetes treatment at screening	No. of subjects randomised	Random isation ratio
NN1250-3948 (key data)	IDeg+Lira+met vs. IDeg+IAsp+met	26 wks	IDeg+met	IDeg+Lira: 88 IDeg+IAsp: 89	1:1
NN9068-3697 (supportive data)	IDegLira+met±pio vs. IDeg+met±pio or Lira+met±pio	26 wks +26 wks extension	met ± pio (insulin-naïve)	IDegLira: 834 IDeg: 414 Lira: 415	2:1:1
NN9068-3912 (supportive data)	IDegLira+met vs. IDeg+met	26 wks	Basal insulin (IDet or IGlar) + met ± SU/ + met ± glinides	IDegLira: 207 IDeg: 206	1:1
NN2211-1842 (supportive data)	IDet+Lira+met vs. Lira+met	12 wks run-in, 26 wks +26 wks extension	met ± SU (insulin-naïve)	IDet+Lira: 162 Lira: 161	1:1

IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; IDegLira: insulin degludec/liraglutide combination product; IGlar: insulin glargine; Lira: liraglutide; met: metformin; pio; pioglitazone; SU: sulphonylurea; wks: weeks

Figure 3 illustrates how the individual trials contribute to the concept of combined use of basal insulin and liraglutide.

Figure 3 Overview of treatment combinations across trials



All 4 trials were conducted in subjects with T2DM using a treat-to-target regimen for adjustment of basal insulin with the primary objective to evaluate the effect on glycaemic control of combined treatment with basal insulin (IDeg or IDet) and liraglutide based on the change in HbA1c from baseline to 26 weeks of treatment.

2.3.2. Methods – analysis of data submitted

Pivotal study, Trial 3948

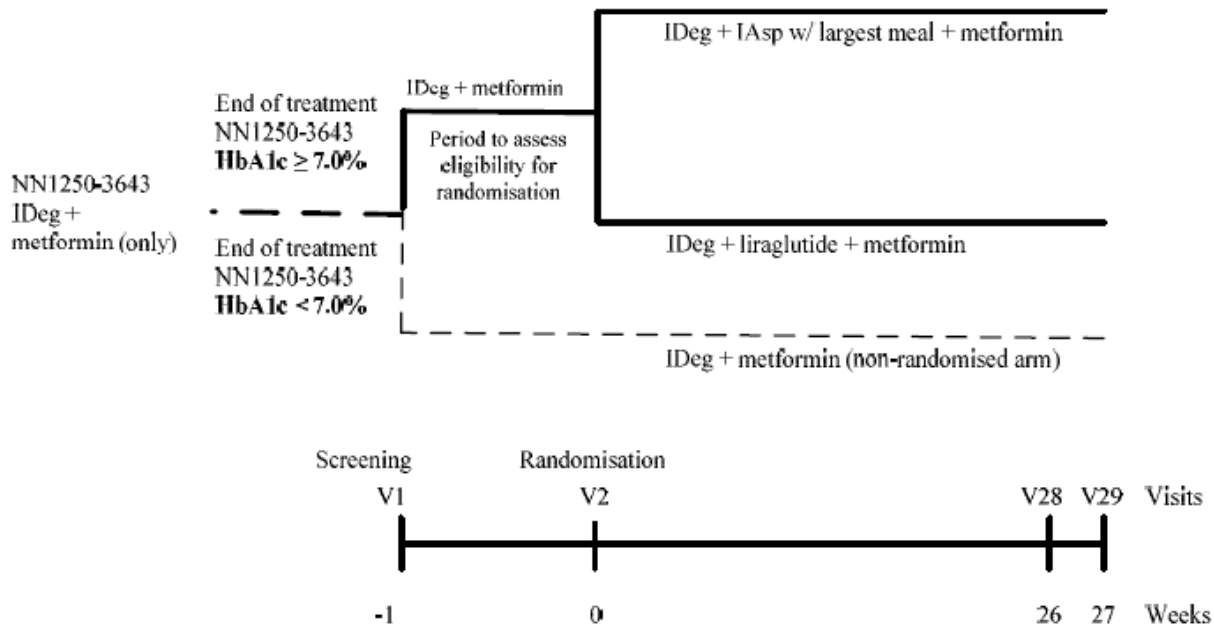
Trial 3948 was a 26-week, randomised, controlled, open label, multicentre, multinational, parallel, treat-to-target trial comparing the efficacy and safety of adding liraglutide versus adding IAsp OD with the largest meal, to treatment with IDeg + metformin, in subjects with T2DM using a 1:1 randomisation. Subjects randomised into Trial 3948 had completed approximately 52+52 weeks of treatment with IDeg + metformin in Trial 3579 and its extension (Trial 3643), with an end of treatment HbA1c ≥ 7.0%, thus qualifying for treatment intensification; see Figure 4. Subjects in Trial 3643 were invited to participate in Trial 3948 and signed a new informed consent.

Subjects with an HbA1c <7% at end of Trial 3643 continued treatment with IDeg + metformin (in the following referred to as the non-randomised arm) and were followed for another 26 weeks to evaluate long-term efficacy and safety of IDeg. No comparisons to the randomised arms were made, and results for these subjects are not discussed in detail in this document.

The trial design for Trial 3948 is shown in Figure 4 below. At the screening visit (V1, which was the same day as the follow-up visit for Trial 3643); subjects discontinued treatment with NPH insulin, which was administered for basal insulin coverage during the follow-up period for NN1250-3643 in order to reduce interference with antibody measurements. During the week between screening and randomisation, subjects resumed treatment with IDeg OD + metformin at the doses taken at end of the active treatment period in Trial 3643.

In the liraglutide arm only, the IDeg dose was reduced by 20% at randomisation and was not to be increased during the first 6 weeks of the trial, during which the dose of liraglutide was escalated. Subjects in the IDeg + IAsp arm initiated treatment with IAsp OD at a dose of 4 U/day at the largest meal. In both treatment arms, the IDeg dose was adjusted once weekly using a treat-to-target regimen aimed to achieve a pre-breakfast self-measured plasma glucose (SMPG) value of 4.0−5.0 mmol/L (72−90 mg/dL).

Figure 4 Trial design of NN1250-3948



Please note that the NN1250-3643 follow-up visit served as Visit 1 of NN1250-3948.

Choice of comparator

IAsp administered OD with the largest meal was added in the comparator arm, thus enabling a direct comparison of two clinically relevant options for treatment intensification (i.e., addition of either GLP-1 or bolus insulin). The comparator treatment reflects a common approach in which bolus insulin is added in a stepwise fashion to OD basal insulin by one extra injection per day. IAsp was chosen as it is a commonly used rapid-acting insulin analogue with a well-known safety and efficacy profile. Metformin was continued at stable pre-trial doses in both treatment arms.

Randomisation and blinding

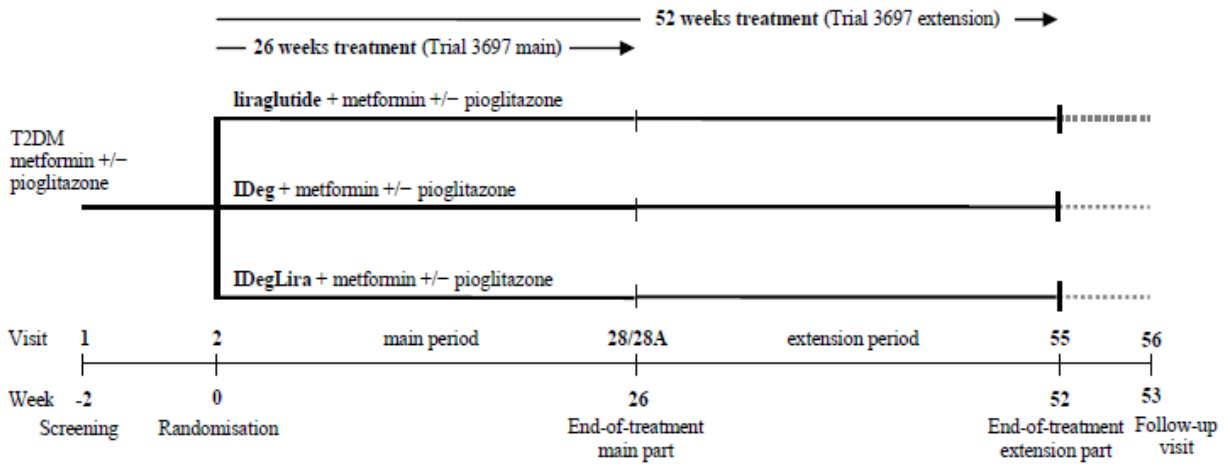
Subjects were randomised 1:1 to add either liraglutide or IAsp OD (with the largest meal) to treatment with IDeg + metformin. Since the comparator trial products, pen injectors, and treatment regimens were inherently different, a double-blind design was not feasible, and the trial was consequently open-labelled.

Supportive data, Trials 3697, 3912 and 1842

Design of Trial 3697

Trial 3697 was a 26-week randomised, controlled, parallel three-arm, open-label, multinational, multi-centre, treat-to-target trial in subjects with T2DM inadequately controlled [HbA1c level of 7.0−10.0% (both inclusive)] with 1−2 OADs (metformin or metformin + pioglitazone); see Figure 5. The trial investigated the efficacy and safety of the IDegLira combination product compared to the monocomponents IDeg and liraglutide.

Figure 5 Design of Trial NN9068-3697



Eligible subjects were randomised in a 2:1:1 manner to receive one of three parallel treatments consisting of once daily IDegLira, IDeg or liraglutide, all in combination with metformin or metformin + pioglitazone. The starting dose of IDegLira and IDeg was 10 dose steps (10 units IDeg and 0.36 mg liraglutide) and 10 units, respectively, followed by a treat-to-target approach with adjustment of doses to achieve pre-breakfast SMPG targets of 4.0−5.0 mmol/L (72−90 mg/dL). The maximum dose of IDegLira was 50 dose steps (50 units IDeg and 1.8 mg liraglutide). Liraglutide treatment was started at 0.6 mg/day and subsequently increased by 0.6 mg in weekly dose escalation steps to a maximum dose of 1.8 mg/day. The trial was followed by a 26-week extension trial to provide evidence of persistence of efficacy and safety during long-term exposure. During the extension period subjects continued on the same treatment at unchanged dose (liraglutide arm) or dosing regimen (IDeg and IDegLira arms) as in the main trial.

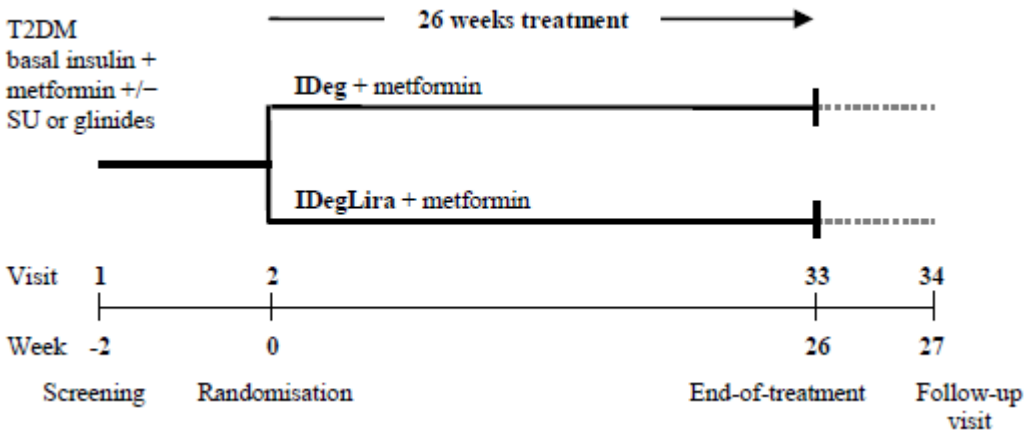
Design of Trial 3912

Trial 3912 was a 26-week parallel two-arm, (1:1) randomised, double-blind, multi-centre, multinational, treat-to-target trial in subjects with T2DM inadequately controlled (HbA1c of 7.5-10.0% [both inclusive]) on 20-40 units/day of basal insulin and 1-2 OADs (metformin ± sulfonylurea or glinides). Randomisation of subjects was stratified by current background treatment: basal insulin + one OAD (metformin) or basal insulin + two OADs (metformin + SU or metformin + glinide), to ensure equal distribution of background treatment in each of the two arms.

As the maximum dose of IDegLira and IDeg was similar and the trial products were visually identical, a double-blind design was used.

Use of basal insulin and sulfonylurea/glinides were discontinued at randomisation, and the trial investigated the efficacy and safety of the combination product IDegLira compared to IDeg, both added to metformin. The starting dose of IDegLira and IDeg was 16 dose steps (16 units IDeg and 0.6 mg liraglutide) and 16 units, respectively, and the dose was adjusted using a treat-to-target regimen aiming for a pre-breakfast SMPG target of 4.0−5.0 mmol/L (72−90 mg/dL). The maximum allowed dose of IDeg was 50 units and hence identical to the maximum dose of IDegLira, enabling an evaluation of the effect of the liraglutide component in the combination product; see Figure 6.

Figure 6 Trial design Trial NN9068-3912



Supportive liraglutide + IDet combination, Trial 1842

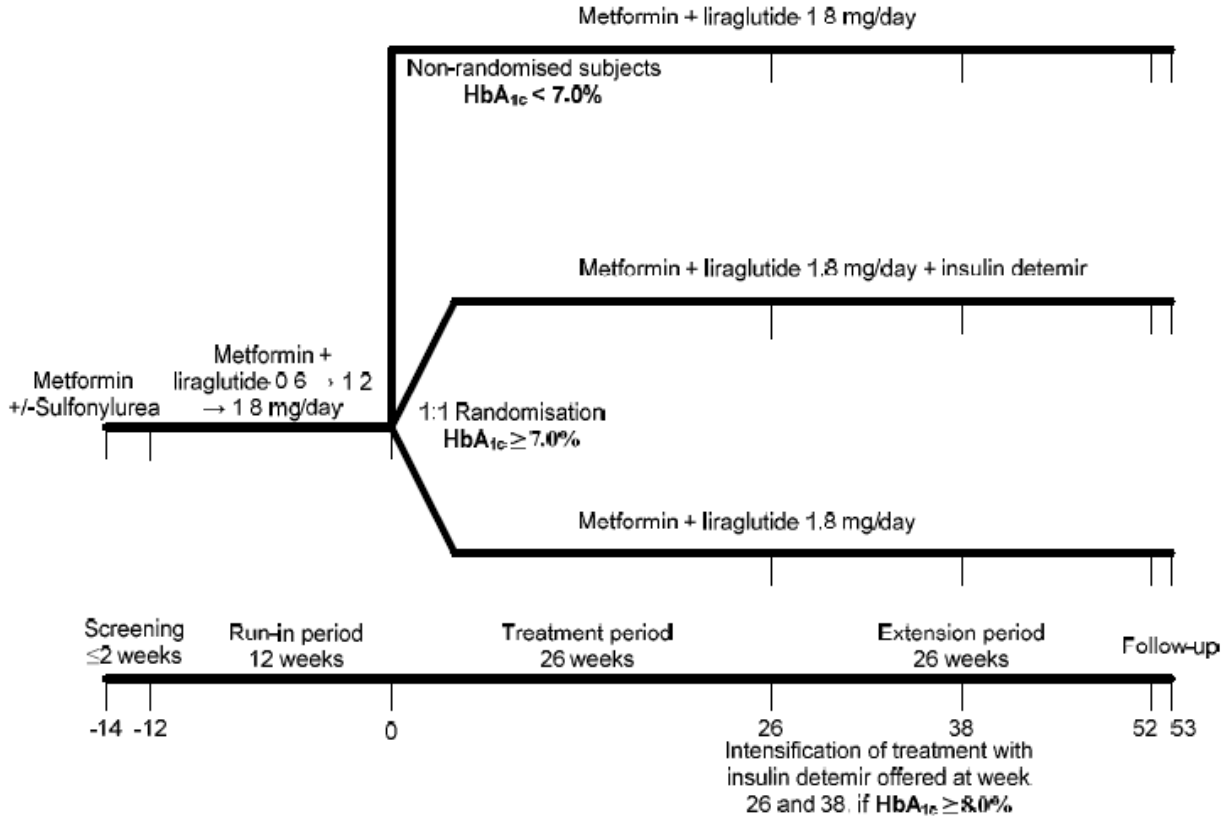
Design of Trial 1842

Trial 1842 was a 26-week, randomised, open-label, two-armed, parallel group, multi-centre, multinational trial comparing the efficacy of IDet in combination with liraglutide versus liraglutide (both in combination with metformin) in subjects with T2DM. The trial included a 12-week run-in period before which sulphonylurea treatment was discontinued and during which liraglutide was escalated from 0.6 to 1.8 mg/day in all subjects.

Subjects with an HbA1c ≥ 7.0% after the end of the run-in period were randomised in a 1:1 manner to continued treatment with liraglutide 1.8 mg/day + metformin only or to add IDet at a dose of 10 U/day, followed by once weekly titration to achieve a pre-breakfast target of 4.0-6.0 mmol/L (72-108 mg/dL). The randomisation was stratified by sub-study participation (meal-test), previous treatment with metformin and metformin + pioglitazone, and baseline HbA1c (≤ 8.3% and > 8.3%).

The trial was followed by a 26-week extension period to evaluate long-term efficacy and safety. Intensification of treatment with IDet was offered at Weeks 26 and 38 for subjects with an HbA1c ≥ 8.0% in the randomised and non-randomised liraglutide treatment groups. For more details; see Figure 7.

Figure 7 Trial Design Trial NN2211-1842



Subject population

Selection criteria

IDeg + liraglutide combination, Trial 3948

Subjects in Trial 3948 were originally found eligible to participate in Trial 3579, which included insulin-naïve male or female subjects aged ≥ 18 years, with T2DM ≥ 6 months, HbA1c 7.0-10.0% (both inclusive), body mass index (BMI) ≤ 40.0 kg/m2 and who were treated on metformin monotherapy (1500 mg/day or maximum tolerated dose [at least 1000 mg/day] according to local label) or metformin in any combination with an insulin secretagogue (SU or glinide), dipeptidyl peptidase-IV (DPP-IV) inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to screening. All OADs other than metformin and DPP IV inhibitors were discontinued at the start of Trial 3579.

Subjects who completed the first 52 weeks of treatment in the main trial (Trial 3579) were eligible to participate in the 52-week extension trial (Trial 3643).

Subjects treated with IDeg + metformin at completion of Trial 3643 were eligible for participation in Trial 3948. Subjects with an HbA1c < 7% continued treatment with IDeg + metformin in a nonrandomised arm to evaluate long-term efficacy and safety of IDeg and are not discussed in detail in this report.

The criteria for randomisation are shown in

Table 2.

Table 2 Key selection and randomisation criteria in Trial 3948

Inclusion Criteria
• Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject). • The subject must have completed the end-of-treatment visit of Trial 3643 with IDeg OD + metformin.
Exclusion Criteria
• Participated in Trial 3643 and treated with IGlar + met ± DPP IV inhibitor or IDeg + met + DPP IV inhibitor • Previous treatment with GLP 1 receptor agonists (e.g. exenatide, liraglutide). • Recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during last 12 months) or hypoglycaemic unawareness as judged by the investigator.
Randomisation Criteria
• HbA_{1c} ≥7 % at end of treatment in Trial 3643 • Calcitonin < 50 ng/L at Visit 1 • No personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) • No history of chronic pancreatitis or idiopathic acute pancreatitis (fulfilling at least 2 out of 3 of the following diagnostic criteria: characteristic abdominal pain, amylase and/or lipase > 3 times the upper limit of normal or characteristic findings on computerised axial tomography (CT)/magnetic resonance imaging (MRI) • Subject with no clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genitourinary or haematological system (except for conditions associated with type 2 diabetes), that in the opinion of the investigator, may confound the results of the trial or pose additional risk in administering trial drug.

Supportive IDegLira Trials 3697 and 3912

Trial 3697 included subjects with an HbA1c of 7-10.0% (both inclusive) and a BMI ≤ 40 kg/m2. All subjects were naïve to insulin and GLP-1 receptor agonists and continued on their baseline OAD treatment (metformin ± pioglitazone) throughout the trial.

Trial 3912 included subjects on stable basal insulin treatment (20-40 units) and metformin ± one additional OAD (SU or glinides) with an HbA1c of 7.5–10.0% (both inclusive) and a BMI ≥ 27 kg/m2. Basal insulin treatment and all OADs except metformin were discontinued at baseline.

The key inclusion and exclusion criteria for the two trials are shown in

Table **3**.

Table 3 Key inclusion criteria – Trials 3697 and 3912

Inclusion criteria
• Informed consent obtained before any trial-related activities
• Subjects with T2DM
• Males or females, ≥ 18 years of age[#]
• Baseline HbA_{1c}:
  • Trial 3697: 7.0–10.0%, both inclusive
  • Trial 3912: 7.5–10.0%, both inclusive
• Current antidiabetic treatment:
  • Trial 3697: Stable daily dose of 1–2 OADs (metformin [≥ 1500 mg or maximum tolerated dose] ± pioglitazone [≥ 30 mg]) for at least 90 days prior to screening
  • Trial 3912: Stable daily dose of basal insulin treatment and stable daily dose of 1–2 OADs ([≥ 1500 mg or max tolerated dose] ± SU [≥ half of the max approved dose according to local label] or ± glinides [≥ half of the max approved dose according to local label]) for at least 90 days

Exclusion criteria
• Use of any drug, which in the investigator's opinion could interfere with the glucose level (e.g. systemic corticosteroids)
  • Trial 3697: except for OADs (metformin and pioglitazone)
  • Trial 3912: except for basal insulin, metformin, SU and glinides
• Treatment with GLP-1 receptor agonists (e.g., exenatide, liraglutide) or the following specific OADs within 90 days prior to trial
  • Trial 3697: sulphonylurea or dipeptidyl peptidase 4 (DPP-4) inhibitors
  • Trial 3912: dipeptidyl peptidase 4 (DPP-4) inhibitors and/or thiazolidinediones

Supportive liraglutide + IDet combination, Trial 1842

Trial 1842 included insulin-naïve male and female subjects with T2DM previously treated with metformin monotherapy or metformin + SU. A stable treatment regimen prior to trial enrolment was considered important to prevent carry-over effects on trial endpoints.

Key inclusion and exclusion criteria are listed in Table 4.

Table 4 Key selection criteria, Trial 1842

Inclusion criteria • Informed consent obtained before any trial-related activities • Subjects aged 18-80 years, both inclusive (or as allowed according to local guidelines) • HbA_{1c} 7.0-10.0% (both inclusive) for subjects on metformin monotherapy, HbA_{1c} 7.0-8.5% (both inclusive) for subjects on metformin in combination with a sulphonylurea • Subjects diagnosed with T2DM, insulin naïve and treated with metformin as monotherapy for ≥3 months prior to screening, at a stable dose of ≥1500 mg/day or metformin (≥1500 mg/day) and a sulphonylurea (less than or equal to ½ of the maximum approved dose according to local label), both at a stable dose for ≥3 months prior to screening.
Exclusion criteria • Use of any drug (except for those stated in the inclusion criteria) that in the investigator's opinion could interfere with the glucose level (e.g. systemic corticosteroids) • Previous treatment with insulin (except for short-term treatment in connection with inter-current illness at the discretion of the investigator) • Treatment with glucose-lowering agent(s) other than those stated in the inclusion criteria for a period of 3 months prior to screening • Receipt of any other investigational drug within 3 months prior to screening into this trial • Any contraindications to metformin or insulin detemir according to local labels • Recurrent major hypoglycaemia or hypoglycaemic unawareness as judged by the investigator

Withdrawal Criteria

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. If the investigator suspected acute pancreatitis, all drugs suspected to relate to this condition should be discontinued until confirmatory tests had been conducted and appropriate treatment initiated; see Table 5.

Table 5 Key withdrawal criteria across trials

Trial 3948
• Subjects randomised in error (not fulfilling the inclusion and/or meeting exclusion criteria) must be withdrawn from the trial. • Subjects with an $HbA_{1c} \geq 7\%$ at end of treatment in NN1250-3643 and not fulfilling criteria for randomisation must be withdrawn. • Development of any life threatening disease (e.g. cancer). • Calcitonin ≥ 50 ng/L. • Subjects randomised to the liraglutide arm who are unable to tolerate a dose of liraglutide 1.2 mg must be withdrawn. • Unacceptable hyperglycaemia: At and after week 12, the subject must be withdrawn if there is: o No reduction in HbA_{1c} AND o Three pre-breakfast SMPG readings higher than 13.3 mmol/L (240 mg/dL) within a two week period and FPG measured at the central laboratory exceeds 13.3 mmol/L (240 mg/dL) AND o If there is no treatable cause for the hyperglycaemia
Supportive trials
Trials 3697 and 3912 • Initiation of any systemic treatment with products which in the investigator's opinion could interfere with glucose or lipid metabolism (e.g., systemic corticosteroids) **Trials 3697, 3912 and 1842** • If the fasting SMPG values taken on three consecutive days or if any of the 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 or 52, 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.

Further rescue criteria were generally not considered relevant, as the vast majority of subjects were expected to benefit from intensified treatment. In Trial 3948, subjects inadequately treated on IDeg metformin in Trial 3643 added IAsp OD at the main meal to ensure adequate glycaemia control in the comparator arm. In Trial 1842, subjects randomised to liraglutide + metformin had the option to intensify treatment with IDet during the 26 week extension trial if HbA1c ≥ 8.0%.

Trial objectives

Primary objective

IDeg + liraglutide combination, Trial 3948

The primary objective of Trial 3948 was to compare the efficacy of adding liraglutide versus IAsp to the largest meal to treatment with IDeg + metformin in controlling glycaemia as measured by change from baseline in HbA1c. This was done by comparing the difference in change from baseline in HbA1c at end of treatment between IDeg + liraglutide and IDeg+IAsp OD, both in combination with metformin.

Supportive Trials

The primary objective of Trial 3697 was to confirm the efficacy of IDegLira in controlling glycaemia in subjects with T2DM by determining whether the effect (change in HbA1c) of IDegLira was non-inferior to that of IDeg and superior to that of liraglutide after 26 weeks of treatment.

The primary objective of Trial 3912 was to confirm superiority of IDegLira vs. IDeg in controlling glycaemia in subjects with T2DM. In Trial 3912, the insulin dose in the IDeg treatment arm was limited to 50 units (i.e., equivalent to the insulin dose administered with the proposed maximum dose of IDegLira) in order to specifically assess the contribution of the liraglutide component to glycaemic control with IDegLira.

The primary objective of Trial 1842 was to confirm the efficacy of IDet in combination with liraglutide and metformin in controlling glycaemia in subjects with T2DM by determining whether the effect (change in HbA1c) of IDet + liraglutide was superior to that of liraglutide, both in combination with metformin, after 26 weeks of treatment.

Secondary objectives

The secondary objectives varied slightly between the trials, but were generally to evaluate the efficacy and safety of IDeg + liraglutide, IDegLira, or IDet + liraglutide with that of the respective active comparators.

Primary and secondary endpoints

Primary as well as secondary endpoints for the four trials are listed in Table 6. Overall, the endpoints were very similar between the trials.

Trials 3697 and 1842 both included a 26 week extension period, and a number of efficacy assessments and endpoints were repeated after 52 weeks of treatment.

Table 6 Key endpoints for assessment of efficacy across trials

Trial	3948 (26 wks)	3697 (26+26 wks)	3912 (26 wks)	1842 (26+26 wks)
Primary endpoint	• Change in HbA_{1c} (0-26 wks)	• Change in HbA_{1c} (0-26 wks)	• Change in HbA_{1c} (0-26 wks)	• Change in HbA_{1c} (0-26 wks)
Secondary endpoints Proportion of responders#	• HbA_{1c} <7% • HbA_{1c} <7% w/o confirmed hypoglycaemia • HbA_{1c} <7% w/o weight gain and confirmed hypoglycaemia	• HbA_{1c} <7% • HbA_{1c} <7% w/o confirmed hypoglycaemia • HbA_{1c} <7% w/o weight gain • HbA_{1c} <7% w/o weight gain and confirmed hypoglycaemia • All of the above repeated for $HbA_{1c} \leq 6.5\%$	• HbA_{1c} <7% • HbA_{1c} <7% w/o confirmed hypoglycaemia • HbA_{1c} <7% w/o weight gain • HbA_{1c} <7% w/o weight gain and confirmed hypoglycaemia • All of the above repeated for $HbA_{1c} \leq 6.5\%$	• HbA_{1c} <7% • $HbA_{1c} \leq 6.5\%$ • HbA_{1c} <7% w/o weight gain and major or minor hypoglycaemia
FPG	• Change in FPG (0-26 wks)	• Change in FPG (0-26 wks)	• Change in FPG (0-26 wks)	• Change in FPG (0-26 wks)
Prandial increments	• Difference between PG values 90 min. after meal and before meal (based on 9-point SMPG profiles)	• Change from baseline in $iAUC_{0-4h}$ derived from the glucose concentration profile during meal test • Mean of postprandial increments (based on 9-point SMPG profiles)	• Mean of postprandial increments (based on 9-point SMPG profiles)	• Difference between PG values 90 min. after meal and before meal (based on 7-point SMPG profiles)
Post-prandial glucose	• Post-prandial plasma glucose by meal and across all meals	• Post-prandial plasma glucose by meal and across all meals	• Post-prandial plasma glucose by meal and across all meals	• Post-prandial plasma glucose by meal
Hypoglycaemia	• Number of severe episodes • Number of confirmed episodes • All of the above repeated for nocturnal hypoglycaemia	• Number of severe episodes • Number of confirmed episodes • All of the above repeated for nocturnal hypoglycaemia	• Number of severe episodes • Number of confirmed episodes • All of the above repeated for nocturnal hypoglycaemia	• Number of major episodes • Number of minor episodes
Weight	• Change in weight (0-26 wks)	• Change in weight (0-26 wks)	• Change in weight (0-26 wks)	• Change in weight (0-26 wks)
Insulin dose	• Total daily IDeg dose • Total daily insulin dose	• Total daily IDeg dose	• Total daily IDeg dose	• Total daily IDet dose

Wks: weeks. #Responder analyses in Trials 3948, 3697 and 3912 relates to responders without confirmed hypoglycaemia during the last 12 weeks of treatment. In Trial 1842 it refers to hypoglycaemia during the entire trial period of randomised treatment.

Safety endpoints as part of efficacy evaluation

Treatment emergent hypoglycaemic episodes

Episodes of hypoglycaemia were self-reported based on the subjects' SMPG recordings and symptoms, reflecting common clinical practice.

The categorisation and analyses of hypoglycaemia used in Trial 3948 were identical to those used in the clinical phase 3a development programme for IDeg. Statistical analyses were based on treatment emergent episodes of confirmed hypoglycaemia (i.e. episodes that were either severe (requiring assistance from another person) or where plasma glucose was biochemically confirmed to be <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia. The two supportive IDegLira trials used the same definition for statistical analyses.

The MAH has historically used the cut-off level of <3.1 mmol/L to define hypoglycaemia rather than the American Diabetes Association (ADA) criterion of ≤3.9 mmol/L, because glucose levels below 3.1 mmol/L is typically where counter-regulatory mechanisms set in and patients report clinical symptoms of hypoglycaemia. Furthermore, a cut-off of < 3.1 mmol/L is sufficiently below the FPG target of 4-5 mmol/L used in the IDeg and IDegLira development programmes (and the target of 4-6 mmol/L used in Trial NN2211-1842) to avoid a high incidence of borderline hypoglycaemic episodes with plasma glucose values marginally below the target.

In Trial 1842, hypoglycaemic episodes were classified as 'major' (identical to severe) and 'minor' (episodes of hypoglycaemia with or without symptoms with a plasma glucose measurement <3.1 mmol/L). In Trial 1842, these two categories were not collapsed to represent 'confirmed hypoglycaemia' but were analysed separately.

In Trials 3948, 3697 and 3912, hypoglycaemic episodes were considered treatment emergent if the onset of the episode was on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. In Trial 1842, events were considered as treatment emergent if occurring on or after the first day of treatment and no later than the last day of treatment. Hypoglycaemic episodes with an onset between 00:01 and 05:59 (both inclusive) were considered nocturnal except in Trial 1842 where no nocturnal period was prespecified.

Statistical methods

Analysis sets

The following analysis sets were defined in Trial 3948 in accordance with the ICH-E9 guidance. Corresponding definitions of FAS and SAS were used in the three supportive trials.

- Full Analysis Set (FAS): all randomised subjects. The subjects contributed to the evaluation "as randomised". (In Trial 1842 only subjects with at least one efficacy value after the randomisation visit were included in the FAS)
- Safety Analysis Set (SAS): All subjects that received at least one dose of the investigational product or its comparator. Subjects in the safety set contributed to the evaluation "as treated".

In all four trials, descriptive statistics and inferential statistics of all efficacy endpoints as well as analyses of hypoglycaemia (except for Trial 1842), body weight, and insulin dose were based on the FAS. All descriptive statistics of hypoglycaemia and insulin dose were based on the SAS. The robustness of the results for the primary endpoint was explored by additional sensitivity analyses including analysis on all completers.

General considerations

Handling of missing data was prespecified in the protocols, and unless otherwise specified missing values (including intermittent missing values) were imputed using the Last Observation Carried Forward (LOCF) method. In previous treat-to-target trials with insulin degludec, LOCF has generally provided results similar to those obtained from alternative methods applicable for handling of missing data, such as repeated measures models.

Statistical Methods:

The continuous endpoints (primary endpoint of change in HbA1c and secondary endpoints pertaining to FPG, prandial increment and body weight) were analysed using a pre-specified linear normal model. The included factors and covariates varied slightly between trials but as a minimum included treatment, all stratification factors and country/region as fixed effects and the relevant baseline values of the response as covariates.

Trial 3948 investigated whether the change in HbA1c after 26 weeks of treatment was statistically significantly different with IDeg + liraglutide relative to IDeg + IAsp OD at a 5% level. In Trials 3697 and 3912, non-inferiority and superiority were formulated and tested as one-sided hypotheses at a 2.5% level of significance with two-sided 95% confidence intervals. Non-inferiority of IDegLira compared to IDeg was confirmed when the 95% confidence interval for the treatment differences for change in HbA1c was entirely below 0.3%. Superiority of IDegLira compared to liraglutide was confirmed when the 95% confidence interval for the treatment difference for change in HbA1c was entirely below 0%. In Trial 1842, superiority of IDet + liraglutide was confirmed if the upper limit of the 95% confidence interval was below 0%.

As a sensitivity analysis, the primary endpoint was analysed with a linear mixed model where all observed HbA1c measurements available post baseline where included. There were minor differences between the implementation of this model for the four trials, but as a minimum the model included the factors and covariates included in the primary analysis as well as time and treatment by time interaction as fixed factors and subject as a random factor.

Responders (subjects reaching HbA1c < 7% with or without hypoglycaemia and/or weight gain) were analysed using a logistic regression model. As for the continuous endpoints the included covariates varied slightly between trials, but as a minimum treatment, all stratification factors and region/country were included as fixed factors and the corresponding baseline values as covariates.

Number of hypoglycaemic episodes were analysed using a pre-specified negative binomial regression model with a log-link function and the logarithm of the relevant exposure time as offset.

Also here, the included covariates varied slightly between trials, but as a minimum treatment, all stratification factors and region/country were included as fixed factors. For this particular analysis, in Trial 1842 the model could only be fitted with treatment as factor and the logarithm to the exposure time as offset.

The minor differences in included covariates are unlikely to affect any of the conclusions from the different trials.

In Trial 3697, four confirmatory secondary endpoints were pre-specified in addition to the primary endpoint. In order to test superiority of IDegLira vs. IDeg while controlling the Type-1 error rate,the Holm-Bonferroni method was used.

2.3.3. Results

Subject disposition

The subject disposition in the four trials is shown in **Table 7**. The specified reasons for withdrawal differed slightly between trials. Thus, in Trial 1842 some subjects were withdrawn due to 'protocol deviation' or 'lost to follow-up', while in the three remaining trials these reasons were included under some of the other withdrawal criteria. If a subject chose to withdraw from the trial without any further explanation it was recorded as 'meeting a withdrawal criteria'.

IDeg + liraglutide combination, Trial 3948

In total, 419 subjects completing Trial 3643 were screened, and 413 subjects entered Trial 3948. A total of 88 and 89 subjects were randomised to IDeg + liraglutide and IDeg + IAsp, respectively, and 236 (57%) subjects continued treatment with IDeg + metformin in a non-randomised arm. Six (6) subjects were considered randomisation failures and were not exposed to liraglutide or IAsp, and another four (4) randomised subjects withdrew their informed consent before exposure to liraglutide (N=1) or IAsp (N=3).

In general, the subject withdrawals occurred evenly throughout the trial period, with no apparent clustering of withdrawals at any specific time point during the trial.

The most common reason for withdrawal in both randomised groups was meeting one or more withdrawal criteria: 11 subjects were randomised in error as they did not fulfil the selection criteria, 5 subjects withdrew consent, and 1 subject was withdrawn by the investigator. Six (6) randomised subjects were withdrawn due to adverse events.

Table 7 Subject disposition across trials

	NN1250-3948		NN9068-3697			NN9068-3912		NN2211-1842	
	IDeg + Lira	IDeg + IAsp OD	IDegLira	IDeg	Lira	IDegLira	IDeg	IDet + Lira	Lira
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomised	**88 (100.0)**	**89 (100.0)**	**834 (100.0)**	**414 (100.0)**	**415 (100.0)**	**207 (100.0)**	**206 (100.0)**	**162 (100.0)**	**161 (100.0)**
Exposed	87 (98.9)	86 (96.6)	826 (99.0)	413 (99.8)	413 (99.5)	207 (100.0)	206 (100.0)	162 (100.0)	161 (100.0)
Withdrawn	**12 (13.6)**	**14 (15.7)**	**98 (11.8)**	**48 (11.6)**	**73 (17.6)**	**32 (15.5)**	**35 (17.0)**	**18 (11.1)**	**34 (21.1)**
Adverse event	5 (5.7)	1 (1.1)	10 (1.2)	8 (1.9)	24 (5.8)	1 (0.5)	3 (1.5)	4 (2.5)	6 (3.7)
Ineffective therapy	ND	ND	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)	2 (1.2)	5 (3.1)
Non-compliance	0 (0.0)	2 (2.2)	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.2)	3 (1.9)
Withdrawal criteria	7 (8.0)	10 (11.2)	69 (8.3)	34 (8.2)	40 (9.6)	13 (6.3)	15 (7.3)	0 (0.0)	11 (6.8)
Protocol deviations	ND	ND	ND	ND	ND	ND	ND	3 (1.9)	1 (0.6)
Lost to follow-up	ND	ND	ND	ND	ND	ND	ND	1 (0.6)	1 (0.6)
Other	0 (0.0)	1 (1.1)	16 (1.9)	5 (1.2)	9 (2.2)	17 (8.2)	13 (6.3)	6 (3.7)	7 (4.3)
Completed	**76 (86.4)**	**75 (84.3)**	**736 (88.2)**	**366 (88.4)**	**342 (82.4)**	**175 (84.5)**	**171 (83.0)**	**144 (88.9)**	**127 (78.9)**
Full analysis set	88 (100.0)	89 (100.0)	833 (99.9)*	413(99.8)	414 (99.8)	199 (96.1)#	199 (96.6)	162 (100.0)	157 (97.5)
Safety analysis set	87 (98.9)	86 (96.6)	825 (98.9)	412 (99.5)	412 (99.3)	199 (96.1)	199 (96.6)	163 (101.0)	159 (98.8)

*Trial 3697: Three subjects from one prematurely closed site was excluded from FAS and SAS due to lack of sign-off on patient case books.

#Trial 3912: A total of 15 subjects from one site were excluded from FAS and SAS due to site misconduct.

ND: Not defined

Supportive IDegLira Trials 3697 and 3912

In Trial 3697, the withdrawal pattern was similar in the IDegLira and IDeg treatment groups, whereas more adverse event withdrawals were noted in the liraglutide group. More subjects treated with liraglutide withdrew during the first weeks of the trial (Week 1−6) than subjects treated with IDegLira or IDeg, reflecting the known (primarily transient) gastrointestinal side effects of liraglutide.

The main reason for withdrawal in all three groups was meeting one or more withdrawal criteria: 73 subjects chose to withdraw without providing any further explanation, 56 withdrew due to incompliance or safety concerns, and 13 subjects were withdrawn due to continuously high SMPG levels (9 in the liraglutide arm). Furthermore, 30 subjects were withdrawn due to 'other reasons'. This included 17 subjects randomised in error and 8 subjects withdrawn due to trial site closure. Of the latter, 3 subjects from one site were not included in any analysis sets as the resigning investigator did not sign off on the patient case books, rendering the data invalid for inclusion in analyses.

The withdrawal pattern in Trial 3912 was similar between the IDegLira and IDeg treatment groups. The most frequent reason for withdrawal in both groups was meeting one or more withdrawal criteria. Of these, more subjects in the IDeg group withdrew due to continuous high SMPG compared to the IDegLira treatment group. Furthermore, 30 subjects were withdrawn due to 'other reasons'. This included 15 subjects withdrawn due to closure of a trial site (excluded from the full analysis set due to compromised data integrity) and 15 subjects randomised in error who violated some of the selection criteria (most often related to pretrial treatment regimens).

Supportive liraglutide + IDet combination, Trial 1842

A total of 60.7% of subjects (N=498) who completed the 12-week run-in phase on liraglutide 1.8 mg/day + metformin achieved adequate glycaemic control (HbA1c < 7%) and continued the trial in the non-randomised treatment arm. The remaining 39.3% of subjects were randomised to IDet+liraglutide or liraglutide 1.8 mg/day (162 and 161 subjects, respectively), both in combination with metformin.

The withdrawal rate differed between treatments. A higher proportion of subjects were withdrawn in the liraglutide arm (21.1%) than in the IDet + liraglutide arm (11.1%). The higher withdrawal rate in the liraglutide arm was primarily due to subjects meeting a withdrawal criterion or due to ineffective therapy.

Demographics and diabetes characteristics

IDeg + liraglutide combination, Trial 3948

Subjects in Trial 3948 had all been treated with IDeg + metformin for a period of two years. The population consisted of male and female subjects with a mean age of 61.0 years (ranging from 35.5 to 81.3 years), a mean HbA1c of 7.7% and a mean BMI of 32.2 kg/m2. Approximately one third of subjects in both treatment arms were >65 years of age, and 58.2% had a diabetes duration ≥10 years. Furthermore, subjects had a BMI ranging from 19.5 to 48.8 kg/m2.

The trial included subjects from Europe and United States (32.8%), and the majority were White (91.5%) and of non-Hispanic/Latino origin (80.2%). The demographics and baseline characteristics were similar between the treatment groups apart from a lower proportion of female subjects in the IDeg + liraglutide group (28.4% vs. 40.4%), which was also reflected in a higher mean body weight in this treatment arm (95.4 kg vs. 91.3 kg). BMI was similar between the two treatment groups.

Subjects in the IDeg + liraglutide-group also had a slightly longer duration of diabetes (12.9 years) than subjects in the IDeg + IAsp group (11.8 years). The demographic, baseline, and diabetes characteristics of all subjects in the FAS are summarised descriptively in Table 8 and Table 9.

The proportion of subjects with diabetes complications at baseline was 29.5% in the IDeg + liraglutide group and 25.8% in the IDeg + IAsp group.

The type and frequency of diabetic complications reported at screening appeared similar between treatment groups, with the most frequently reported complications being diabetic neuropathy and diabetic retinopathy. In general, the pattern of concomitant illnesses and concomitant medication was representative for a population with T2DM, and there were no apparent differences between treatment

groups. Mild, moderate, and severe renal impairment was observed in 18%, 1%, and 0% of subjects, respectively.

All subjects were optimised on metformin prior to entry into Trial 3948, and the mean dose was comparable between treatments at 2003 mg/day in the IDeg + liraglutide arm and 2005 mg/day in the IDeg + IAsp arm.

Table 8 Summary of subject demographics and diabetes characteristics at baseline across trials, FAS

	NN1250-3948		NN9068-3697			NN9068-3912		NN2211-1842°	
	IDeg + Lira	IDeg + IAsp OD	IDegLira	IDeg	Lira	IDegLira	IDeg	IDet + Lira	Lira
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of subjects	88	89	833	413	414	199	199	162	161
Age (years)	61.1 (9.5)	60.9 (8.8)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	56.8 (8.9)	57.5 (10.5)	56.8 (9.4)	57.3 (9.8)
Body weight (kg)	95.4 (19.2)	91.3 (16.8)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	95.4 (19.4)	93.5 (20.0)	96.0 (20.9)	95.3 (21.1)#
BMI (kg/m^2)	32.5 (5.4)	32.0 (4.8)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)	33.6 (5.7)	33.8 (5.6)	34.9 (6.3)	33.9 (6.0)
Duration of diabetes (years)	12.9 (6.4)	11.8 (6.5)	6.6 (5.1)	7.0 (5.3)	7.2 (6.1)	10.3 (6.0)	10.9 (7.0)	8.6 (5.8)	8.5 (6.0)
HbA_{1c} (%)	7.7 (0.6)	7.7 (0.8)	8.3 (0.9)	8.3 (0.9)	8.3 (1.0)	8.7 (0.7)	8.8 (0.7)	7.6 (0.6)	7.6 (0.7)#
FPG (mmol/L)	6.4 (2.4)	6.1 (1.7)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	9.7 (2.9)	9.6 (3.1)	9.2 (1.9)	8.8 (2.1)#
FPG (mg/dL)	115.2 (43.2)	109.8 (30.6)	165.6 (43.4)	169.2 (47.8)	162.7 (47.3)	174.6 (52.2)	172.8 (55.8)	166.1 (34.2)	158.6 (37.8)#

#Data pertain to time of randomisation. ¤ Exposed subjects.

Table 9 Subject characteristics for age, sex, BMI, and diabetes duration - FAS

	NN1250-3948		NN9068-3697			NN9068-3912		NN2211-1842°	
	IDeg + Lira	IDeg + IAsp OD	IDegLira	IDeg	Lira	IDegLira	IDeg	IDet + Lira	Lira
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of subjects	88	89	833	413	414	199	199	162 (100.0)	161 (100.0)
Age group (years)#									
≥18 ≤65 years	55 (62.5)	59 (66.3)	715 (85.8)	352 (85.2)	357 (86.2)	161 (80.9)	150 (75.4)	ND	ND
>65 years	33 (37.5)	30 (33.7)	118 (14.2)	61 (14.8)	57 (13.8)	38 (19.1)	49 (24.6)	ND	ND
Sex									
Female	25 (28.4)	36 (40.4)	398 (47.8)	213 (51.6)	206 (49.8)	87 (43.7)	93 (46.7)	74 (45.7)	72 (44.7)
Male	63 (71.6)	53 (59.6)	435 (52.2)	200 (48.4)	208 (50.2)	112 (56.3)	106 (53.3)	88 (54.3)	89 (55.3)
BMI category(kg/m^2)									
≥0 < 25	5 (5.7)	2 (2.2)	99 (11.9)	55 (13.3)	47 (11.4)			ND	ND
≥25 <30	28 (31.8)	31 (34.8)	257 (30.9)	119 (28.8)	120 (29.0)	60 (30.2)	58 (29.1)	ND	ND
≥30 <35	24 (27.3)	32 (36.0)	258 (31.0)	123 (29.8)	136 (32.9)	75 (37.7)	76 (38.2)	ND	ND
≥35	30 (34.1)	24 (27.0)	219 (26.3)	116 (28.1)	111 (26.8)	64 (32.2)	65 (32.7)	ND	ND
Diabetes duration									
<10 years	32 (36.4)	42 (47.2)	637 (76.5)	308 (74.6)	294 (71.0)	113 (56.8)	111 (55.8)	ND	ND
≥10 years	56 (63.6)	47 (52.8)	196 (23.5)	105 (25.4)	119 (28.7)	86 (43.2)	88 (44.2)	ND	ND

#In Trials 3697 and 3912 age was defined as ≥ 18 <65 years and ≥ 65 years, respectively. ¤ Exposed subjects. ND: not defined

Supportive IDegLira Trials 3697 and 3912

Subjects in Trial 3697 were representative of insulin-naïve subjects with T2DM, with respect to both demographic characteristics and other key baseline characteristics; see Table 8 and Table 9. The racial distribution reflected the international trial conduct, with 61.9% of subjects being White, 21.7% being Asian Indian and 7.4% being Black or African American. A total of 15.1% of subjects were of Hispanic or Latino origin. Diabetic neuropathy was reported in 14.3% of subjects at baseline and was the most prevalent diabetes complication, while close to 7% had diabetic retinopathy. Mild and moderate renal

function was observed in 14.9% and 1.4% of subjects, respectively. All subjects were on metformin therapy at screening, with 17.3% of subjects receiving pioglitazone concomitantly.

In Trial 3912, the majority of subjects (77.4%) were White, and 16.3% were Asian Indians. A total of 10.1% were of Hispanic or Latino origin. Baseline characteristics were indicative of a relatively more advanced stage of T2DM compared to subjects in Trial 3697 (greater BMI, higher HbA1c and FPG and a longer duration of diabetes). Basal insulin dose at screening were equally distributed between treatment groups with a mean daily dose varying from 28.1–32.5 units for the IDegLira group and from 28.1–31.3 units for the IDeg group. The most frequent diabetic complications were neuropathy (reported in 43.7% of subjects) and retinopathy (reported by 16.1%). The overall prevalence of complications was comparable between treatment groups. Mild and moderate renal function was observed in 10.3% and 0.5% of subjects, respectively. The proportion of subjects receiving OADs was equally distributed between subjects receiving metformin (48.5%) and subjects receiving metformin + SU (49.5%). Only a minor proportion of subjects received metformin + glinides (1.5%) or metformin with sulphonylurea or glinides (0.5%).

Supportive liraglutide + IDet combination, Trial 1842

All subjects were insulin-naïve, and glycaemic control at randomisation, following the 12-week run-in period, was similar to that observed in Trial 3948 (**Table 8**). The majority of subjects were White (88.2%), while 4.9% in the IDet+liraglutide arm were Black or African America compared to 10.6% in the liraglutide arm. About 15% of subjects were of Hispanic or Latino ethnicity. The most frequent diabetic complications were neuropathy and retinopathy (reported by 15.5% and 9.3% of randomised subjects, respectively), and the overall prevalence of complications were comparable across treatment groups. Approximately 50% of subjects in both treatment arms had been treated with metformin mono-therapy prior to the trial, while the other 50% had been treated with metformin in combination with SUs.

Primary efficacy endpoint: Change in HbA1c

In Trial 3948, addition of liraglutide to IDeg + metformin resulted in a greater reduction in HbA1c compared to addition of IAsp with the largest meal to IDeg + metformin, and addition of liraglutide was therefore more effective in improving glycaemic control. This was supported by the results of Trials 3697 and 3912, where IDegLira resulted in a greater improvement in HbA1c as compared to IDeg or liraglutide alone, and by Trial 1842 where addition of IDet to liraglutide resulted in superior glycaemic control compared to liraglutide alone.

The observed mean HbA1c at baseline and end of trial as well as the observed change in mean HbA1c are shown in **Table 10**. Mean baseline HbA1c differed between trials and was lowest in Trial 3948 where subjects had been treated for two years on IDeg + metformin and in Trial 1842 where subjects had been optimised on liraglutide during a 12 week run-in period (during this period HbA1c decreased from 8.3% at screening to 7.6% at randomisation). Importantly, HbA1c at baseline was similar between the active treatment group and the comparator group in all four trials.

Table 10 HbA1c (%) over time – FAS

(Week 26)	NN1250-3948		NN9068-3697			NN9068-3912		NN2211-1842[#]	
	IDeg + Lira Mean (SD)	IDeg + IAsp OD Mean (SD)	IDegLira Mean (SD)	IDeg Mean (SD)	Lira Mean (SD)	IDegLira Mean (SD)	IDeg Mean (SD)	IDet + Lira Mean (SD)	Lira Mean (SD)
Number of subjects	88	89	833	413	414	199	199	162	157
Baseline	7.7 (0.6)	7.7 (0.8)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.7 (0.7)	8.8 (0.7)	7.6 (0.6)	7.6 (0.7)
End of trial (LOCF)	7.0 (0.7)	7.3 (0.8)	6.4 (1.0)	6.9 (1.1)	7.0 (1.2)	6.9 (1.0)	8.0 (1.2)	7.2 (0.75)	7.6 (0.9)
Change[$]	-0.74 (0.73)	-0.39 (0.72)	-1.91 (1.07)	-1.44 (1.03)	-1.28 (1.13)	-1.90 (1.09)	-0.89 (1.18)	-0.48 (0.73)	0.03 (0.72)

Values are based on observed means using LOCF

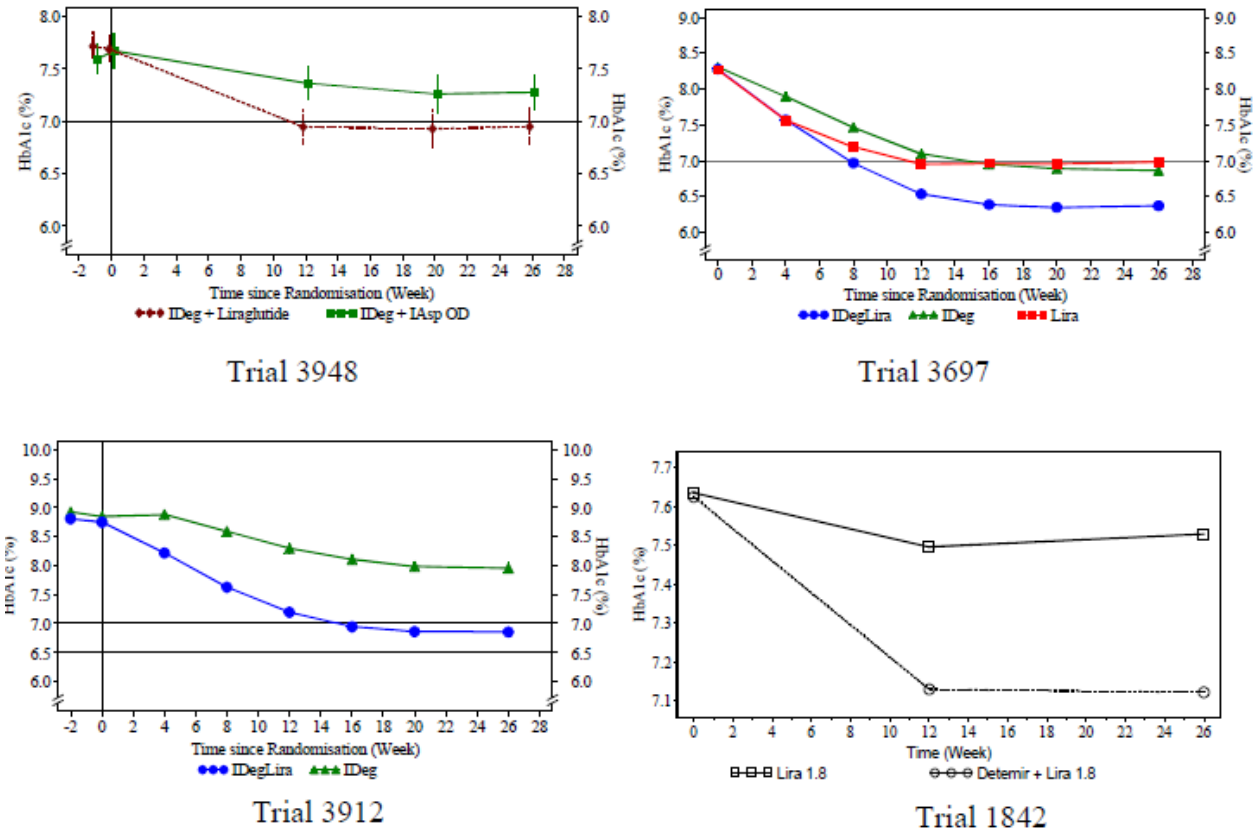
LOCF: last observation carried forward. #Baseline is identical to time of randomisation following 12 week run-in period

with optimisation of liraglutide

§Change from baseline (randomisation) to end of treatment (Week 26) based on LOCF

HbA1c over time is shown for the four trials in Figure 8 below. HbA1c decreased over time in all four trials, and the most pronounced reduction was observed within the first 12 weeks of treatment where most of the dose adjustments were performed; see Figure 8.

Figure 8 HbA1c (%) by treatment week – Mean plots – FAS



FAS; LOCF imputed data (except for 1842). Error bars: ± standard error (mean).

Trial 3948: Screening values are from end of treatment in Trial 3643, while baseline values are from blood samples draws at randomisation in Trial 3948.

The observed mean reduction in HbA1c was larger with IDeg + liraglutide than with IDeg + IAsp in Trial 3948, larger with IDegLira than with IDeg or liraglutide in Trials 3697 and 3912, and larger with IDet + liraglutide than with liraglutide in Trial 1842; see Table 10. These differences were statistically significant for all comparisons; see

Table **11**. This was supported by the pre-planned sensitivity analyses in the individual trials. Thus, the greater reduction in HbA1c observed with IDeg + liraglutide in Trial 3948 was supported by the results from the three supportive trials. Based on the non-inferiority and superiority criteria defined for the individual trials, treatment with IDegLira was confirmed to be non-inferior to IDeg and superior to liraglutide in Trial 3697 and superior to IDeg in Trial 3912. Furthermore, IDet + liraglutide was confirmed to be superior to liraglutide in Trial 1842.

Table 11 HbA1c (%) change from baseline to end of trial – statistical analysis - FAS

Trial	Treatment contrast	N (Active)	N (Comp)	Estimate [95% CI]
NN1250-3948	(IDeg + Lira) – (IDeg + IAsp)	88	89	-0.32 [-0.53; -0.12]*
NN9068-3697	IDegLira - IDeg	833	413	-0.47 [-0.58; -0.36]*
NN9068-3697	IDegLira - Lira	833	414	-0.64 [-0.75; -0.53]*
NN9068-3912	IDeglira - IDeg	199	199	-1.05 [-1.25; -0.84]*
NN2211-1842	(IDet + Lira) - Lira	162	157	-0.52 [-0.68; -0.36]*

N: FAS, *Statistically significant difference; CI: confidence interval. Missing data is imputed using last observation carried forward (LOCF).

The statistically significant improvements in HbA1c observed with IDegLira and IDet + liraglutide after 26 weeks in Trials 3697 and 1842 were maintained at 52 weeks of treatment; see Section 5 for further details.

Secondary efficacy endpoints

Subjects reaching HbA1c with or without hypoglycaemia and/or weight gain

In Trial 3948, the proportion of subjects who achieved the ADA defined HbA1c target of <7% was numerically higher with IDeg + liraglutide than with IDeg + IAsp (see

Table 12), albeit these proportions were not statistically significant different between the treatment arms; see Table 13.

In Trials 3697 and 3912, which included a considerably larger number of subjects than Trial 3948, the proportion of subjects reaching the ADA defined target of <7% was consistently greater with IDegLira than with comparator treatments, and a similar pattern was observed for the HbA1c target of ≤ 6.5%. Logistic regression analysis showed that the estimated odds of achieving these HbA1c targets after 26 weeks of treatment were statistically significantly greater for subjects treated with IDegLira than for subjects treated with either IDeg or liraglutide (Table 13).

In line with this, Trial 1842 demonstrated that combined use of IDet and liraglutide could get more subjects to target than treatment with liraglutide alone (Table 13).

Data from Trial 3948 show that the combined use of IDeg and liraglutide can get more subjects to target without the unwanted side effects of hypoglycaemia and weight gain compared to treatment with IDeg + IAsp OD; see

Table **12**. These findings were supported by the results from the three supportive trials. In Trials 3697 and 3912, treatment with IDegLira resulted in consistently higher proportions of subjects achieving the target HbA1c without hypoglycaemia, without weight gain, and without both hypoglycaemia and weight gain, as compared to treatment with IDeg alone.

A similar consistent benefit on responder endpoints was not observed when comparing IDegLira with liraglutide alone in Trial 3697, which reflects the low risk of hypoglycaemia and weight gain with liraglutide. In trial 1842, more subjects treated with IDet + liraglutide than with liraglutide alone achieved an HbA1c < 7% without hypoglycaemia and weight gain; see Table 13.

Table 12 Proportion of subjects (%) achieving HbA1c <7% at end of treatment (FAS)

(Week 26) (LOCF)	NN1250-3948		NN9068-3697			NN9068-3912		NN2211-1842#	
	IDeg + Lira	IDeg + IAsp OD	IDegLira	IDeg	Lira	IDegLira	IDeg	IDet + Lira	Lira
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of subjects	88	89	833	413	414	199	199	162	157
HbA_{1c} < 7%	51 (58)	40 (44.9)	671 (80.6)	269 (65.1)	250 (60.4)	120 (60.3)	46 (23.1)	71 (44.4)	30 (20.1)
HbA_{1c} < 7% w/o confirmed hypoglycaemia	44 (54.3)	16 (19.3)	503 (60.4)	169 (40.9)	239 (57.7)	97 (48.7)	31 (15.6)	ND	ND
HbA_{1c} < 7% w/o confirmed hypoglycaemia and weight gain	40 (49.4)	6 (7.2)	296 (35.5)	58 (14.0)	215 (51.9)	80 (40.2)	17 (8.5)	42 (26.3)	19 (12.5)

N = Number of subjects; LOCF: Last Observation Carried Forward, w/o: without. ND: not done

Responder for HbA1c without confirmed hypoglycaemia: subject meeting the HbA1c target at end of trial without treatment emergent confirmed hypoglycaemia during the last 12 weeks of treatment.. End of Trial: last end of trial visit of subject excluding follow-up visit. Confirmed hypoglycaemia: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL). Without Weight Gain: Body weight at week 26 is less than or equal to weight at baseline

Table 13 Responder analyses for HbA1c at end of trial - FAS

		N (Active / N Comp.)	HbA_{1c} <7%	HbA_{1c} <7% w/o confirmed hypoglycaemia and weight gain
Trial	Treatment odds ratio		Estimate [95% CI]	Estimate [95% CI]
NN1250-3948	(IDeg + Lira) / (IDeg + IAsp)	88 / 89	1.87 [0.96; 3.64]	13.79 [5.24; 36.28]*
NN9068-3697	IDegLira / IDeg	833 /413	2.38 [1.78; 3.18]*	3.56 [2.59; 4.90]*
NN9068-3697	IDegLira / Lira	833/ 414	3.26 [2.45; 4.33]*	0.49 [0.38; 0.63]*
NN9068-3912	IDeglira / IDeg	199/199	5.44 [3.42 ; 8.66]*	7.44 [4.08 ; 13.57]*
NN2211-1842	(IDet + Lira) / Lira	162/157	3.75 [2.19 ; 6.45]*	2.77 [1.47 ; 5.21]*

*Statistically significant difference. Missing data is imputed using LOCF. w/o: without

Responder for HbA1c without hypoglycaemia and weight gain: subject meeting the HbA1c target at end of trial without confirmed hypoglycaemia during the last 12 weeks of treatment and with change in body weight from baseline to end of trial below or equal to zero. End of Trial: last visit before follow-up visit. Confirmed hypoglycaemia: subject unable to treat himself/herself and/or have a recorded plasma glucose < 3.1 mmol/L (56 mg/dL).

Responder rates were higher for the combination of IDeg and liraglutide when compared to either IDeg and bolus insulin or liraglutide although not statistically significant. Larger differences were observed in the supportive studies where the combination was compared to each of the components (basal insulin or liraglutide). The difference increased when hypoglycaemias and weight gain was included in the analysis.

Fasting plasma glucose, FPG

In Trial 3948, mean FPG was relatively low at baseline compared to the other trials as subjects had been treated with IDeg for a period of two years prior to the trial using a treat-to-target regimen. Therefore, only marginal additional reductions in FPG were observed in both treatment groups at similar mean daily doses of IDeg. This is in line with the results from the pre-breakfast SMPG measurements used for adjustment of basal insulin doses, which were similar between treatment arms in Trial 3948.

Similar results were observed in Trial 3697, where treatment with IDegLira and IDeg resulted in similar reductions in FPG, albeit at lower doses of insulin in the IDegLira arm than in the IDeg arm. As expected, combined use of basal insulin and liraglutide had a greater effect on FPG than liraglutide alone as shown in Trials 3697 and Trial 1842.

In general, baseline FPG values were lowest in Trial 3948 where subjects had been treated with IDeg + metformin for an extended period of time in the preceding Trials 3579 and 3643 using a treat-to-target regimen. In Trial 1842, subjects had been optimised on liraglutide during a 12-week run-in period, while subjects in Trial 3697 were insulin-naïve and subjects in Trial 3912 had been treated with basal insulin, albeit not in a clinical trial setting. For the trial populations having a relatively high baseline FPG, the most pronounced decrease in FPG was observed within the first 12 weeks of treatment.

The change from baseline in FPG were not statistically significantly different with IDeg + liraglutide and IDeg + IAsp OD in Trial 3948, and the same was the case when comparing treatment with IDegLira and IDeg in Trial 3697; see Table 14. In contrast, reductions in mean FPG were statistically significantly greater with IDegLira and with IDet + liraglutide than with liraglutide alone in Trial 3697 and Trial 1842, respectively. Trial 3912 showed the added effect of the liraglutide component on FPG at similar doses of IDeg.

Table 14 Change in FPG (mmol/L) – statistical analysis – FAS

Trial	Treatment contrast	N (Active)	N (Comp.)	Estimate [95% CI] (mmol/L)
NN1250-3948	(IDeg + Lira) – (IDeg + IAsp)	88	89	0.06 [-0.65; 0.77]
NN9068-3697	IDegLira - IDeg	833	413	-0.17 [-0.41 ; 0.07]
NN9068-3697	IDegLira - Lira	833	414	-1.76 [-2.00 ; -1.53]*
NN9068-3912	IDegLira - IDeg	199	199	-0.73 [-1.19;-0.27]*
NN2211-1842	(IDet + Lira) - Lira	162	157	-1.73 [-2.16 ; -1.30]*

Missing data is imputed using last observation carried forward (LOCF).

9-point SMPG profiles and prandial increments

IDeg + liraglutide combination, Trial 3948

No difference in prandial increments or in mean postprandial glucose levels was observed in Trial 3948 where treatment with IDeg + liraglutide was compared to IDeg + IAsp. The 9-point SMPG profiles were similar between the two treatment groups at baseline and decreased in both groups during the course of the trial. Nearly all of the subjects treated with IAsp administered bolus insulin before lunch (47.3%) or before the main evening meal (47.3%), and this was reflected by a modestly lower SMPG value 90 minutes post-lunch, post-evening meal and at bedtime in the IDeg + IAsp group as compared to the IDeg + liraglutide group. Consequently, the observed mean prandial increments were slightly higher in the IDeg + liraglutide group than in the IDeg + IAsp group at lunch, evening meal, and across all meals. No statistically significant differences were observed between treatment groups at specific meals or across all meals.

Supportive IDegLira Trials 3697 and 3912

In Trial 3697, change in prandial glucose increment was a confirmatory secondary endpoint and was included to specifically evaluate to what extent the meal-related glucose levels are reduced by treatment intervention. The prandial glucose increment (iAUC0-4h) at baseline and at week 26 was calculated for a pre-specified population of 260 subjects undergoing a meal test. The results demonstrated that the liraglutide component of IDegLira contributed significantly to postprandial glycaemic control. With very similar mean baseline iAUC0-4h across treatment groups (IDegLira: 4.11 mmol/L, IDeg: 4.12 mmol/L, and liraglutide: 4.12 mmol/L), iAUC0-4h after 26 weeks of treatment had decreased by 0.87 mmol/L with IDegLira, by 0.17 mmol/L with IDeg and by 0.78 mmol/L with liraglutide. The reduction in prandial glucose increment was statistically significantly greater with IDegLira than with IDeg (estimated mean treatment difference: -0.71 mmol/L [-1.17; -0.26]95% CI), thus confirming superiority for this confirmatory secondary endpoint. Results were similar for IDegLira and liraglutide (estimated mean

treatment difference: -0.09 mmol/L [-0.56; 0.37]95% CI), which provides support for the preserved contribution of liraglutide to postprandial glycaemic control when combined with exogenous insulin.

The results from the meal test corresponded with the results from the 9-point SMPG profiles for the full trial population. These indicated improved overall postprandial glycaemic control across all meals with IDegLira relative to IDeg after 26 weeks.

In Trial 3912, the mean prandial increment across all meals based on 9-point SMPG measurements was lower with IDegLira (2.2 mmol/L [39.6 mg/dL]) than with IDeg (2.4 mmol/L [43.2 mg/dL]) after 26 weeks of treatment. This difference was statistically significant, with an estimated treatment difference of -0.37 mmol/L [-0.69;-0.04]95%CI.

Supportive liraglutide + IDet combination, Trial 1842

Treatment with both IDet + liraglutide and liraglutide alone led to mean decreases in post-prandial glucose at breakfast, lunch, and dinner, with the greatest decrease consistently observed with IDet + liraglutide. The estimated mean decrease in post-prandial glucose was statistically significantly greater with IDet+liraglutide compared to liraglutide alone for all meal times (estimated treatment differences of -1.12 mmol/L, -0.60 mmol/L and -0.70 mmol/L for breakfast, lunch and dinner, respectively).

As expected, no statistically significant difference between IDet + liraglutide and liraglutide was observed for change in prandial increments at breakfast, lunch or dinner.

Safety endpoints as part of efficacy evaluation

Treatment emergent hypoglycaemic episodes

In Trial 3948 treatment with IDeg + liraglutide resulted in a lower rate of both confirmed and nocturnal confirmed hypoglycaemia compared to treatment with IDeg + IAsp OD at the main meal. In Trial 3697, IDegLira was also associated with a lower risk of hypoglycaemia compared to IDeg; see Table 15.

No episodes of severe hypoglycaemia were reported in Trials 3948 and 1842, while a total of four severe hypoglycaemic episodes were reported in Trial 3697 (two with IDegLira and two with IDeg) and one severe episode was reported with IDegLira in Trial 3912.

Table 15 Hypoglycaemic episodes by classification – 26-week results – summary - SAS

	NN1250-3948				NN9068-3697						NN9068-3912				NN2211-1842#			
	IDeg + Lira		IDeg+IAsp OD		IDegLira		IDeg		Lira		IDegLira		IDeg		IDet + Lira		Lira	
	Rate	(%)	Rate	(%)	Rate	(%)	Rate	(%)	Rate	(%)	Rate	(%)	Rate	(%)	Rate	(%)	Rate	(%)
Number of subjects	87		86		825		412		412		199		199		163		158	
Severe	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.5)	0	(0.0)	1.1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Confirmed#	100	(27.6)	815	(67.4)	180	(31.9)	257	(38.6)	22	(6.8)	153	(24.1)	263	(24.6)	29	(9.2)	3	(1.3)
(including outlier)															29	(9.2)	26	(1.9)
Nocturnal confirmed	17	(5.7)	111	(25.6)	22	(6.4)	28	(8.3)	3	(1.2)	22	(6.0)	32	(8.5)	ND		ND	

N: Number of subjects %: Percentage of subjects with the event, Rate: Event rate per 100 patient year(s) of exposure, Confirmed hypoglycaemia: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL), Nocturnal period: the period between 00:01 and 05:59 a.m. (both included).
#Trial 1842 excluding outlier

In Trial 3948, both the percentage of subjects who experienced confirmed hypoglycaemic episodes as well as the rate of confirmed hypoglycaemic episodes was lower with IDeg + liraglutide than with IDeg + IAsp OD; see **Table 15**. The estimated rate of confirmed hypoglycaemic episodes was statistically significantly lower (by 87%) with IDeg + liraglutide compared to IDeg + IAsp OD; see **Table 16**. This finding was supported by the results from Trial 3697 showing a statistically significant 32% relative

reduction in the rate of confirmed hypoglycaemic episodes with IDegLira relative to IDeg. In Trial 3912, the rate of confirmed hypoglycaemia was numerically, albeit not statistically significantly, lower with IDegLira compared to IDeg (given at a maximum dose of 50 units).

A statistically significantly lower rate of confirmed hypoglycaemia with liraglutide compared to IDet + liraglutide in Trial 1842 was observed; see Table 16. One subject in the liraglutide arm reported a total of 25 minor hypoglycaemic episodes during the trial and was considered an outlier prior to database lock. The statistical analyses were prepared with and without this outlier. When the outlier was included in the above analyses, no differences were observed between the treatment groups.

In Trial 3948, only few episodes of nocturnal confirmed hypoglycaemia were reported with IDeg + liraglutide (7) compared to IDeg + IAsp (45), and the benefit of IDeg + liraglutide was also reflected in a statistically significant 86% lower estimated rate of nocturnal confirmed hypoglycaemic episodes (**Table 16**). In Trials 3697 and 3912, the rate of nocturnal confirmed hypoglycaemic episodes was similar between IDegLira and IDeg with no statistically significant differences (**Table 16**).

Table 16 Confirmed hypoglycaemia (rate per 100 PYE) – statistical analysis – FAS

Trial	Treatment ratio	N (Active / N Comp.)	Estimate [95% CI]
Confirmed			
NN1250-3948	(IDeg + Lira) / (IDeg + IAsp)	88 / 89	0.13 [0.08; 0.21]*
NN9068-3697	IDegLira / IDeg	833 /413	0.68 [0.53 ; 0.87]*
NN9068-3697	IDegLira / Lira	833/ 414	7.61 [5.17 ; 11.21]*
NN9068-3912	IDeglira / IDeg	199/199	0.66 [0.39 ; 1.13]
NN2211-1842	(IDet + Lira) / Lira (excl. outlier)	162/157	9.91 [2.11 ; 46.62]*
NN2211-1842	(IDet + Lira) / Lira (incl. outlier)	162/157	1.15 [0.34 ; 3.91]
Nocturnal confirmed			
NN1250-3948	(IDeg + Lira) / (IDeg + IAsp)	88 / 89	0.14 [0.05 ; 0.40]*
NN9068-3697	IDegLira / IDeg	833 /413	0.87 [0.52;1.46]
NN9068-3697	IDegLira / Lira	833/ 414	8.32 [3.10 ; 22.31]*
NN9068-3912	IDeglira / IDeg	199/199	0.81 [0.35 ; 1.90]
NN2211-1842	(IDet + Lira) / Lira	162/157	ND

*statistically significant difference; ND: not done

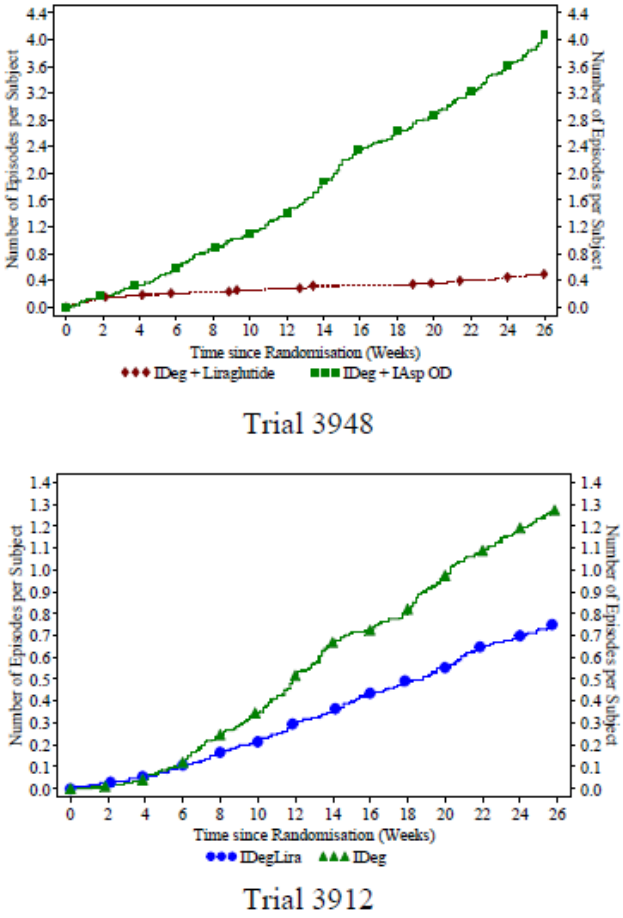
Mean cumulative graphs for confirmed hypoglycaemic episodes are shown for Trials 3948, 3697 and 3912 in

Figure **9** (evaluation not available for Trial 1842). For Trial 3948, the number of confirmed hypoglycaemic episodes per subject appeared similar with IDeg + liraglutide and IDeg + IAsp OD during the first two weeks of Trial 3948, while a lower number of episodes were observed with IDeg + liraglutide in the remaining part of the trial. A similar pattern was observed for episodes of nocturnal confirmed hypoglycaemia.

Similar results were obtained in Trials 3697 and 3912, i.e., the number of confirmed hypoglycaemic episodes was similar between treatment arms during the first weeks of treatment after which the rate was reduced with IDegLira relative to IDeg (

Figure 9).

Figure 9 Confirmed hypoglycaemic episodes – treatment emergent – mean cumulative function – SAS



Body weight

The results from Trial 3948 demonstrated that treatment with IDeg + liraglutide resulted in a weight reduction of 2.8 kg, while IDeg + IAsp OD was associated with a weight gain of about 1 kg; see Table 17. A decrease in weight was also observed with IDegLira compared to IDeg in the supportive Trials 3697 and 3912. In contrast, the observed reduction in body weight was less with IDegLira compared to liraglutide alone in Trial 3697 and with IDet + liraglutide compared to liraglutide in Trial 1842. All of these differences were statistically significant as shown in Table 18.

Table 17 Weight (kg) over time - FAS

(Week 26)	NN1250-3948		NN9068-3697			NN9068-3912		NN2211-1842#	
	IDeg + Lira Mean (SD)	IDeg + IAsp OD Mean (SD)	IDegLira Mean (SD)	IDeg Mean (SD)	Lira Mean (SD)	IDegLira Mean (SD)	IDeg Mean (SD)	IDet + Lira Mean (SD)	Lira Mean (SD)
Number of subjects	88	89	833	413	414	199	199	162	161
Baseline	95.4 (19.2)	91.3 (16.8)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	95.4 (19.4)	93.5 (20.0)	96.0 (20.9)	95.3 (21.1)
End of trial (LOCF)	92.5 (18.5)	92.2 (17.4)	86.7 (18.9)	89.0 (19.7)	84.4 (17.8)	92.7 (19.7)	93.5 (20.0)	95.7 (21.0)	94.2 (20.9)
Change§	-2.8 (3.8)	0.9 (2.5)	-0.5 (3.5)	1.6 (4.0)	-3.0 (3.5)	-2.7 (3.7)	0.0 (3.4)	-0.3 (3.3)	-1.1 (3.1)

Values are based on observed means using LOCF

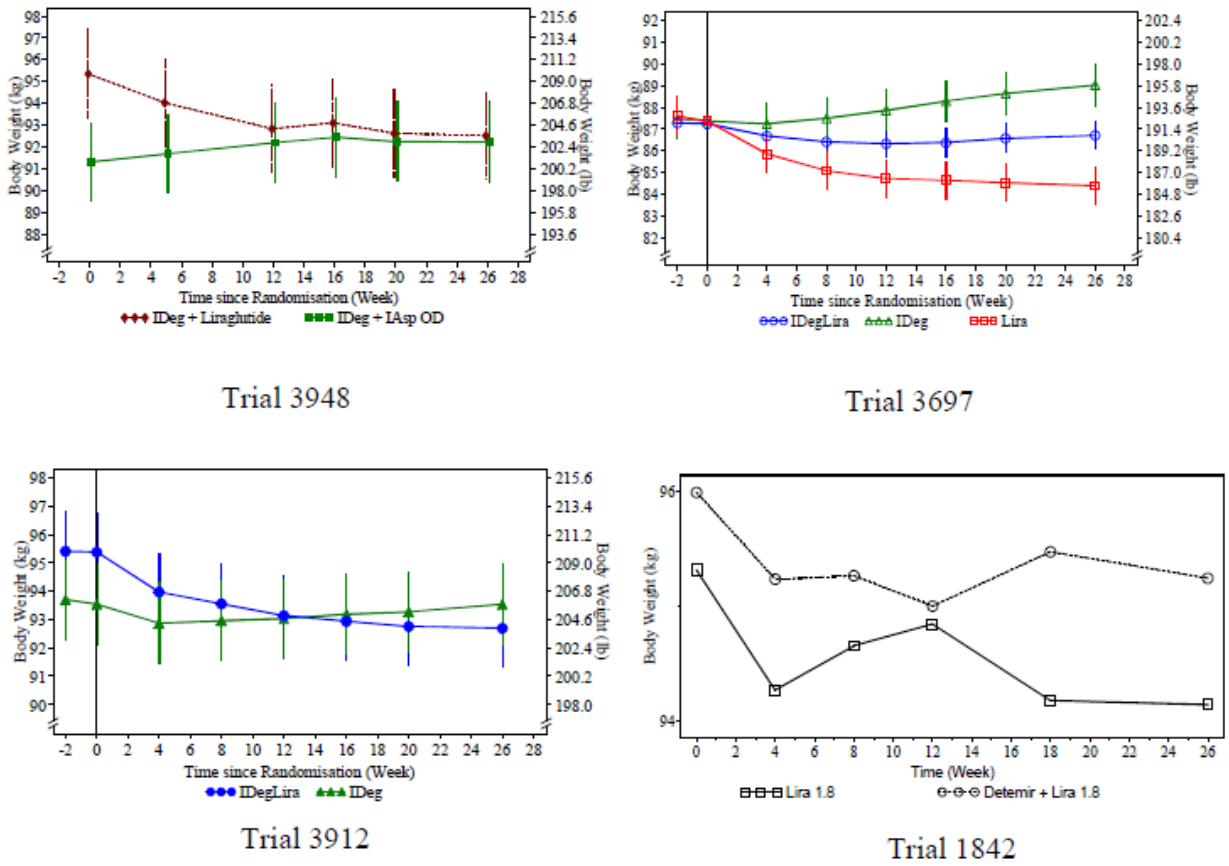
LOCF: last observation carried forward.

#Baseline is identical to time of randomisation following 12 week run-in period with optimisation of liraglutide.

§Change from baseline (randomisation) to end of treatment (Week 26) based on LOCF

Mean body weight at baseline differed between the treatment arms in Trials 3948 and 3912, while it was similar between treatment arms in Trials 3697 and 1842; see Figure 10. The mean body weight decreased with IDeg + liraglutide, IDegLira and IDet+ liraglutide in all four trials, with the reduction ranging between 0.3 and 2.8 kg. In Trial 3948, the main decrease in the IDeg + liraglutide group was observed during the initial part of the trial where the dose of liraglutide was uptitrated. In Trial 1842, a mean reduction in body weight of about 3.5 kg was observed during the 12-week run-in prior to randomisation.

Figure 10 Body weight – Mean plot – FAS



FAS; LOCF imputed data (except for Trial 1842). Error bars: ± standard error (mean)

Table 18 Change in weight (kg) – statistical analysis – FAS

Trial	Treatment contrast	N (Active)	N (Comp)	Estimate [95% CI]
NN1250-3948	(IDeg + Lira) – (IDeg + IAsp)	88	89	-3.75 [-4.70; -2.79]*
NN9068-3697	IDegLira - IDeg	833	413	-2.22 [-2.64; -1.80]*
NN9068-3697	IDegLira - Lira	833	414	2.44 [2.02; 2.86]*
NN9068-3912	IDeglira - IDeg	199	199	-2.51 [-3.21; -1.82]*
NN2211-1842	(IDet + Lira) - Lira	162	157	0.79 [0.08 ; 1.49]

Missing data is imputed using last observation carried forward (LOCF).

Dose of insulin and liraglutide

A 'treat-to-target' concept was applied in all four trials, adjusting the dose for each individual subject with the aim of achieving identical glycaemic targets between the treatment arms. When comparing the end-of trial doses in the four trials it should be kept in mind that subjects in Trials 3948 and 3912 were previously insulin-treated, while subjects in Trials 1842 and 3697 were insulin-naïve. This is reflected in both the starting doses and the doses at end of treatment.

IDeg + liraglutide combination, Trial 3948

Metformin dose

The mean daily dose of metformin was similar between the two treatment arms, being 2003 mg/day in the IDeg + liraglutide arm both at baseline and after 26 weeks of treatment compared to 2005 mg/day at both time points in the IDeg + IAsp group.

Insulin dose

After 26 weeks of treatment, the mean daily dose of IDeg was 62 U (0.65 U/kg) in the IDeg + liraglutide arm and 61 U (0.64 U/kg) in the IDeg + IAsp arm with a mean daily dose ratio close to one.

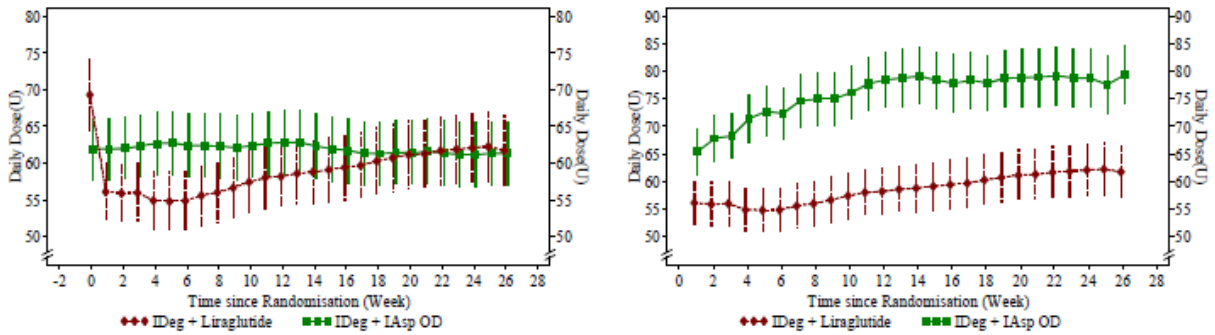
When considering changes from baseline, the mean daily dose of IDeg in the IDeg + liraglutide group after 26 weeks was lower than the dose at randomisation (0.62 versus 0.69 U/kg); see left panel of **Figure 11**. The mean daily dose of IDeg remained relatively stable over 26 weeks of treatment with IDeg + IAsp at around 60-62 units.

The mean daily dose of IAsp at week 1 was 4 units (0.05 U/kg), which increased gradually to a mean of 19 units (0.21 U/kg) at Week 26. The distribution of IAsp across meals remained relatively constant during the trial. At Week 25, 5.4% of subjects injected IAsp before breakfast, 47.3% before lunch, and 47.3% before the main evening meal.

While the mean daily total insulin dose increased slightly over time in the IDeg + liraglutide group, a more substantial increase in daily total insulin dose was observed in the IDeg + IAsp OD group. In the liraglutide arm only, the IDeg dose was reduced by 20% at randomisation and was not to be increased during the first 6 weeks of the trial, during which the dose of liraglutide was escalated.

This is as expected due to the use of both basal and bolus insulin in the IDeg + IAsp OD group (right panel of **Figure 11**). After 26 weeks of treatment, the mean total daily insulin dose was 62 units (0.65 U/kg) in the IDeg + liraglutide arm and 79 units (0.84 U/kg) in the IDeg + IAsp arm.

Figure 11 Daily IDeg dose (actual) left panel and total daily insulin dose (actual) right panel in units by treatment week – Mean plot – Safety analysis set



LOCF imputed data. Error bars: ± standard error (mean)

There was a good correspondence between the IDeg dose specified in the titration algorithm, the dose prescribed by the investigator, and the actual dose taken by the subject throughout the trial, which indicates close adherence to the titration algorithm in both treatment groups.

Liraglutide dose

In Trial 3948, liraglutide was initiated at a dose of 0.6 mg/day at randomisation and titrated to 1.2 mg/day or 1.8 mg/day during the first six weeks of the trial at the discretion of the investigator based on

pre-breakfast SMPG recordings. Approximately 97% of subjects remained on 1.2 mg/day until Week 6, at which point about half of the subjects taking 1.2 mg were transferred to 1.8 mg/day.

Liraglutide doses remained relatively stable from week 8 and onwards, and after 26 weeks of treatment, 2 (2.3%) subjects were taking liraglutide 0.6 mg/day, 28 (32.2%) were taking 1.2 mg/day, and 57 (65.5%) were taking 1.8 mg/day.

Supportive IDegLira Trials 3697 and 3912

In Trial 3697, the insulin dose increased steadily during the first part of the trial and levelled off after 8−12 weeks in both treatment groups. Hereafter, the insulin dose in the IDegLira treatment group remained relatively stable, whereas the insulin dose continued to increase in the IDeg treatment group. After 26 weeks, the mean daily insulin dose was 38 units with IDegLira and 53 units with IDeg. This corresponds to a 28% lower basal insulin dose with IDegLira compared to IDeg.

The actual daily dose of liraglutide was 1.4 mg/day in the IDegLira group and 1.8 mg/day in the liraglutide group after 26 weeks of treatment.

As expected, the dose distribution in Trial 3912 was skewed towards higher doses at baseline, reflecting the trial population of previous basal insulin users. After 26 weeks, the mean daily insulin dose was 45 units with both IDegLira and IDeg, consistent with the fact that the maximum dose of IDeg in the IDeg treatment arm was set to 50 units, i.e., equivalent to the maximum dose of the IDeg component with IDegLira. The mean daily dose of 45 units of IDegLira corresponds to 1.62 mg liraglutide.

Supportive liraglutide + IDet combination, Trial 1842

In Trial 1842, the mean prescribed daily dose of IDet after 26 weeks was 39.5 units in combination with 1.8 mg/day of liraglutide.

Comparison of results in sub-populations

IDeg + liraglutide combination, Trial 3948

The potential impact of age and duration of diabetes on the observed treatment differences in HbA1c, body weight, and confirmed hypoglycaemia were evaluated in Trial 3948. Overall only small differences were observed in Trial 3948 as described below.

Change in HbA1c was similar in subjects treated with IDeg + liraglutide irrespective of age and duration of diabetes. In subjects treated with IDeg + IAsp, subjects >65 years as well as subjects with a duration of diabetes ≥ 10 years appeared to have a slightly higher change in HbA1c compared to subjects aged 18-65 years and subjects with a duration of diabetes <10 years.

No differences were observed with respect to change in weight between subjects aged ≤ 65 and > 65 years or subjects with a duration of diabetes <10 years and ≥10 years.

The observed rate of confirmed hypoglycaemia was lower in adult subjects aged 18-65 years than in elderly subjects > 65 years (66.8 vs. 157.5 episodes per 100 PYE), and this pattern was observed in both treatment arms. In contrast, no difference was observed in the rate of confirmed hypoglycaemia between subjects with a diabetes duration < 10 years and ≥ 10 years. The small number of nocturnal confirmed hypoglycaemic episodes did not allow a relevant comparison in these sub-populations.

Supportive IDegLira Trials 3697 and 3912

The efficacy of IDegLira in sub-populations was assessed through statistical analysis of interaction between treatment effect (measured as change from baseline in HbA1c) and a large number of intrinsic/extrinsic factors. The analyses were based on individual data from each of the two therapeutic confirmatory trials. No consistent and clinically relevant interactions were demonstrated between these

factors and HbA1c. Specifically, no treatment-by-age or treatment by disease duration interactions was observed for IDegLira in relation to HbA1c.

Furthermore, no such interactions were observed with respect to confirmed hypoglycaemia. No interaction analyses were made in relation to body weight.

Supportive liraglutide + IDet combination, Trial 1842

The impact of age and diabetes duration on these parameters was not investigated in Trial 1842.

Analysis of results for dosing

The doses of IDeg, IAsp and liraglutide used across the clinical trials were in alignment with the dosing information in the SmPCs for the marketed products. All trials used a treat-to-target concept.

Starting dose of IDeg when added to liraglutide

According to the approved SmPC for Tresiba, subjects with T2DM should initiate treatment with IDeg at a dose of 10 units per day followed by individual dosage adjustments. A starting dose of 10 units per day was also used in Trial 3697 with IDegLira and in Trial 1842 with IDet.

So far, no clinical trial has been performed to specifically investigate addition of IDeg to liraglutide, but there is no reason to believe that addition of IDeg to liraglutide should be less efficacious or safe than addition of IDet as investigated in Trial 1842.

Dose adjustment of IDeg when adding liraglutide

In Trial 3948, the dose of IDeg was reduced by 20% at initiation of liraglutide. In this trial, it was not recommended to increase the IDeg dose during the first 6 weeks after randomisation where the dose of liraglutide was escalated, as it is common medical practice only to change one product dose at any given time.

Initiation and dose escalation of liraglutide

Treatment with liraglutide may be associated with gastrointestinal symptoms. These side effects are mostly transient and can be limited if liraglutide is initiated at the lowest dose of 0.6 mg/day according to the approved label for Victoza®. After at least one week of treatment, the dose of liraglutide should be increased to 1.2 mg/day, which is the approved minimum effective dose. Following at least one week of treatment, the dose may be further escalated to 1.8 mg/day if needed.

In Trial 3948, subjects were only to increase the dose to 1.8 mg/day if mean pre-breakfast SMPG values were $\geq$ 5.0 mmol/L (90 mg/dL).

In Trial 1842, the dose of liraglutide was titrated from 0.6 mg/day to 1.8 mg/day according to the approved label during a 12-week run-in phase. During the trial the liraglutide dose was maintained at 1.8 mg/day in all subjects.

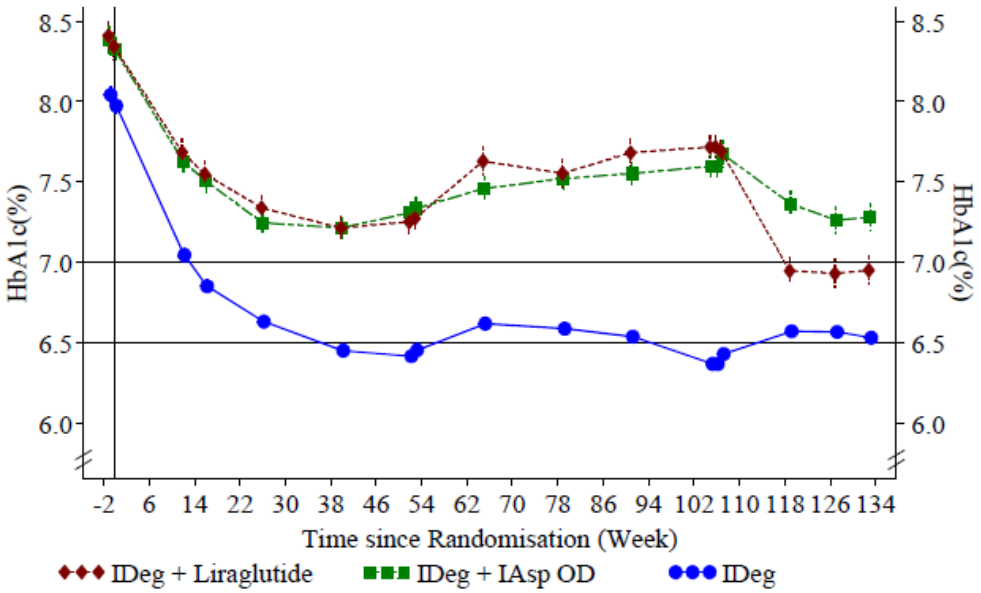
Persistence of efficacy and/or tolerance effects

In Trial 3948, HbA1c decreased within the initial 12 weeks and remained stable thereafter; see Figure 8. The IDeg dose was reduced by 20% in the IDeg + liraglutide arm at randomisation and was only to be increased after 6 weeks of treatment. This was reflected in an increase in the IDeg dose from Week 6 to around Week 20, after which the dose stabilised and were identical to the IDeg dose used in the IDeg+IAsp arm after 26 weeks; Figure 11.

A retrospective plot (Figure 12) was made for subjects in the three treatment arms of Trial 3948, showing HbA1c development over time during the preceding Trials 3579 and 3643 (weeks 0-52 and 52-104, respectively) and during Trial 3948 (weeks 104-134). The total decrease in HbA1c over the total period of

134 weeks was approximately -1.4%-points for subjects randomised to IDeg+ liraglutide in Trial 3948 and -1.04%-points for subjects randomised to IDeg + IAsp. The results show that additional improvements in HbA1c can be gained by adding liraglutide to IDeg also when using a sequential treatment concept.

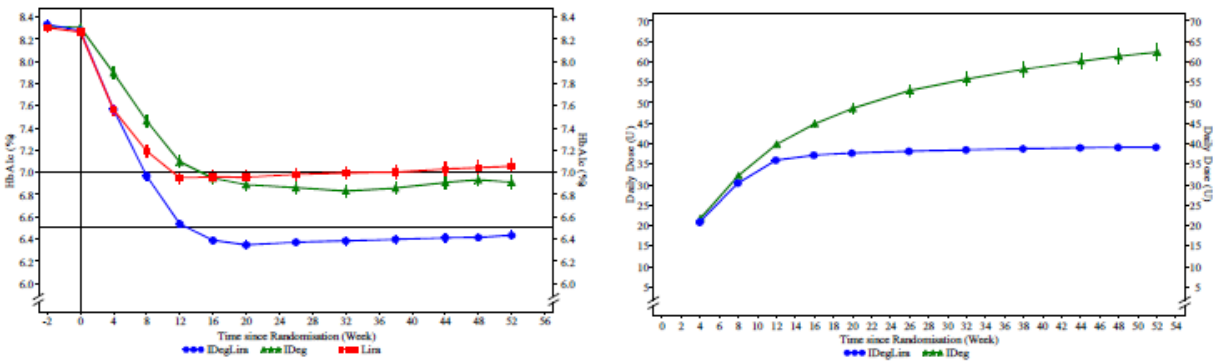
Figure 12 HbA1c (%) by Treatment Week – Mean Plot – Safety Analysis Set and Non-randomised Analysis Set



LOCF imputed data. Error bars ± standard error (mean)

Trial 3697 including the 26-week extension period provides evidence for persistence of efficacy during extended treatment with IDeg and liraglutide, both administered as IDegLira. Sustained good glycaemic control as reflected by HbA1c was demonstrated with IDegLira as shown in Figure 13.

Figure 13 HbA1c (%) by treatment week – FAS (left) and Actual daily insulin dose (U) by treatment week – SAS (right) including the 26-week extension period – mean plot - Trial 3697



FAS, LOCF imputed data. Error bars: standard error (mean)

Hence, the improvement in overall glycaemic control relative to comparator treatment after the main 26-week trial period was maintained during extended exposure, with mean HbA1c well below the target level of 7%; see Figure 13. This was achieved with stable doses of insulin (mean of 38 U) and liraglutide (1.4 mg/day); see Figure 13.

Similarly for the remaining key secondary endpoints of the trial, the treatment benefit of IDegLira relative to comparators was maintained during extended exposure for up to 52 weeks. Specifically, the estimated

rate ratio of confirmed hypoglycaemia for IDegLira relative to IDeg was 0.63[0.50; 0.79]95% CI for the full 52-week trial period versus 0.68 [0.53; 0.87]95% CI for the 26-week period. Results for the estimated treatment contrast (IDegLira – IDeg) for change from baseline in body weight was -2.80 kg [-3.34;-2.27]95% CI for the full 52-week period versus -2.22 kg [-2.64 ; -1.80]95% CI for the 26-week period.

In Trial 1842, the observed mean HbA1c also remained stable with liraglutide + IDet at around 7.2%up to 52 weeks of treatment. The mean prescribed dose of IDet was also fairly stable over time and was 39.5 U at Week 26 and 42 U at Week 52.

Antibodies

Insulin antibodies

While antibodies were not measured in Trial 3948, antibody development has been thoroughly investigated as part of the IDeg development programme. The immunogenic response to treatment with IDeg was low and did not result in reduced efficacy or a need for increased doses to maintain glycaemic control.

In Trials 3697 and 3912, there was no clinically relevant IDeg-specific antibody development during treatment with IDeg or IDegLira for up to 52 weeks (Trial 3697) or 26 weeks (Trial 3912).

Only very few subjects in either treatment arm (IDeg and IDegLira) developed antibodies cross-reacting with human insulin. There was no correlation in either the IDegLira or the IDeg group between antibodies cross-reacting to human insulin and HbA1c, change from baseline in HbA1c or total insulin dose at Week 52.

Antibody development has been observed with the use of IDet. However, this does not appear to have any impact on glycaemic control. In Trial 1842, there was no correlation between change in IDet-specific antibody titres and change in HbA1c for subjects treated with IDet + liraglutide, and no correlation was observed for cross-reacting antibodies versus change in HbA1c.

Liraglutide antibodies

Clinical studies have shown that less than 10% of subjects treated with liraglutide develop antibodies, and antibody formation has not been associated with reduced efficacy of liraglutide.

Anti-liraglutide antibody development was very limited in Trials 3697 and 3912 (< 3%), and none of these subjects developed antibodies with cross-reactivity towards native GLP-1. A positive result for in vitro neutralising antibodies was found in about 0.5% of the subjects. The effect on HbA1c did not appear to be adversely affected in any of the anti-liraglutide antibody positive subjects.

In Trial 1842, 4 (3.7%) subjects treated with IDet + liraglutide and 2 (2.1%) subjects treated with liraglutide were positive for liraglutide antibodies after 52 weeks of treatment. No correlation between presence of liraglutide antibodies and change in HbA1c was observed. Furthermore, there was no correlation between change in liraglutide antibody titres and change in HbA1c in either of the two randomised treatment groups.

2.3.4. Discussion

Design and conduct of clinical studies

In support of the current application, the MAH has submitted one pivotal study (3948) and three supportive studies (3697, 3912 and 1842). Trials 3697 and 3912 are further the two pivotal studies in the MAA for IDegLira. Trial 1842, where the combination of IDet and liraglutide was investigated, was

part of the liraglutide phase 3b programme. This trial has been included as supportive data, as it investigated the combined use of basal insulin (IDet) and liraglutide treatment, in the reverse add-on sequence (IDet added to Lira) compared to Trial 3948 (Lira added to IDeg). The study is considered to mainly contribute with proof-of-concept and safety data for the combination of IDeg and GLP-1 analogue. Trial 3948 was also included in the MAA for IDegLira as supportive data.

Data from a clinical phase 1 trial showed no clinically relevant differences in pharmacokinetic properties of IDeg or liraglutide when administered as IDegLira (100 units/3.6 mg per mL) or as free IDeg and liraglutide mono-components which justifies the use of studies 3697 and 3912 as supportive data in the current application.

The pivotal study 3948 was generally of adequate design and enrolled patients with T2DM who were in need of intensified treatment, i.e. HbA1c > 7 in spite of treatment with IDeg and metformin in the context of a two-year treat-to-target study. The inclusion and exclusion criteria were adequate to recruit T2DM patients that would be expected to benefit from intensified treatment. Subjects with significant concomitant illnesses were excluded. The required pre-trial oral antidiabetic (OAD) dose levels were adequate in order to ensure that inadequate glycaemic control at baseline was not caused by suboptimal OAD dosing.

The choice of comparator (insulin aspart, IAsp) per se is acceptable since the addition of bolus insulin is an adequate measure if intensified treatment is needed. The MAH has, however, chosen a OD insulin aspart regimen in order to add the same number of injections in both groups. This may not be optimal since dose escalation can only be made with one meal of the day thereby limiting the possibility to exhaust this treatment option. Dose increases will be hindered by the occurrence of (post-prandial) hypoglycaemias that could have been avoided by instead adding doses of IAsp to other meals. The comparator is acceptable when it comes to a scientific comparison of the outcomes; however, a OD bolus insulin regimen may not truly reflect how bolus insulin would be used in the clinic. The justification for performing an open label study is accepted by the CHMP.

Trial 3697 studied the combination of IDeg and liraglutide compared to the two mono-components in patients who were naïve to both insulin and GLP-1 analogues. Due to the fixed ratio between the two mono-components in IDegLira, the liraglutide doses at start of treatment are lower than when used in the free combination. The study design is considered acceptable by the CHMP.

Trial 3912 studied the combination of IDeg and liraglutide compared to IDeg in patients on a combination of basal insulin and a metformin based OAD therapy. The study was designed to investigate the contribution of liraglutide to the effect of the combination; therefore the IDeg dose was not to exceed 50 units. Since the patients included were already on basal insulin, a higher dose of IDegLira was given at study start resulting in a liraglutide dose comparable to the starting dose in study 3948. The study design is considered acceptable by the CHMP.

Trial 1842 studied the efficacy and safety of adding basal insulin IDet to liraglutide plus metformin compared to liraglutide and metformin. The overall study design was adequate. Treatments were administered open-label and the justification is accepted by the CHMP.

All studies applied withdrawal criteria to ensure patient safety. Rescue medications were not allowed in any of the studies. The objectives of the studies were adequate. The study endpoints were adequate and well established. Adequate statistical methods were applied.

In study 3948, hypoglycaemia was included as a secondary efficacy endpoint. Throughout the studies, a cut-off of <3.1 mmol/L was used for the definition of confirmed hypoglycaemia. This is not entirely in line with the current EMA Guideline on the development of medicinal products for the treatment of diabetes (CPMP/EWP/1080/00 Rev.1) where the ADA (American Diabetes Association) criteria are preferred, however as the same criteria was applied across the studies the definition used is

considered acceptable.

Efficacy data and additional analyses

Withdrawal rates were generally low across the four studies. In study 3948, more patients dropped-out due to adverse events in the IDeg+Lira group compared to IDeg + IAsp but overall the withdrawal rates were balanced. In study 3697 a higher drop-out rate due to AEs was observed in the study arm treated with liraglutide. In study 1842 a higher withdrawal rate was observed in the liraglutide treated group, mainly related to lack of efficacy.

The study populations in the pivotal study were not entirely balanced with regards to gender distribution and proportion of patients with diabetes duration < 10 years/> 10 years. This may be due to the small sample size. However, other baseline characteristics did not differ between groups. The study populations in the supportive studies were generally well balanced.

Differences in baseline characteristics observed between studies can be explained by the different populations included, i.e. insulin naïve patients or patients with multiple treatments at inclusion.

In study 3948, the addition of liraglutide resulted in a clinically relevant reduction of HbA1c of - 0.74 % compared to -0.39 % in the IDeg + IAsp arm. Superiority for liraglutide when added to IDeg compared to IAsp was shown with a statistically significant difference in HbA1c reduction of -0.32 % (95 % CI; -0.53, -0.12). Although the primary endpoint was met, the once daily dosing of the comparator IAsp is considered suboptimal and thus the difference in treatment effect between the combination IDeg and liraglutide versus IDeg and bolus insulin may be somewhat overestimated. The data support the addition of GLP-1 analogues to basal insulin as an efficient treatment option. The proportion of patients achieving a HbA1c < 7 % was higher for the combination of IDeg and liraglutide (58 %) when compared to IDeg and bolus insulin (45 %) although the difference was not statistically significant. The difference increased when hypoglycaemias and weight gain was included in the analysis. Furthermore the treatment effect on HbA1c is achieved in conjunction with a low risk of hypoglycaemias. A decrease in body weight (-2.8 kg) was also observed in the IDeg + liraglutide arm.

These observations were supported by the findings from studies 3697, 3912 and 1842, where comparable reductions in HbA1c in the order of 0.5-1 % were observed with combination therapy compared to monotherapy with either basal insulin or liraglutide. Differences in effect size between studies can be explained by the populations included in the studies and restrictions laid on the possibility to titrate the basal insulin or liraglutide. Responder rates were higher for the combination of IDeg and liraglutide when compared to either IDeg or liraglutide. The differences in responder rates were larger in the supportive studies where the combination was compared to each of the components (basal insulin or liraglutide) than in the pivotal study. In addition, hypoglycaemia rates were consistently lower with the combination therapy compared to monotherapy with basal insulin. Reduction in body weight was also consistently shown in the combination therapy arms, although not as large as in monotherapy with liraglutide.

The effect on FPG varied across the studies due to the differences in previous treatment and diabetes history at inclusion. The data indicate that basal insulin has the most prominent effect on FPG whereas liraglutide contributes somewhat less.

In the pivotal study, no difference in prandial increments or in mean postprandial glucose levels was observed. In the supportive studies, a significant effect of liraglutide on these parameters was shown.

When compared to liraglutide alone, the weight reduction is less prominent with the combination of liraglutide and insulin, whereas the combination results in relevant weight reductions compared to insulin based therapies.

The lowest hypoglycaemic rates were observed in the treatment arms where only liraglutide was given.

When liraglutide was given in combination with basal insulin the hypoglycaemia rates increased but were still lower than observed in treatment arms with basal or bolus/basal insulin. The difference was most prominent in the pivotal study. Even though there is overall no indication of an increased risk of hypoglycaemia with IDeg+liraglutide compared to IDeg, there were 3 hypoglycaemia SAEs reported in trial 3697(2) and 3912(1). Analysis of these cases did not show any common features in terms of medication errors, subject demographics, treatment duration or other parameters that could potentially lead to severe hypoglycaemia.

Subgroup analyses were performed, however, due to the size of the studies these analyses have to be interpreted with caution. The only relevant finding was a higher rate of confirmed hypoglycaemias in older subjects (> 65 years) in the pivotal study.

With study 3948, 2.5 year data for patients treated with IDeg is provided. When retrospectively regrouped in patients either being responders (HbA1c < 7) or non-responders (HbA1c > 7) at two years, it can be seen that the subgroup not able to achieve target starts to deteriorate after about one year (also in this controlled clinical trial setting) and that improvement of HbA1c is possible when adding either GLP-1 analogues or bolus insulin.

Data from study 3967 show a maintained effect with stable doses of IDegLira for up to one year, whereas insulin doses continued to slowly increase in order to maintain HbA1c.

The development of antibodies with the respective mono-components has been thoroughly assessed within the MAAs of the respective products. Antibody development was not assessed in the pivotal study. This is acceptable. There appears to be no increase in liraglutide antibody development when used concomitantly with IDeg.

When liraglutide was given in combination with IDeg, the insulin doses were generally lower than in the IDeg treated arms at the end of trial, while achieving lower HbA1c. In the pivotal study, the insulin dose was reduced by 20 % as liraglutide therapy was started and the insulin dose was then again uptitrated. The insulin dose, however, did not increase to the basal level. In spite of the differences in treatment regimens (free combination vs. combination) the liraglutide doses were comparable in all studies at end of trial.

The data from the pivotal and supportive studies provide strong evidence for the proposed combination therapy, when a GLP-1 analogue is added to IDeg. Trial 1842 lend support to the proposed posology when adding basal insulin in patients already on liraglutide. In this study, basal insulin IDet was administered according to SmPC instructions when introduced in insulin naïve patients already on liraglutide treatment. Although this study was performed with at different basal insulin, the characteristics of the two insulins are deemed sufficiently similar to allow extrapolation of these data from IDet to IDeg.

2.4. Clinical Safety aspects

2.4.1. Introduction

The submitted package included the insulin degludec (IDeg) phase 3b Trial 3948, supportive data from the combination product insulin degludec/liraglutide (IDegLira) phase 3a Trials 3697 and 3912 as well as supportive data from the concomitant treatment of liraglutide and insulin determir (IDet) in phase 3b Trial 1842. A tabular overview of the trials is presented in

Table **1**.

In addition to the above trial data, blinded safety data from 5 ongoing Novo Nordisk trials combining basal insulin with GLP-1 receptor agonists (Table 19) are included.

Table 19 Overview of ongoing clinical trials

Trial	Trial description and treatment	Subject Population	Antidiabetic therapy at screening	Duration of treatment period (weeks)/ FPFV (date)	Rando-mised	No. subjects (safety analysis set)
Ongoing trial – IDeg						
NN1250-3944	IDeg vs. Placebo (double-blind) *(+ Lira + Met)*	T2DM, Insulin naïve	Met or Met + [SU ± α-GI ± DPP-4 inhib.]	26[a]/ 01 Oct 2012	1:1	Ongoing
Ongoing trials - Combined use of liraglutide and basal insulin products						
NN2211-3917	Lira vs. Placebo (double-blind) *(+ IDet or IGlar ± Met)*	T2DM, insulin treated	Basal insulin ± Met	26/ 10 Sep 2012	1:1	Ongoing
NN2211-3925	Lira vs. Placebo (double-blind) *(+ pretrial insulin therapy (basal, pre-mixed or basal-bolus insulin regimen))*	T2DM, insulin treated	basal, premixed or basal-bolus regimen	26/ 05 Apr 2012	1:1	Ongoing
Ongoing trials – IDegLira						
NN9068-3851	IDegLira vs. GLP-1 RA[b] (open-label) *(+ Met)*	T2DM, Insulin-naïve	GLP-1 RA[c] + Met	26/ 29 Aug 2012	2:1	Ongoing
NN9068-3951	IDegLira vs. placebo (double-blinded) *(+ SU ± Met)*	T2DM GLP-1 RA and insulin-naïve	SU ± Met	26/ 29 Aug 2012	2:1	Ongoing

[a] The trial included a 15-week run-in period on liraglutide, followed by randomised treatment

[b] Pretrial GLP-1 RAs (Trial 3851).

[c] In the IDegLira group, pretrial GLP-1 RAs were discontinued at randomisation (Trial 3851).

Abbreviations: α-GI = alpha-glucosidase inhibitor; DPP-4 inhib. = Dipeptidyl peptidase-4 inhibitors; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDeg = insulin degludec; IDegLira = insulin degludec/liraglutide; IDet = insulin detemir; IGlar = insulin glargine; Lira = liraglutide; met = metformin; SU = sulphonylurea; TW = twice weekly;T2DM = type 2 diabetes mellitus; U = unit; FPFV: first patient first visit

2.4.2. Methods – analysis of data submitted

Data from Trial NN9068-3632 (a PK phase 1 trial) showed no clinically relevant differences in pharmacokinetic properties of IDeg or liraglutide when administered as IDegLira (100 units/3.6 mg per mL) or as free IDeg and liraglutide mono-components. This substantiates the use of the data from the IDegLira trials 3697 and 3912 as supportive data. Because of the inherent differences in trial design, trial populations and objectives between these two IDegLira trials compared to the IDeg Trial 3948, no pooling of safety data has been performed across the IDeg and IDegLira trials.

Liraglutide Trial 1842 investigated the efficacy and safety of adding basal insulin (insulin detemir; IDet) treatment to liraglutide treatment. This trial has been included as supportive data, as it investigated the combined use of basal insulin (IDet) and liraglutide treatment, in the reverse add-on sequence (IDet added to Lira) compared to Trial 3948 (Lira added to IDeg).

Key and supportive trials

Safety data from the 4 trials included in this report are primarily presented trial-by-trial, however for selected events of special interest the 2 IDegLira Trials 3697 and 3912 are pooled. The safety evaluation of Trials 3697 and 1842 is based on the full trial period of 52 weeks (26 weeks main trial period + 26 weeks extension period). These data are only denoted 'ext' in the cross-references and in the table and figure captions.

Definitions of safety populations and cut-off dates

This summary is based on 4 trials for which final clinical trial reports (CTRs) exist; hence, no further cut-offs for data inclusion was specified in this regard. The cut-off date for the serious adverse events (SAEs) from ongoing trials was 15 January 2013.

Analysis sets

Two analysis sets will be used for the safety evaluation, as defined below:

- Safety analysis set (SAS): includes subjects receiving at least one dose of the investigational medicinal product or comparators. Subjects in the safety analysis set will contribute to the evaluation 'as treated'.
- Full analysis set (FAS): all randomised 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". In Trial 1842 only subjects with at least one efficacy value after the randomisation visit were included in the FAS.

The descriptive safety data are based on the safety analysis set, although subject disposition and analysis of all withdrawals is based on FAS. The statistical analyses of hypoglycaemia are based on the full analysis set and are discussed in the Efficacy section of this report.

Overall extent of exposure

Exposure

Completed trials

IDeg + liraglutide, Trial 3948

The overall extent of exposure was similar in the IDeg + liraglutide group and in the IDeg + IAsp OD group (40.04 vs. 40.50 exposure years; SAS), consistent with the 1:1 randomisation ratio in the trial (

Table **20**), and the majority of all randomised subjects (approximately 87%) were exposed for 25–28 weeks. More male subjects (114) than female subjects (59) were randomised; accordingly, greater exposure to trial products occurred in male than in female subjects in both randomised treatment groups. The exposure by race and ethnicity was approximately equal in the two treatment groups; the majority of exposure occurred in White and in non-Hispanic subjects. The proportion of adult (18-65 years) and elderly (>65 years) subjects exposed to the trial products was similar between the randomised groups. In the IDeg + liraglutide group more subjects had a duration of diabetes of more than 10 years (55) than

less than 10 years (32); in the IDeg +IAsp treatment group the number of subjects with a duration of diabetes of more than 10 years and less than 10 years was similar (40 and 46, respectively). The exposure to trial products in subjects with a duration of diabetes of more or less than 10 years reflected this. The proportion of subjects with a BMI from 25 kg/m2 to >35 kg/m2 was similar between treatment groups, and the exposure of subjects with BMI ranging from 25 to >35 kg/m2 was evenly distributed.

Table 20 Exposure – descriptive statistics – Trial 3948 – SAS

	IDeg + Liraglutide	IDeg + IAsp OD	Total
Number of Subjects	87	86	173
Total Exposure, yrs	40.04	40.50	80.54
Exposure (yrs)			
N	87	86	173
Mean (SD)	0.46 (0.11)	0.47 (0.09)	0.47 (0.10)
Median	0.50	0.50	0.50
Min ; Max	0.02 ; 0.52	0.01 ; 0.54	0.01 ; 0.54

N = Number of Subjects, SD = Standard Deviation

Supportive Trials 3697, 3912 and 1842

In the 2 IDegLira Trials 3697 and 3912, 1024 subjects were exposed to IDegLira, 611 subjects were exposed to IDeg and 412 subjects were exposed to liraglutide (Table 21). The number of subjects exposed as well as the patient years of exposure (PYE) reflected the duration as well as the randomisation in the individual trials. Table 21 shows both the exposure in the main part (first 26 weeks) and the main + extension part (52 weeks) of Trial 3697 (randomisation 2:1:1), as well as exposure in Trial 3912 (26 weeks, randomisation 1:1).

The total exposure in PYE to IDegLira was almost 2 times greater than the exposure to IDeg and approximately 2.5 times greater than the exposure to liraglutide (liraglutide was only used as comparator in Trial 3697).

Table 21 Exposure by trial – Trials 3697 and 3912 - SAS

	IDegLira N (PYE)	IDeg N (PYE)	Lira N (PYE)	Total N (PYE)
Therapeutic Confirmatory Trials				
NN9068-3697	825 (387.9)	412 (193.2)	412 (186.1)	1649 (767.3)
NN9068-3697-main-ext	825 (705.6)	412 (350.1)	412 (334.3)	1649 (1390)
NN9068-3912	199 (91.9)	199 (90.0)		398 (181.9)
Total	1024 (797.5)	611 (440.1)	412 (334.3)	2047 (1572)

Data is based on trials NN9068-3697, NN9068-3697-ext and NN9068-3912.

Total is based on trials NN9068-3697-ext and NN9068-3912.

N = number of subjects; PYE = patient years of exposure (1 PYE = 365.25 days).

A total of 914 subjects (89.3%) were exposed to IDegLira for at least 6 months (both Trials 3697 and 3912) and 623 subjects (60.8%) were exposed to IDegLira for at least 12 months (Trial 3697 only). The proportion of subjects exposed to trial products was similar across the 3 treatment groups up to 6

months, where after the proportion of subjects decreased and differed across the groups due to the lack of exposure from Trial 3912 after 6 months.

In Trial 1842, 162 subjects were exposed to IDet + liraglutide and 142 subjects exposed to liraglutide in the randomised treatment groups (Table 22). The total exposure in PYE was 144.5 PYE in the IDet + liraglutide group and 143.6 PYE to liraglutide in the randomised liraglutide treatment group. All subjects treated with IDet also received liraglutide 1.8 mg and metformin.

For the 2 randomised treatment groups, the mean duration of treatment was 364 days for liraglutide + IDet and 369 days for liraglutide (Table 22).

Table 22 Summary of Exposure - All exposed subjects after randomisation – Trial 1842 ext

	Lira 1.8	Detemir + Lira 1.8
Safety Analysis Set	142	163
Duration of Liraglutide Treatment (days)		
N	142	163
Mean (SD)	369.3 (124.1)	411.3 (93.1)
Median	448.0	449.0
Min ; Max	92.0 ; 489.0	89.0 ; 495.0
Total lira exposure in subject years **	143.6	183.6
Duration of Detemir Treatment (days)		
N		162
Mean (SD)		325.7 (90.0))
Median		364.0
Min ; Max		28.0 ; 406.0
Total detemir exposure in subject years**		144.5

** One patient year equals 365.25 days

2.4.3. Results

Adverse events

Summary of adverse events

The proportion of subjects with AEs with the concomitant treatment of IDeg and liraglutide was higher than with the concomitant treatment of IDeg and IAsp, but not different from treatment with liraglutide. The combined use of IDeg with liraglutide in Trial 3948 led to a higher rate of adverse events compared to IDeg used with IAsp. This was mainly caused by more gastrointestinal AEs (nausea, diarrhoea, vomiting) as expected from liraglutide and was also observed in the IDegLira Trials 3697 and 3912 and in Trial 1842 (IDet + liraglutide).

No new types of adverse events were reported for the combined use of IDeg + liraglutide. There was no difference in seriousness and severity of AEs between the different groups (

Table **23**).

Table 23 Treatment-emergent adverse events across trials

	NN1250-3948		NN9068-3697ext			NN9068-3912		NN2211-1842ext	
	IDeg + Lira	IDeg + IAsp OD	IDegLira	IDeg	Lira	IDegLira	IDeg	IDet + Lira	Lira
Safety analysis set, N	87	86	825	412	412	199	199	163	159
Adverse events									
N (%) E	61 (70.1) 207	47 (54.7) 111	587 (71.2) 2878	291 (70.6) 1342	318 (77.2) 1696	115 (57.8) 366	122 (61.3) 320	124 (78.0) 716	132 (81.0) 845
Rate, events/100 PYE	517	274	408	383	507	398	356	-	-
Severe adverse events									
N (%) E	5 (5.7) 6	4 (4.7) 4	42 (5.1) 59	19 (4.6) 27	30 (7.3) 43	5 (2.5) 7	7 (3.5) 8	14 (8.8) 19	17 (10.4) 19
Rate, events/100 PYE	15	10	8	8	13	8	9	-	-
Serious adverse events									
N (%) E	4 (4.6) 4	5 (5.8) 5	38 (4.6) 47	22 (5.3) 31	24 (5.8) 31	7 (3.5) 11	11 (5.5) 13	11 (6.9) 16	17 (10.4) 21
Rate, events/100 PYE	10	12	7	9	9	12	14	-	-
Adverse events leading to withdrawal									
N (%)	5 (5.7)	1 (1.1)	16 (1.9)	9 (2.2)	26 (6.3)	1 (0.5)	3 (1.5)	7 (4.3)	9 (5.6)
Deaths, N	0	0	2#	0	0	0	0	0	1*

N: number of subjects; PYE: patient years of exposure; # In addition, one non treatment-emergent death was reported in the IDegLira group * One death was additionally reported in the non-randomised treatment group (liraglutide).

Analysis of adverse events

The safety evaluation focuses on the data from the 2 randomised groups of Trial 3948 and is supported by the safety data from Trials 3697, 3912 and the 2 randomised groups of Trial 1842. Due to differences in trial drug, trial designs and regimens, the AE data from the trials have not been pooled across IMPs, except for the selected AEs of interest where data have been pooled for the two IDegLira trials.

Common adverse events

IDeg + liraglutide, Trial 3948

In total, 62.4% of all subjects reported 318 events. The observed rate of AEs was 517.0 events per 100 PYE in the IDeg + liraglutide group and 274.1 events per 100 PYE in the IDeg + IAsp group (

Table **23**).

The majority of AEs were mild or moderate in severity and were assessed as unlikely related to IDeg, liraglutide, IAsp or the device by the investigator. Approximately 29% of AEs in the IDeg + liraglutide group were considered possibly or probably related to liraglutide by the investigator. The majority of AEs had recovered by the end of the trial.

The most frequently reported AEs in the IDeg + liraglutide treatment group were nausea (reported by 20.7% of the subjects), diarrhoea (10.3% of the subjects) and nasopharyngitis (10.3% of the subjects). The most frequently reported AE in the IDeg + IAsp treatment group was nasopharyngitis, reported by 12.8% of the subjects (Table 24). The observed rate of AEs was generally similar between the IDeg + liraglutide and IDeg + IAsp treatment groups for most SOCs and PTs, apart from more gastrointestinal disorders with IDeg + liraglutide. Differences in rates were also seen in the following system organ classes (SOCs) as presented below; however, the differences in rates should be interpreted with caution given the low number of events:

- *Musculoskeletal and connective tissue disorders:* The observed rate of AEs was 57 events per 100 PYE in the IDeg + liraglutide group compared with 32 events per 100 PYE in the IDeg + IAsp treatment group (23 versus 13 events, respectively). The most common AEs within this SOC were 'Pain in extremity' (5 and 1 event reported in IDeg + liraglutide and IDeg + IAsp groups, respectively).
- *General disorders*: The observed rate of AEs was 27 events per 100 PYE in the IDeg + liraglutide group compared with 7 events per 100 PYE in the IDeg + IAsp treatment group (11 versus 3 events, respectively). Injection site reactions were reported in the IDeg + liraglutide group (2 events), both were possibly/probably related to liraglutide, whereas no injection site reactions were reported in the IDeg + IAsp group.
- *Skin and subcutaneous tissue disorders:* The observed rate of AEs was 25 events per 100 PYE in the IDeg + liraglutide group compared with 7 events per 100 PYE in the IDeg + IAsp treatment group (10 versus 3 events, respectively). Only 1–2 events of the same type were reported in each group, thus no clustering was seen within any type of AEs in this SOC.
- *Investigations*: The observed rate of AEs was 40 events per 100 PYE in the IDeg + liraglutide group (16 events) compared with 2 events per 100 PYE in the IDeg + IAsp treatment group (1 event). This difference is mainly due to a higher number of reports of increased lipase and amylase in the IDeg + liraglutide group (7 and 4 reports respectively)

Table 24 Adverse events by system organ class and preferred term – most frequent [>=5%] – treatment-emergent – summary – Trial 3948 – SAS

	IDeg + Liraglutide				IDeg + IAsp OD				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	87				86				173			
Events	37	(42.5)	65	162	13	(15.1)	16	40	50	(28.9)	81	101
Gastrointestinal disorders												
Diarrhoea	9	(10.3)	12	30	1	(1.2)	2	5	10	(5.8)	14	17
Nausea	18	(20.7)	25	62	1	(1.2)	1	2	19	(11.0)	26	32
Vomiting	5	(5.7)	5	12					5	(2.9)	5	6
Infections and infestations												
Nasopharyngitis	9	(10.3)	11	27	11	(12.8)	12	30	20	(11.6)	23	29
Investigations												
Lipase increased	6	(6.9)	7	17					6	(3.5)	7	9
Musculoskeletal and connective tissue disorders												
Pain in extremity	5	(5.7)	5	12	1	(1.2)	1	2	6	(3.5)	6	7

N: Number of Subjects, %: Percentage of Subjects, E: Number of Events
R: Event Rate per 100 Exposure Years

Supportive Trials 3697, 3912 and 1842

The safety profile for subjects treated with IDeglira or liraglutide + IDet in the supportive Trials 3697, 3912 and 1842 was similar to the safety profile for the IDeg + liraglutide treatment group of Trial 3948. The proportion of subjects with AEs for subjects treated with IDegLira or liraglutide + IDet were within the same range as the proportions of subjects with AEs in the IDeg + liraglutide group in Trial 3948: 70.1% in Trial 3948; 71.2% in Trial 3697; 57.8% in Trial 3912 and 81.0 % in Trial 1842 (

Table **23**). The majority of AEs were mild and unlikely related to trial products, but subjects treated with a liraglutide component generally had a higher rate of gastrointestinal events than subjects not treated with liraglutide. The differences between the trials are described below and are mostly attributed to differences between trial designs and populations (primarily stage of diabetes).

Trial 3697

In Trial 3697, the rate of AEs with IDegLira (407.9 events per 100 PYE) was similar to IDeg (383.3 events per 100 PYE) and lower than with liraglutide (507.3 events per 100 PYE). Most AEs were mild in all 3 treatment groups and the rate of severe AEs in the IDegLira group (8.4 events per 100 PYE) was similar to the IDeg group (7.7 events per 100 PYE) and lower than with the liraglutide (12.9 events per 100 PYE) group (

Table **23**). Most AEs were assessed as unlikely to be related to trial product by the investigator in all 3 treatment groups. The rates of AEs assessed as probably or possibly related to trial product by the investigator were higher with IDegLira than with IDeg but lower than with liraglutide in this open-label trial.

AEs reported for at least 5% of subjects during the 52-week treatment period are shown in Table 25. For the events 'nasopharyngitis' and 'upper respiratory tract infection', the event rate in the IDegLira group was similar to the rates in the IDeg and the liraglutide groups. For all events in the gastrointestinal SOC, 'lipase increased' and 'decreased appetite', the rate with IDegLira was higher than with IDeg and lower than with liraglutide.

Table 25 Adverse events by system organ class and preferred term - most frequent [>=5%] – treatment-emergent - summary – Trial 3697ext - SAS

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	825				412				412			
Events	393	(47.6)	1026	145.4	168	(40.8)	429	122.5	243	(59.0)	719	215.1
Gastrointestinal disorders												
Nausea	85	(10.3)	102	14.5	16	(3.9)	21	6.0	92	(22.3)	118	35.3
Diarrhoea	84	(10.2)	128	18.1	28	(6.8)	33	9.4	67	(16.3)	94	28.1
Vomiting	41	(5.0)	62	8.8	10	(2.4)	10	2.9	38	(9.2)	55	16.5
Dyspepsia	28	(3.4)	35	5.0	5	(1.2)	5	1.4	22	(5.3)	28	8.4
Constipation	26	(3.2)	34	4.8	4	(1.0)	4	1.1	21	(5.1)	23	6.9
Infections and infestations												
Nasopharyngitis	115	(13.9)	162	23.0	52	(12.6)	74	21.1	55	(13.3)	81	24.2
Upper respiratory tract infection	64	(7.8)	79	11.2	34	(8.3)	40	11.4	33	(8.0)	37	11.1
Urinary tract infection	23	(2.8)	28	4.0	15	(3.6)	17	4.9	21	(5.1)	30	9.0
Nervous system disorders												
Headache	106	(12.8)	207	29.3	45	(10.9)	143	40.8	60	(14.6)	100	29.9
Dizziness	24	(2.9)	30	4.3	10	(2.4)	14	4.0	22	(5.3)	25	7.5
Musculoskeletal and connective tissue disorders												
Back pain	45	(5.5)	45	6.4	20	(4.9)	23	6.6	23	(5.6)	29	8.7
Arthralgia	30	(3.6)	36	5.1	15	(3.6)	23	6.6	22	(5.3)	27	8.1
Investigations												
Lipase increased	48	(5.8)	55	7.8	18	(4.4)	20	5.7	35	(8.5)	40	12.0
Metabolism and nutrition disorders												
Decreased appetite	22	(2.7)	23	3.3	2	(0.5)	2	0.6	30	(7.3)	32	9.6

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

Trial 3912

In Trial 3912, the percentage of subjects reporting AEs was similar for IDegLira (57.8%) and IDeg (61.3%) (

Table **23**). The rate of AEs in the IDegLira group (398.1 events per 100 PYE) was similar to the rate in the IDeg group (355.5 events per 100 PYE). Most AEs were mild or moderate in both treatment groups and the rate of severe AEs in the IDegLira group (7.6 events per 100 PYE) was similar to the rate in the IDeg group (8.9 events per 100 PYE) (

Table **23**). Most AEs were assessed as unlikely to be related to trial product by the investigator in both treatment groups. The rates of AEs considered probably or possibly related to trial product by the investigator in the IDegLira group were higher than the rates in the IDeg group.

AEs reported for at least 5% of subjects (in any of the treatment groups) are shown in (Table 26). The rate of events of 'nasopharyngitis' were lower with IDegLira than IDeg, whereas rates of 'diarrhoea', 'nausea', 'lipase increased' and 'headache' were higher with IDegLira than with IDeg.

Table 26 Adverse events in >=5% of subjects by system organ class and preferred term - treatment-emergent - Trial 3912 - SAS

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	199				199			
Events	45	(22.6)	81	88.1	29	(14.6)	42	46.7
Gastrointestinal disorders								
Diarrhoea	13	(6.5)	21	22.8	7	(3.5)	8	8.9
Nausea	13	(6.5)	20	21.8	7	(3.5)	7	7.8
Investigations								
Lipase increased	12	(6.0)	12	13.1	7	(3.5)	7	7.8
Infections and infestations								
Nasopharyngitis	5	(2.5)	5	5.4	12	(6.0)	14	15.6
Nervous system disorders								
Headache	12	(6.0)	23	25.0	4	(2.0)	6	6.7

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

Trial 1842

In Trial 1842, the percentage of subjects reporting AEs during the entire trial (run-in to end of trial) was similar for the liraglutide group (78.0%) and the IDet + liraglutide group (81.0%) (

Table **23**). Most AEs were mild or moderate in both treatment groups and the percentage of subjects having severe AEs in the liraglutide group (8.8%) was similar to the IDet + liraglutide group (10.4%). Most AEs were assessed as unlikely related to trial product by the investigator in both treatment groups with no difference between the treatment groups.

The most commonly reported adverse events for the entire trial period (including run-in and extension) were within the system organ classes 'Gastrointestinal disorders' (reported by 46.5% and 47.2% of subjects in the liraglutide and IDet + liraglutide group, respectively) and 'Infections and infestations' (reported by 46.5% and 44.2% of subjects in the liraglutide and IDet + liraglutide group, respectively). The most common events in these two SOCs were 'nasopharyngitis', 'nausea', and 'diarrhoea' (

Table **27**). No overall treatment group difference with respect to type or frequency of adverse events by system organ class was noted for subjects during the trial. Most of the gastrointestinal AEs, including those that occurred within the IDet + liraglutide group, are typical of those seen in liraglutide trials.

Table 27 Adverse events in ≥ 5% of subjects by system organ class and preferred term - Trial 1842ext - SAS

	Lira 1.8 N	(%)	E	Detemir + Lira 1.8 N	(%)	E
Safety Analysis Set	159			163		
All Adverse Events	124	(78.0)	716	132	(81.0)	845
Adverse Events >= 5%	100	(62.9)	303	102	(62.6)	312
Gastrointestinal disorders						
Diarrhoea	26	(16.4)	29	29	(17.8)	42
Nausea	37	(23.3)	51	30	(18.4)	40
Vomiting	19	(11.9)	21	17	(10.4)	26
Dyspepsia	8	(5.0)	11	10	(6.1)	11
Constipation	11	(6.9)	11	8	(4.9)	10
Abdominal Pain	8	(5.0)	11	6	(3.7)	7
Infections and infestations						
Nasopharyngitis	40	(25.2)	57	33	(20.2)	45
Upper Respiratory Tract Infection	9	(5.7)	14	13	(8.0)	13
Nervous system disorders						
Headache	23	(14.5)	41	21	(12.9)	54
Investigations						
Lipase Increased	16	(10.1)	17	26	(16.0)	27
General disorders and administration site conditions						
Fatigue	9	(5.7)	10	12	(7.4)	13
Musculoskeletal and connective tissue disorders						
Back Pain	10	(6.3)	10	4	(2.5)	6
Respiratory, thoracic and mediastinal disorders						
Oropharyngeal Pain	10	(6.3)	11	5	(3.1)	5
Metabolism and nutrition disorders						
Decreased Appetite	9	(5.7)	9	13	(8.0)	13

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occur before intensification. If the AE
increase in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Deaths

IDeg + liraglutide, Trial 3948

No deaths were reported in Trial 3948.

Supportive Trials 3697, 3912 and 1842

A total of 4 deaths were reported in the randomised treatment groups of the supportive trials: 2 treatment-emergent and 1 non treatment-emergent deaths in Trial 3697; all subjects were treated with IDegLira, and 1 treatment-emergent death in Trial 1842; the subject was treated with liraglutide. No deaths were reported in Trial 3912. A brief description of the 4 deaths is given below.

- A 49-year-old woman (Trial 3697) in the IDegLira group died due to unknown causes 66 days after initiation of the trial product. Medical history included hypertension, hypercholesterolaemia and

T2DM. The investigator considered this event unlikely to be related to trial product. The death was adjudicated and classified as a cardiovascular death.

- A 66-year-old woman (Trial 3697) in the IDegLira group was hospitalised 182 days after initiation of trial product due to fever, chills, and confusion. Medical history included hypertension, hyperlipidaemia, aortic stenosis, prosthetic valve placement, congestive heart failure, and hypercholesterolemia. The subject was a smoker. Diagnosis at admission to hospital was urinary tract infection with sepsis and mild congestive heart failure (medical history). The patient died of cardiopulmonary arrest the day after admission. Both 'sepsis' and 'urinary tract infection' were severe events but considered unlikely related to trial product by the investigator. The death was adjudicated and classified as a cardiovascular death.
- A 47-year-old woman (Trial 3697) in the IDegLira group was fatally wounded in a gunshot attack 295 days after initiation of trial product and died the same day. The death was adjudicated and not confirmed as a cardiovascular death.
- A 58-year-old man (Trial 1842) treated with liraglutide 1.8 mg, died of metastases to the central nervous system and pulmonary mass, approximately 6 months after initiation of trial drug. Medical history included hypertension and hyperlipidaemia. No death certificate or autopsy report was available.

In addition, 1 death in Trial 1842 in the non-randomised treatment group was reported:

- A 79-year-old woman (Trial 1842) died from adenocarcinoma of the gall bladder with liver metastasis. The subject was treated with non-randomised liraglutide 1.8 mg.

Ongoing trials

No deaths were reported in the ongoing Trial 3944 (IDeg), Trial 3917 (liraglutide), Trial 3925 (liraglutide) and Trial 3851 (IDegLira) as of 15 January 2013.

One death was reported in the ongoing IDegLira Trial 3951, as of 15 January 2013. The death is briefly described below.

- A 77-year-old man treated with blinded trial product IDegLira vs. placebo for T2DM, with no medical history of neoplasms (e.g., benign neoplasm disease or cancer), but a previous smoker and a history of working with asbestos, was hospitalised with dyspnoea. A CT of thorax showed suspicion of left pleural mesothelioma with lymph nodules and infiltration of pericardium. No autopsy was performed. The 'malignant pleural mesothelioma' was confirmed as the cause of death.

Serious adverse events (SAEs)

<u>IDeg + liraglutide, Trial 3948</u>

There were 9 SAEs in the randomised groups of Trial 3948: 4 in the IDeg + liraglutide group and 5 in the IDeg + IAsp group, corresponding to a rate of 10 and 12 events per 100 PYE, respectively. All 9 SAEs were assessed as unlikely related to trial products and device; 6 SAEs had the outcome 'recovered' or 'recovered with sequelae' by the end of the trial, while 3 SAEs had the outcome 'not recovered'. No pattern was observed in the SAEs reported.

Table 28 Serious adverse events - Trial 3948 – SAS

Subject ID	Treatment Group	Age (yrs)/ Sex (M/F)/ BMI (kg/m^2)	System Organ Class/ Preferred Term	Serious/ Severity/ Relationship[a]	Study day/ Duration	Outcome/ Action
154006	IDeg + Lira	58/M/37.42	Neoplasms benign, malignant and unspecified (incl cysts and polyps) / Bladder cancer	Y / Mild/ Unlikely	165/ NA	Not recovered/ Dose not changed
958006	IDeg + Lira	55/M/36.35	Gastrointestinal disorders / gastrooesophageal reflux disease	Y/ Moderate/ Unlikely	98/ 11	Recovered/ dose not changed
964009	IDeg + Lira	47/ M/ 40.03	Cardiac disorders / Coronary artery disease	Y/ Severe/ Unlikely	103/ NA	Not recovered/ Product withdrawn temporarily
993008	IDeg + Lira	79/ F/34.20	Vascular disorder / Peripheral vascular disorder	Y/ Severe/ Unlikely	132/ 14	Recovered/ Product withdrawn temporarily
206005	IDeg + IAsp OD	62/F/37.06	Eye disorders/ Vitreous detachment	Y/ Mild/ Unlikely	87/ NA	Not recovered/ Dose not changed
304008	IDeg + IAsp OD	51/M/31.02	Nervous system disorders / Cerebrovascular accident	Y/ Moderate/ Unlikely	88/ 4	Recovered with sequelae/ Dose not changed
401002	IDeg + IAsp OD	73/M/31.25	Metabolism and nutrition disorders / diabetes mellitus inadequate control	N/ Mild/ Unlikely	28/ 45	Recovered/ Dose not changed
802013	IDeg + IAsp OD	75/ F/ 27.81	Injury, poisoning and procedural complications / Humerus fracture	Y/ Severe/ Unlikely	48/ 135	Recovered/ Dose not changed
915003	IDeg + IAsp OD	37/ M/ 36.32	Gastrointestinal disorders / pancreatitis	Y/ Mild/ Unlikely	127/ 4	Recovered/ Product withdrawn temporarily

a Relationship according to investigator tabulated.

F: female; M: male; N: no; NA: not applicable; Y: yes

In addition to the 9 SAEs, one non-treatment-emergent SAE (prostate cancer; IDeg + IAsp) was reported 40 days after ended treatment.

Supportive Trials 3697, 3912 and 1842

The percentage of subjects with SAEs was low for all supportive trials and in the same range as in Trial 3948. No pattern or clustering of events was observed during the trials, and no preferred terms were reported for more than 1% of the subjects. The most frequently reported SAEs were represented in the SOCs 'cardiac disorders', 'infections and infestations' and 'nervous system disorders'.

Trial 3697

In total, 109 SAEs were reported by 84 subjects. The percentage of subjects reporting SAEs during the 52-week treatment period was 4.6% in the IDegLira group, 5.3% in the IDeg group and 5.8% in the liraglutide group. The rate of SAEs with IDegLira (6.7 events per 100 PYE) was similar to the IDeg (8.9 events per 100 PYE) and the liraglutide (9.3 events per 100 PYE) groups. The rate of SAEs assessed as severe were similar between the IDegLira group and the IDeg and liraglutide groups.

The most frequently reported SAEs in all treatment groups were represented in the SOCs 'cardiac disorders' (16 events), 'infections and infestations' (13 events) and 'gastrointestinal disorders' (10 events). No clustering of types of SAEs was observed, except for events in the SOC 'gastrointestinal disorders', where all events were reported in the IDegLira and liraglutide groups. No SAE preferred term was reported for more than 1% of the subjects.

Most SAEs were considered unlikely related to trial product by the investigator in all 3 treatment groups, while 10 events (4 in the IDegLira group, 1 in the IDeg group and 5 in the liraglutide group) were considered possibly or probably related to trial product by the investigator in this open-label trial.

Trial 3912

In total, 24 SAEs were reported by 18 subjects during this trial. The percentage of subjects reporting SAEs was 3.5% in the IDegLira group and 5.5% in the IDeg group, while the rate of SAEs was 12.0 events per 100 PYE with IDegLira and 14.4 events per 100 PYE with IDeg with no major differences between treatment groups. Most of the SAEs in the IDegLira group were of moderate severity and 2 events were severe, while most of the SAEs in the IDeg group were severe.

The most frequently reported SAEs in all treatment groups were presented in the SOCs 'nervous system disorders' (5 events) and 'cardiac disorders' (5 events). No clustering could be detected with the low number of events. No SAE was reported for more than 1% of subjects. The only preferred terms reported for more than 1 subject were 'acute myocardial infarction' and 'pneumonia'; both for 1 subject in each group.

Most SAEs in both treatment groups were assessed as unlikely related to trial product by the investigator, while 1 event in each treatment group were considered possibly or probably related to trial product by the investigator.

Trial 1842

In total, 37 SAEs were reported by 28 subjects in the 2 randomised treatment groups across the entire treatment period. The percentage of subjects reporting SAEs was 6.9% in the liraglutide group and 10.4% in the IDet + liraglutide group. Most SAEs in both treatment groups were assessed as unlikely related to trial product by the investigator, while 4 events in the liraglutide group were considered possibly or probably related to trial product by the investigator.

The most frequently reported SAEs in all treatment groups were presented in the SOCs 'neoplasms benign, malignant and unspecified' (5 events), 'injury, poisoning and procedural complications' (4 events) and 'cardiac disorder' (4 events). No SAE was reported for more than 1% of subjects and with the low numbers of events no clustering could be detected, except for events in the SOCs 'neoplasms benign, malignant and unspecified' and 'injury, poisoning and procedural complications' which occurred more frequently in the IDet + liraglutide treatment group.

Ongoing trials

In the ongoing Trial 3944 with the add-on of IDeg to liraglutide, no treatment-emergent SAEs were reported as of 15 January 2013. However, 9 SAEs were reported by 6 subjects either before first trial drug or in the run-in period.

In the ongoing trials with IDegLira (Trials 3851 and 3951), a total of 13 SAEs were reported for 11 (1.4%) subjects as of 15 January 2013. No PT was reported for more than 1 subject.

In the ongoing double-blind liraglutide Trial 3917, 5 SAEs were reported for 4 subjects as of 15 January 2013. One subject was involved in a car accident and had 3 events reported in relation to this, 1 subject experienced hyperglycaemia and 1 subject reported a non-treatment-emergent event of 'arrhythmia' at screening.

In the ongoing double-blind liraglutide Trial 3925, 11 SAEs were reported for 10 subjects as of 15 January 2013. Of these, 9 SAEs for 8 (3.1%) subjects were treatment-emergent.

Other significant adverse events

This section describes AEs leading to withdrawal and AEs leading to dose reduction.

IDeg + liraglutide, Trial 3948

Adverse events leading to withdrawal

A total of 6 (3.5%) subjects in the randomised treatment groups withdrew from the trial due to an AE: 5 (5.7%) in the IDeg + liraglutide group and 1 (1.2%) in the IDeg + IAsp group (Table 29).

Five of the 6 AEs that led to withdrawal were classified by the investigator as possibly or probably related to treatment. The events ('vomiting', 'lipase increased', 'constipation' and 'injection site rash') assessed as probably related to liraglutide are known adverse drug reactions of the liraglutide monocomponent. The remaining AE which was assessed as unlikely related to trial products by the investigator was reported as 'cellulitis' (chronic condition) for a subject in the IDeg + liraglutide group.

Table 29 Adverse events leading to discontinuation by system organ class and preferred term – Trial 3948 - safety analysis set

	IDeg + liraglutide				IDeg + IAsp			
	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	87				86			
Total Exposure (yrs)	40.0				40.5			
All Adverse Events	5	(5.7)	5	12.5	1	(1.2)	1	2.5
Gastrointestinal disorders	2	(2.3)	2	5.0				
Constipation	1	(1.1)	1	2.5				
Vomiting	1	(1.1)	1	2.5				
General disorders and administration site conditions	1	(1.1)	1	2.5				
Injection site rash	1	(1.1)	1	2.5				
Infections and infestations	1	(1.1)	1	2.5				
Cellulitis	1	(1.1)	1	2.5				
Investigations	1	(1.1)	1	2.5				
Lipase increased	1	(1.1)	1	2.5				
Skin and subcutaneous tissue disorders					1	(1.2)	1	2.5
Dermatitis allergic					1	(1.2)	1	2.5

N: Number of subjects with adverse events, %: Proportion of subjects in analysis set having adverse events, E: Number of adverse events,
R: Number of events divided by subject years of exposure multiplied by 100
Total Exposure (yrs): Total exposure in years for safety analysis set

Adverse events leading to dose reduction in investigational product

A total of 6 subjects reported AEs leading to a dose reduction during the trial: 5 (5.7%) subjects in the IDeg + liraglutide group (7 events) and 1 (1.2%) subject in the IDeg + IAsp group (1 event). The rate of AEs leading to dose reduction during the trial was 17 and 2 events per 100 PYE with IDeg + liraglutide and IDeg + IAsp, respectively.

Note, that liraglutide was initiated at 0.6 mg/day and then increased to 1.2 mg/day after 1 week. The liraglutide dose was to be maintained at 1.2 mg until Week 5. Then the dose could be increased to 1.8 mg/day depending on glycaemic control and tolerability. After 26 weeks of treatment, 2 (2.3%) subjects were taking liraglutide 0.6 mg/day, 28 (32.2%) were taking 1.2 mg/day and 57 (65.5%) were taking 1.8 mg/day.

In the IDeg + liraglutide group, the following AEs were reported and liraglutide dose was reduced in response: 'diarrhoea' (both subjects recovered), 'nausea' (one subject recovered and one subject not recovered), 'goitre' (subject not recovered), 'eructation' (subject recovered) and 'dizziness' (subject recovered).

In the IDeg + IAsp group, one subject reported 'viral gastroenteritis' (recovered) and IDeg dose was reduced in response.

In 2 cases where trial product was temporarily withdrawn, the AE was considered possibly or probably related to trial product by the investigator:

- one subject (IDeg + liraglutide): liraglutide temporarily withdrawn due to injection site reaction ('pruritis' and 'rash') considered by the investigator to have probable relation to liraglutide
- one subject (IDeg + liraglutide): liraglutide temporarily withdrawn due to elevated amylase and lipase

Supportive Trials 3697, 3912 and 1842

Adverse events leading to withdrawal

The number and type of adverse events leading to withdrawal in the 3 supportive trials resembled the findings from Trial 3948. Up to approximately 5% of subjects in the 3 trials were withdrawn due to AEs. Apart from 'gastrointestinal disorders', no clustering in type of adverse event withdrawals was observed and no treatment group difference was apparent with respect to number of subject withdrawals due to adverse events. For 'gastrointestinal disorders', the event rate was lowest with IDeg, higher with IDeg or IDet + liraglutide and IDegLira, and highest with liraglutide. The subjects recovered from the majority of the AEs that led to withdrawal.

In Trial 3697, a total of 51 (3.1%) subjects out of 1663 randomised subjects were withdrawn due to AEs during the entire 52-week trial period: 14 (1.7%) in the IDegLira group, 9 (2.2%) in the IDeg group and 26 (6.3%) in the liraglutide group. Two (2) of these events were non-treatment-emergent and are not included in the table showing treatment-emergent AEs leading to withdrawal (

Table **30**).

Table 30 Adverse events leading to withdrawal by system organ class – treatment-emergent - Trial 3697 (52 weeks) – safety analysis set

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	825				412				412			
Events	14	(1.7)	16	2.3	9	(2.2)	12	3.4	26	(6.3)	35	10.5
Gastrointestinal disorders	4	(0.5)	4	0.6					16	(3.9)	20	6.0
Investigations	2	(0.2)	3	0.4	3	(0.7)	4	1.1	5	(1.2)	6	1.8
Musculoskeletal and connective tissue disorders	2	(0.2)	3	0.4	2	(0.5)	2	0.6	1	(0.2)	1	0.3
General disorders and administration site conditions	3	(0.4)	3	0.4	1	(0.2)	1	0.3	0			
Nervous system disorders	0				2	(0.5)	2	0.6	2	(0.5)	2	1.1
Cardiac disorders	1	(0.1)	1	0.1	1	(0.2)	1	0.3	1	(0.2)	1	0.3
Infections and infestations	1	(0.1)	1	0.1	0				1	(0.2)	1	0.3
Eye disorders	1	(0.1)	1	0.1	0				0			
Injury, poisoning and procedural complications	0				1	(0.2)	1	0.3	0			
Metabolism and nutrition disorders	0				0				1	(0.2)	1	0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				0				1	(0.2)	1	0.3
Renal and urinary disorders	0				0				1	(0.2)	1	0.3
Respiratory, thoracic and mediastinal disorders	0				1	(0.2)	1	0.3	0			
Skin and subcutaneous tissue disorders	0				0				1	(0.2)	1	0.3

N = Number of subjects; % = Percentage of subjects; E = Number of events; R = Event rate per 100 exposure years

In Trial 3912, a total of 4 (1.0%) subjects out of 398 randomised subjects were withdrawn from the trial due to AEs: 1 (0.5%) subject in the IDegLira group and 3 (1.5%) subjects in the IDeg group (Table 31). All AEs leading to withdrawal were considered unlikely related to trial product.

Table 31 Adverse Events leading to withdrawal by system organ class and preferred term – treatment-emergent - Trial 3912 - safety analysis set

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	199				199			
Events	1	(0.5)	1	1	3	(1.5)	3	3
Cardiac disorders					1	(0.5)	1	1
Acute myocardial infarction					1	(0.5)	1	1
Hepatobiliary disorders					1	(0.5)	1	1
Cholelithiasis					1	(0.5)	1	1
Nervous system disorders					1	(0.5)	1	1
Ischaemic stroke					1	(0.5)	1	1
Psychiatric disorders	1	(0.5)	1	1				
Major depression	1	(0.5)	1	1				

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

In Trial 1842, 16 subjects withdrew in the trial entire period due to adverse events: 9 (5.7%) subjects in the liraglutide group; and 7 (4.3%) subjects treated with IDet + liraglutide (Table 32). Most withdrawals

due to AEs (about 50%) occurred during the 12-week run-in period of the trial where liraglutide was titrated - these were mostly due to gastrointestinal symptoms (nausea and vomiting). The proportion of subjects withdrawing from both the 26-week main period (3.1% across groups) and the 26-week extension period (1.2%–1.9%) were relatively low and no treatment group difference was observed.

Table 32 Adverse events leading to withdrawal by system organ class – treatment-emergent - Trial 1842 – safety analysis set

	Lira 1.8			Detemir + Lira 1.8		
	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163		
All Adverse Events	9	(5.7)	13	7	(4.3)	8
Investigations	3	(1.9)	5	2	(1.2)	2
Gastrointestinal disorders	3	(1.9)	4	1	(0.6)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1	1	(0.6)	1
Nervous system disorders				1	(0.6)	1
Renal and urinary disorders	1	(0.6)	1	1	(0.6)	1
Respiratory, thoracic and mediastinal disorders				1	(0.6)	1
Hepatobiliary disorders	1	(0.6)	1			
Infections and infestations	1	(0.6)	1			

All subjects also received metformin
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Adverse events leading to dose reduction

As in Trial 3948, a small percentage of AEs led to dose reduction in Trials 3697 and 3912 (2.2% and 1.8 %, respectively). This endpoint was not assessed in Trial 1842. There was a similar pattern of AEs related to 'gastrointestinal disorders' leading to dose reduction in Trial 3697 as in Trial 3948. In Trial 3912, there was no apparent clustering or pattern in the AEs leading to dose reduction, and no apparent difference between treatment groups.

Ongoing trials

Adverse events leading to withdrawal

In the ongoing trials, 3 subjects were withdrawn due to SAEs as of 15 January 2013.

In Trial 3944, 1 subject reported 'gastroenteritis' during the run-in period and was withdrawn.

In Trial 3925, 1 subject reporting 'acute myocardial infarction' could not be contacted by the trial staff and was withdrawn permanently from the trial. One subject reported 'brain stem thrombosis', recovered with sequelae and was withdrawn permanently from the trial.

Analysis of adverse events by organ system or syndrome

Cardiovascular events

In all 4 trials, the numbers of MACEs were low and with no apparent difference in the rate of MACE reported by subjects treated with the combined used of IDeg and Lira (as a free or combination) compared to subjects treated with IDeg + IAsp or with the IDeg or Lira monocomponents. However, the numbers are very small and should be interpreted with caution.

Pancreatitis or suspicion of pancreatitis

In Trial 3948, 1 SAE of pancreatitis was identified (IDeg +IAsp group) and 6 subjects in the IDeg + liraglutide group had reports of elevated amylase and/or lipase levels. In the IDegLira trials, events of pancreatitis as confirmed by the event adjudicating committee (EAC) comprised 1 event of acute pancreatitis with IDeg (reported 2 months after treatment-emergent period) and 2 events of acute pancreatitis with liraglutide (of which one was identified based on increased lipase levels). In Trial 1842, 2 events of pancreatitis (1 acute and 1 chronic, both SAEs) were reported in the randomised treatment groups; both events were in the liraglutide group.

No events of pancreatitis were identified for subjects receiving IDeg + liraglutide, IDegLira or IDet + liraglutide, and it is concluded that there is no evidence pointing to any increased risk of pancreatitis with the combined use of IDeg and liraglutide relative to liraglutide.

Thyroid disease

In Trial 3948, 3 non-serious thyroid-related AEs for 3 subjects were identified in the IDeg + liraglutide group. Two of these events were assessed as unlikely related to IDeg and probably related to liraglutide by the investigator, and both of these subjects also had elevated calcitonin levels. None of these events were related to thyroid cancer.

In the IDegLira Trials 3697 and 3912, the rate of thyroid events with IDegLira was low and similar to the rate with IDeg and liraglutide. All thyroid events were mild or moderate in severity and were assessed by the investigator as unlikely related to trial product. Three events of 'thyroid neoplasm' (2 with IDegLira and 1 with liraglutide) were sent for adjudication (as neoplasms); none of the events were confirmed as neoplasms by the EAC. A single thyroid event of goitre leading to thyroidectomy in the liraglutide group was adjudicated as a non-neoplasm event. No medullary thyroid cancer events were reported. In Trial 1842, no events of thyroid cancer or thyroid neoplasm were reported in the randomised treatment groups.

The results from these trials do not suggest an increased risk of thyroid disease compared to liraglutide or IDeg when administering IDeg in combination with liraglutide.

Neoplasms

The overall rates of neoplasms reported in the IDeg + liraglutide and IDegLira treatment groups were low and similar to those reported in the comparator groups. The rates of malignant neoplasms were similar between IDeg + liraglutide and IDeg + IAsp and between IDegLira and IDeg. In Trial 1842, there was no clinically relevant difference between the proportion of subjects reporting neoplasm events in the IDet + liraglutide group (4.9%) and the pooled liraglutide groups (randomised and non-randomised) (3.2%).

Allergic reactions

Few events of allergic reactions were reported for the main Trial 3948 and the supportive Trials 3697 and 3912, and there was no difference among treatment groups. The majority of the events were not related to the trial products.

Gastrointestinal events

In Trial 3948, the rates of gastrointestinal events were higher with IDeg + liraglutide than with IDeg + IAsp OD. A similar pattern was seen for the IDegLira trials, with higher rates of gastrointestinal AEs with IDegLira than with IDeg. In Trial 1842, a similar percentage of subjects reported gastrointestinal disorders in the IDet + liraglutide group and the liraglutide group in the entire trial period.

In all 4 trials, most gastrointestinal events were mild or moderate in severity and, as expected, the most frequently reported gastrointestinal events were 'nausea', 'diarrhoea' and 'vomiting'. Most gastrointestinal events occurred shortly after initiation of liraglutide, were transient and diminished over time.

Medication errors

Few AEs of medication errors were reported in all 4 clinical trials. All events were of mild or moderate severity, none were severe and all subjects recovered.

Hypoglycaemic Episodes

No episodes of severe hypoglycaemia were reported in Trial 3948 and no episodes of major hypoglycaemia were reported in Trial 1842. A total of 8 episodes of severe hypoglycaemia were reported in the two IDegLira trials.

Clinical laboratory evaluations

Most subjects had normal haematology, biochemistry, lipid, and other laboratory value (including amylase, lipase, calcitonin and calcium) levels during the trials. Very few subjects had changes from normal to high or low values during the trials.

Vital signs

Completed trials

IDeg + liraglutide, Trial 3948

Vital signs were similar between the IDeg + liraglutide and IDeg + IAsp treatment groups at baseline (Week 0) and after 26 weeks of treatment. In the IDeg + liraglutide group, mean blood pressure (SBP/DBP) and pulse were 133/78 mmHg and 73 beats/min at baseline, and 130/78 mmHg and 76 beats/min after 26 weeks of treatment. In the IDeg + IAsp group, mean blood pressure (SBP/DBP) and pulse were 129/77 mmHg and 74 beats/min at baseline, and 130/78 mmHg and 74 beats/min after 26 weeks of treatment.

The small increase in pulse from baseline to end of trial in the IDeg + liraglutide group was similar to what has been observed with IDegLira and IDet + liraglutide.

Analyses of DBP and SBP after 26 weeks of treatment demonstrated that there was no observed difference between treatment groups. A similar proportion of subjects in both treatment groups has DBP < 80 mmHg and SBP < 130 mmHg at the end of the trial.

Supportive Trials 3697, 3912 and 1842

Both in Trials 3697ext and 3912, there was a statistically significantly greater reduction in systolic blood pressure with IDegLira compared to IDeg. The estimated treatment difference was -1.54 in Trial 3697ext and -3.71 in Trial 3912. There was no difference in diastolic blood pressure between treatment groups.

Also in Trials 3697 and 3912, an increase in pulse of approximately 2.5−3.0 beats/min was noted with IDegLira and liraglutide (only Trial 3697) after 26 weeks of treatment. The increase had diminished to approximately 1.5−2.0 beats/min above the baseline level after 52 weeks of treatment and is considered of minor clinical relevance. A slight increase in pulse is a known effect with liraglutide. Similarly, in Trial 3912, there was an statistically significant increase in pulse with IDegLira (mean change 2.5 beats/min) from baseline to Week 26, whereas the pulse did not seem to change from baseline to Week 26 with IDeg.

In Trial 1842ext, mean pulse increased from approximately 73 beats pr. min at the run-in period, to approximately 79 beats pr. min at randomisation in both randomised treatment groups, but decreased to approximately 76 beats pr. min thereafter. No change was observed from Week 26 to Week 52 for the

two randomised treatment groups. Blood pressure was assessed in Trial 1842 as an efficacy parameter. The estimated mean changes in systolic blood pressure from randomisation to Week 52 were +0.16 mmHg for subjects treated in the randomised IDet + liraglutide group and -0.74 for subjects treated in the randomised liraglutide group. Similarly, estimated mean change in diastolic blood pressure from randomisation to Week 52 were +0.05 mmHg for subjects treated with IDet + liraglutide and -0.74 for subjects treated with liraglutide. There was no difference between the 2 treatment groups for either systolic or diastolic blood pressure and the results did not indicate any safety concerns.

Safety in special groups and situations

Adverse events by intrinsic factors

Adverse events by age

IDeg + liraglutide, Trial 3948

About one third of the subjects included in the trial were elderly subjects (> 65 years): 36.8% of the subjects in the IDeg + liraglutide group and 33.7% in the IDeg + IAsp OD group (Table 33). There was no indication of a higher rate of AEs in elderly subjects compared to adult subjects treated with IDeg + liraglutide. The rate of AEs seemed higher for adult subjects, although the number of elderly subjects was low and hence a direct comparison between the age groups should be done with caution. Among the elderly subjects, the proportion of subjects with AEs was similar for the IDeg + liraglutide and IDeg + IAsp OD treatment groups, but the rates was slightly higher in the IDeg + liraglutide treatment group (Table 33).

The difference between treatment groups in the adult group was mainly driven by an increased number of gastrointestinal disorders, and AEs of increased lipase and amylase. Also in the elderly group, the rate and proportions of subjects with gastrointestinal disorders was higher for subjects treated with IDeg + liraglutide than for subjects treated in the IDeg + IAsp OD group.

A review of the reported AEs did not identify any clinically relevant differences across the different age groups treated with IDeg + liraglutide and it was concluded that there was no clinically relevant treatment-by-age interactions for IDeg + liraglutide.

Table 33 Adverse events by age group – summary- Trial 3948 – SAS

	IDeg + liraglutide			IDeg + IAsp OD		
	N (%)	E	R	N (%)	E	R
Safety Analysis Set						
Age 18 - 65 years	55 (63.2)			57 (66.3)		
Age > 65 years	32 (36.8)			29 (33.7)		
Total Exposure (yrs)						
Age 18 - 65 years	25.4			26.9		
Age > 65 years	14.6			13.6		
All Adverse Events						
Age 18 - 65 years	42 (76.4)	149	585.8	31 (54.4)	69	256.7
Age > 65 years	19 (59.4)	58	397.2	16 (55.2)	42	308.4

N: number og subjects, E: number of events R: number of events per 100 PYE (patient years of exposure)

Supportive Trials 3697, 3912 and 1842

The potential impact of age on the rate of AEs was investigated in Trials 3697 and 3912. As in Trial 3948, no impact of age on adverse event rates was apparent. The percentages of subjects reporting AEs was similar for adults (18–65 years) and elderly (> 65 years) subjects in both trials.

No information is available for Trial 1842.

Post-Marketing Data

Summary

Based on the spontaneous AEs reported with the combined use of liraglutide (Victoza) and insulin products, there is no apparent change in the AE profile for Victoza when used in combination with insulin compared to using the products separately.

Tresiba

Tresiba (insulin degludec) received the first marketing authorisation in Japan on 28 September 2012. The Mexican approval was issued on 18 December 2012. Furthermore, Tresiba was approved for use in Europe on 21 Jan 2013 and became commercially available in United Kingdom the 28 January 2013, in Denmark the 4 March 2013 and in Japan the 7 March 2013. Therefore limited post-market data exists. The first Tresiba Periodic Safety Update Report (PSUR) was submitted in June 2013.

The clinical trial safety data for Tresiba remain in accordance with the cumulative experience as described in the current safety reference information (Investigator's brochure (IB)). No new significant safety concerns have been identified in connection with the administration of Tresiba in clinical trials. Tresiba however has only recently been introduced on the market and only limited data are available.

Victoza

The GLP-1 receptor agonist Victoza was approved for use in Europe in June 2009 and became commercially available in Europe in July 2009.

A crude estimate of the total exposure during the reporting period 31 December 2011 – June 2012 was 469,694 patient years of exposure (PYE). The cumulative exposure since June 2009 to 30 December 2012 was 1,296,080 PYE11.

In the post-marketing period the MAH has received 18,592 adverse reaction reports containing 38,614 events. These were reports from all sources other than interventional clinical trials. Therefore it contains reports from spontaneous sources, literature, health authorities and patient support programs. A majority of the reports are related to the MedDRA SOC 'gastrointestinal disorders' (36%) followed by 'general disorders and administration site conditions' (20%) and 'investigations' (14%).

Since the approval of Victoza and based on post-marketing experience, Section 4.8 of the Company Core Data Sheet (CCDS) has been up-dated with the following terms: 'urticaria', 'dehydration', 'renal failure acute', 'renal impairment', 'malaise', 'pruritus', 'rash', 'anaphylactic reactions' and 'increased heart rate'.

As an overall assessment, the MAH evaluates that the benefit-to-risk balance of Victoza remains favourable.

<u>Spontaneous adverse events reported with Victoza in combination with insulin</u>

There is no data available on the post-marketed use of Victoza combined with Tresiba, as Tresiba was approved recently. In October 2011, the European Commission approved to include data to the EU Summary of Product Characteristics (SmPC) for the add-on of once-daily Levemir to treatment with Victoza and metformin in subjects not achieving adequate glycaemic control with Victoza and metformin alone. The use of Victoza in combination with basal insulin is currently not in the Victoza label.

The following section describes spontaneous adverse events with Victoza in concomitant use with insulin for the period from 31 December 2011 to 30 June 2012.

A total of 349 reports (717 events) were reported in the period when Victoza was co-administered with insulin product including insulin analogues. A total of 158 reports (290 events) were medically confirmed and 94 reports (160 events) of the medically confirmed reports were serious.

The pattern of adverse events reported in subjects where Victoza is used in combination with insulin does not differ from the overall pattern of adverse events reported in subjects only being treated with Victoza. The MAH does not consider these events to raise any new safety concerns and no change to the CCDS is warranted.

In addition, in recent years, several publications have described the clinical benefits of combining GLP-1 analogues and basal insulin analogues in the treatment of T2DM, reflecting the wide use of this combination in clinical practice without increased risk of hypoglycaemia.

2.4.4. Discussion

With the current application, safety data from four clinical studies investigating the combination of IDeg and liraglutide and including 2 220 patients has been submitted. In total 1 111 patients have been treated with either the free combination (87 patients) or the combination (1024 patients) for up to one year. Thus the safety database is of adequate size to allow assessment of the safety profile of the combination.

Overall exposure was balanced between treatment groups, however, there were more males than females included in the studies. The exposure to the free combination was rather limited.

Studies 3697 and 3912 contribute with a substantial exposure to the combination of IDeg and liraglutide. This is acceptable from a safety perspective, although the slower uptitration of liraglutide with the liraglutide component may have implications on the safety profile.

In study 3948, the overall reporting of AEs was higher per 100 PYE in the group treated with IDeg + Lira (517 events/100 PYE) compared to IDeg + IAsp (274 events/100 PYE), which was also reflected in a slightly higher withdrawal rate due to AEs. Severe events were balanced between groups (10 vs 12 events/100 PYE) and the event rate was low. In the supportive studies, the rate of AEs was more balanced between groups. Imbalances in the reporting of adverse events between treatment groups were due to a higher reporting rate of gastrointestinal events (nausea, diarrhoea and vomiting) in groups treated with IDeg + liraglutide or liraglutide alone. Injection site reactions were uncommon but more frequently reported in IDeg + liraglutide group in the pivotal study. Thus in the groups treated with a combination of liraglutide and basal insulin, the AEs reported mainly reflect the known safety profile of liraglutide. The reporting rates were somewhat lower in the groups treated with the combination, which may reflect the slower uptitration of liraglutide in these groups.

There were few deaths reported (3 cases in study 3697 and 1 case in study 1842) and none of the cases appear to be related to the medication but rather to underlying disease.

In the analysis of adverse events of special interest, no new safety concerns are evoked. Only 40 of the 216 cardiovascular events in trial 3697 and 3912 identified by search qualified for adjudication and were sent to the event adjudication committee (EAC). This has been partly clarified by the fact that the search to identify cardiovascular events was very broad. The majority of events that did not qualify for adjudication were arrhythmias. Furthermore, the cardiovascular safety profile of IDeg and liraglutide are currently being further investigated in dedicated, large, prospective cardiovascular outcomes trials (DEVOTE and LEADER®, respectively).

A small increase in pulse rate was observed in the IDeg + liraglutide as has previously been described for liraglutide. Otherwise no differences in vital signs were observed between groups. Comparable findings with regards to blood pressure and pulse rate were observed across the supportive studies.

No new safety concerns arise from the clinical laboratory evaluations. There were no indications of a change in the immunogenicity profile when IDeg and liraglutide were used in combination and the rate of antibody development was low.

The subgroup analyses were performed but have to be interpreted with caution due to the small sample sizes. No clinically relevant interactions between age and the reporting of AEs were observed.

Post-marketing data was provided. Tresiba has only recently been introduced on the market and only limited data are yet available. Post-marketing data concerning the concomitant use of liraglutide in combination with insulin does not evoke any safety concerns

The safety data submitted does not indicate any change in the known safety profiles of either IDeg or liraglutide when used in combination.

2.5. Risk management plan

2.5.1. **PRAC advice**

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan edition 4 version 1.0, the PRAC considers by consensus that the risk management system for insulin degludec (Tresiba) in the treatment of diabetes is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hypoglycaemia Immunogenicity-related events (allergic reactions)
Important potential risks	Medication errors due to mix-up between basal and bolus insulin Medication errors due to mix-up between the different concentrations of Tresiba® Immunological events – formation of neutralising insulin antibodies
Missing information	Pregnant and lactating women Children and adolescents <18 years Hepatic impairment Moderate and severe renal impairment Elderly patients (>75 years) with T1DM

The PRAC agreed.

Pharmacovigilance plans

Table 2.2: Ongoing and planned studies in the PhV development plan

Study/activity Type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PASS; UT117; Colour-blindness usability study; Category 3	A study to investigate the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba® as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness	• Medication errors due to mix-up between basal and bolus insulin for colour blind • Medication errors due to mix-up of different strengths of Tresiba® for colour blind	Planned	Planned submission of report: 20-Sep-2014

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the study in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypoglycaemia	**SmPC** Warning in Section 4.4. Potential insulin-interacting medicinal products listed in Section 4.5. Listed in Section 4.8 as an undesirable effect. Warning in Section 4.9 and instruction on what to do in case of overdose.	None
Immunogenicity-related events (allergic reactions)	**SmPC** Contraindications for use in Section 4.3 'Listed in Section 4.8 as an undesirable effect.	None
Medication errors due to mix-up between	Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder, as well as tactile elements on the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
basal and bolus insulin	pen push button (Annexes 11A–D in Table 7-1). **SmPC** Warning in Section 4.4 to verify insulin and dose prior to injection. Described as a special precaution in **Patient information:** Specific information on how to use and check the dose with the FlexTouch® pens containing 100 units/mL and 200 units/mL.	
Medication errors due to mix-up between different concentrations of Tresiba®	Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder, as well as tactile elements on the pen push button (Annexes11A–D in Table 7-1). **SmPC** The two different strengths are described in Section 4.2. Included in Section 4.4 **Patient information** Specific information on how to use and check the dose with the FlexTouch® pens for each strength.	A direct health care professional communication, a poster for display in pharmacies / diabetic units and a patient education leaflet to emphasise that there are two different strengths, and the product differentiation elements; see Table 5-4 and Annexes 11A-11D in Table 7-1.
Immunological events – formation of neutralising insulin antibodies	**SmPC** Included in Section 4.4.	None
Pregnant and lactating women	**SmPC** In Section 4.6, the lack of clinical experience with Tresiba® in pregnant women or during breast-feeding is described. Results from nonclinical studies are described.	None
Children and adolescents < 18 years	**SmPC** That the safety and efficacy of Tresiba® have not been established in children and adolescents < 18 years is described in Section 4.2. Included in Section 4.8. What is known about the pharmacokinetic properties of Tresiba® in 6-12-year-olds and 12–17 years olds is summarised in Section 5.2.	None
Hepatic impairment	**SmPC** Use in patients with hepatic impairment described in Section 4.2. In Section 4.8, it is described that there is no difference in the frequency, type and severity of adverse reactions in patients with hepatic impairment compared to the general population. Pharmacokinetic properties of Tresiba® in patients with hepatic impairment described in Section 5.2.	None
Moderate and severe renal impairment	**SmPC** Use in patients with renal impairment described in Section 4.2.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	In Section 4.8, it is described that there is no difference in the frequency, type and severity of adverse reactions in patients with renal impairment compared to the general population. Pharmacokinetic properties of Tresiba® in patients with renal impairment described in Section 5.2.	
Elderly patients (>75 years) with T1D	**SmPC** Use in elderly patients is described in Section 4.2. In Section 4.8, it is described that there is no difference in the frequency, type and severity of adverse reactions in elderly patients compared to the general population. Pharmacokinetic properties of Tresiba® in elderly patients described in Section 5.2.	None

Abbreviations: ACE = angiotensin-converting enzyme; GLP-1 = glucagon-like peptide-1; MAOI = monoamine oxidase inhibitor; SmPC = summary of product characteristics; T1DM = type 1 diabetes mellitus.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The RMP has been updated in all relevant sections and these changes are endorsed by the PRAC with some minor comments:

- The RMP has been amended with exposure data from study 3948 (assessed within the ongoing type II variation). These data have been presented separately from the currently available Tresiba data. The rationale for this is questioned since the summary data for Tresiba presented in tables 2-10, 2-12, 2-14 and 2-16 includes patients treated both with monotherapy and combinations with other antihyperglycaemic agents. It may therefore be considered to include the data from study 3948 in the summary tables. Further to this it should be considered to include information on the exposure to the combination since these data provides relevant information for important safety considerations on the combination.
- Section 4.1 in the RMP has been amended with a discussion on efficacy in the target population. The amendment is endorsed although the final wording is pending the outcome of the ongoing type II variation.
- The entire section 6 in the RMP has been amended in the current version of the RMP. This is in general endorsed. Table 6-1 should be updated as indicated in double strike through since "co-administration with GLP-1" is no longer missing information.

The comments made should be taken into consideration with the next scheduled update of the RMP.

The CHMP endorsed this advice without changes.

2.6. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Section 4.2 of the SmPC

[…]

In patients with type 2 diabetes mellitus, Tresiba can be administered alone, or in any combination with oral anti-diabetic medicinal products, GLP-1 receptor agonists ~~as well as in combination with~~ and

bolus insulin (see section 5.1).

[…]

Use of *Tresiba in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus*

When adding Tresiba to GLP-1 receptor agonists, the recommended daily starting dose is 10 units followed by individual dosage adjustments.

When adding GLP-1 receptor agonists to Tresiba, it is recommended to reduce the dose of Tresiba by 20% to minimise the risk of hypoglycaemia. Subsequently, dosage should be adjusted individually.

Section 5.1 of the SmPC

[…]

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with Tresiba (insulin degludec) in combination with metformin achieved a target HbA_{1c} < 7.0% and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs -0.40% for comparator, estimated means) and body weight (-3.03 vs 0.72 kg, estimated means). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Section 1 of the Package Leaflet

1. What Tresiba is and what it is used for

Tresiba is a long-acting basal insulin called insulin degludec. It is used to treat diabetes mellitus in adults. Tresiba helps your body reduce your blood sugar level. It is used for once-daily dosing. On occasions when you cannot follow your regular dosing schedule you can change the time of dosing because Tresiba has a long blood-sugar-lowering effect (see section 3 for 'Flexibility in dosing time'). In type 2 diabetes mellitus, Tresiba may be used in combination with tablets for diabetes or with injectable anti-diabetic products, other than insulin. Tresiba can also be used with meal-related rapid acting insulin products.

In type 1 diabetes mellitus, Tresiba must always be used in combination with meal-related rapid acting insulin products.

Editorial changes have been made to the PI which is acceptable to the CHMP.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

2.7. Significance of paediatric studies

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/44/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/44/2010 was not yet completed as some measures were deferred.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

The purpose of the current variations application is to propose a labelling update for the use of insulin degludec (IDeg) in combination with GLP-1 receptor agonists.

Beneficial effects

In support of the current application, the MAH has submitted one pivotal study (3948) and three supportive studies (3697, 3912 and 1842). Data have been provided showing that there are no clinically relevant differences in pharmacokinetic properties of IDeg or liraglutide when administered as IDegLira (100 units/3.6 mg per mL) or as free IDeg and liraglutide mono-components which justifies the use of studies 3697 and 3912 as supportive data in the current application.

The pivotal study included 177 patients with T2DM who were in need of intensified treatment, i.e. HbA1c > 7 in spite of treatment with IDeg and metformin in the context of a two-year treat-to-target study. After 26 weeks a clinically relevant HbA1c reduction of -0.74 % was observed in patients treated with IDeg + liraglutide as compared to -0.39 % in the group treated with IDeg + IAsp. The treatment difference was statistically significant (- 0.32%-point $[-0.53;-0.12]_{95\%CI}$).

This finding was supported by the data from studies 3697 and 3912 where the difference in HbA1c reduction between IDegLira and the mono-components ranged between -0.47 and -1.05 % depending on the study design and population included. Maintenance of the efficacy of the combination up to one year has been shown.

In addition, data from study 1842 has shown that a comparable effect on HbA1c reduction is observed when basal insulin IDet is added to liraglutide.

The overall hypoglycaemia rates were comparable across the studies in the groups treated with the combination of IDeg and liraglutide (range: 100 - 180 events per 100 PYE) and lower compared IDeg alone (range: 257 – 263 events per 100 PYE). The highest hypoglycaemia rate was observed in patients treated with IDeg + IAsp (815 events per 100 PYE) and the lowest rate was seen in patients on liraglutide monotherapy (22 events per 100 PYE).

Across the studies, combination therapy resulted in a change in body weight ranging from -0.5 kg to -2.8 kg.

The data from the pivotal and supportive studies support the posology proposed for the combination therapy, when a GLP-1 analogue is added to IDeg. Trial 1842 lend support to the proposed posology when adding basal insulin in patients already on liraglutide. Although this study was performed with at different basal insulin, the characteristics of the two insulins are deemed sufficiently similar to allow extrapolation of these data from IDet to IDeg.

Uncertainty in the knowledge about the beneficial effects

The choice to administer the comparator (IAsp) OD in the pivotal study 3948 is questioned. This was done in order to add the same number of injections in both groups. This regimen is however not considered optimal since dose escalation can only be made with one meal of the day thereby limiting the possibility to exhaust this treatment option. Dose increases will be hindered by the occurrence of (post-prandial) hypoglycaemias that could have been avoided by instead adding doses of IAsp to other meals.

Therefore the once daily dosing of the comparator IAsp is suboptimal and thus the difference in treatment effect between the combination IDeg and liraglutide versus IDeg and bolus insulin may be somewhat overestimated. The overall data however support that the addition of liraglutide to IDeg is an efficient treatment option.

Administering bolus insulin once daily may indeed provoke hypoglycaemias; however, the currently proposed description of hypoglycaemia data in the SmPC is considered acceptable.

Risks

Unfavourable effects

With the current application, safety data from four clinical studies investigating the combination of IDeg and liraglutide and including 2 220 patients has been submitted. In total 1 111 patients has been treated with either the free combination (87 patients) or the combination (1024 patients) for up to one year. Thus the safety database is of adequate size to allow assessment of the safety profile of the combination.

The most commonly reported adverse events in patients treated with the combination across the studies were gastrointestinal events (i.e. nausea, diarrhoea and vomiting) which are known to occur with liraglutide treatment.

There were no indications of a change in the immunogenicity profile when IDeg and liraglutide were used in combination and the rate of antibody development was low.

The safety data submitted does not indicate any change in the safety profiles of either IDeg or liraglutide when used in combination.

Uncertainty in the knowledge about the unfavourable effects

There are no new uncertainties or safety concerns evoked in relation to the combination therapy.

Balance

Importance of the favourable and unfavourable effects

The addition of liraglutide to IDeg treatment has been shown to result in clinically relevant (additional) reductions of HbA1c. This reduction was achieved at a relatively low risk of hypoglycaemia. Although the comparison in the pivotal study is not entirely accepted, the totality of data indicates that the risk of hypoglycaemia is lower with this approach than with intensified insulin therapy. Furthermore, improvement of metabolic control was achieved concomitantly with a reduction of body weight.

The effects on HbA1c, risk of hypoglycaemia and body weight are all considered of benefit in a T2DM population in need of intensified treatment.

The safety data provided does not indicate any changes in the safety profiles for IDeg or liraglutide when administered in combination. The adverse events known to occur with liraglutide predominated the adverse event reporting. These events are well known and are considered manageable.

Benefit-risk balance

Discussion on the benefit-risk balance

The data provided is considered sufficient to conclude that combination treatment with IDeg and liraglutide is efficient and that no new safety concerns have been evoked by the presented data.

The clinical trials included with this variation application all evaluate use of basal insulin (IDeg or IDet) in combination with liraglutide. The MAH argues that liraglutide has been shown to be as least as effective as Byetta, Bydureon, and Lyxumia with regard to improvements in HbA1c. This is supported by published data (Buse JB, et al. Lancet 2009; 374:39-47 [Byetta]; Buse JB, et al. Lancet. 2013; 12;381(9861):117-

24 [Bydureon]; Kapitza C, et al. Diabetes Obes Metab. 2013; 15(7):642-9) [Lyxumia]). The comparative data includes both short-acting and long-acting GLP-1 receptor agonists. It is therefore accepted that the data obtained with liraglutide can be extrapolated to achieve a general claim of IDeg in combination with GLP-1 receptor agonists from an efficacy point of view. Considering the similarities in safety profile within the class of GLP-1 receptor agonists, no difference in the safety profile is expected if IDeg is combined with other GLP-1 receptor agonists than liraglutide. The recommendation to reduce the IDeg dose when initiating GLP-1 receptor agonist is deemed adequate in order to minimise the risk of hypoglycaemia.

Conclusion

The benefit risk balance for the use of insulin degludec (Tresiba) in combination with GLP-1 receptor agonists is considered positive. The overall benefit risk balance for Tresiba remains positive.

4. Recommendations

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 change:

Variation requested		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

Update of sections 4.2 and 5.1 of the SmPC in order to include guidance for prescribers on the use of Tresiba in combination with GLP-1 receptor agonists. The Package Leaflet is updated accordingly.

Furthermore, the PI is being brought in line with the latest QRD template version 9 and to include some editorial changes.

This variation application contains an updated RMP.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch targeting all physicians and nurses who are expected to be involved in the treatment and management of diabetic patients and all pharmacists who are expected to dispense Tresiba.

The educational pack is aimed at increasing awareness about the introduction of a new strength of insulin in the European market and describing key differences in the design of the packages and the prefilled pen devices to minimise the risk of medication errors and mix up between the two different strengths of Tresiba.

The educational pack should contain:

– Direct Healthcare Professional Communication letter as described below;

– Summary of Product Characteristics and Package Leaflet;

– Poster for display in pharmacies/diabetic units

– Patient Brochures.

The MAH shall ensure that healthcare professionals are informed that all patients who have been prescribed Tresiba should be provided with a patient brochure and be trained on the correct use of the prefilled pen before prescribing or dispensing Tresiba.

The Poster for pharmacies/diabetic units shall contain the following key elements:

– That Tresiba is available in 2 strengths;

– Key differences in the design of the packages and the prefilled pen devices;

– When prescribing to make sure that the correct strength is mentioned in the prescription slip;

– Always check the insulin label before dispensing to make sure the correct strength is delivered to the patient;

– Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;

– Do not use outside of the prefilled pen device (e.g. syringes);

– Reporting of medication errors or any side effects.

The patient brochure shall contain the following key elements:

– That Tresiba is available in 2 strengths;

– Key differences in the design of the packages and the prefilled pen devices;

– Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;

– Patients who are blind or have poor vision must be instructed always to get help/assistance from another person who has good vision and is trained in using the insulin device;

– Always use the dose recommended by your healthcare provider;

– Always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose;

– Check how many units were selected before injecting the insulin;

– The dose counter shows the number of units regardless of strength and no dose conversion should be done;

– Reporting of medication errors or any side effects.

The MAH shall agree the final text of the Direct Healthcare Professional Communication letter and the content of the patient brochure together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational pack in the Member State.