24 July 2014
EMA/CHMP/369341/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xultophy

International non-proprietary name: insulin degludec / liraglutide

Procedure No. EMEA/H/C/002647/0000

Note

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

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List of abbreviations

ADA	American Diabetes Association
ALAT	alanine aminotransferase
ANCOVA	analysis of covariance
ASAT	aspartate aminotransferase
BMI	body mass index
BNP	brain natriuretic peptide
CAS	completers analysis set
C. Hypo	confirmed hypoglycaemia
CGM	continuous glucose monitoring
DPP-4	dipeptidyl peptidase 4
E	number of events
EOT	end of text
ext	extension (Trial 3697, 52 weeks)
FAS	full analysis set
FPG	fasting plasma glucose
GI	gastrointestinal
glin	glinide
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin
HDL	high density lipoprotein
hsCRP	highly sensitive C-reactive protein
iAUC	incremental area under curve
IDeg	insulin degludec
IDegLira	insulin degludec/liraglutide
IDF	International Diabetes Federation
LDL	low density lipoprotein
Lira	liraglutide
LOCF	last observation carried forward
met	metformin
OAD	oral anti-diabetic drug
pio	pioglitazone
PYE	patient-years of exposure
R	event rate
s.c.	subcutaneous(ly)
SMPG	self-measured plasma glucose
SU	sulphonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
U	unit
UNR	upper normal range
VLDL	very low density lipoprotein

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 31 May 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xultophy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 .

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/310/2011 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP in September 2010. The Scientific Advice pertained to non-clinical, clinical and device development of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Novo Nordisk A/S
Novo Allé, Bagsværd, 2880, Denmark

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 31 May 2013.
- The procedure started on 26 June 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2013.
- During the meeting on 24 October 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 October 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 21 February 2014.
- During the CHMP meeting on 20 March 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding Issues to all CHMP members on 3 June 2014.
- During the CHMP meeting on 24 June 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The applicant submitted the responses to the CHMP List of outstanding Issues on 2 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding Issues to all CHMP members on 9 July 2014.
- During the meeting on 24 July 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Xultophy.

2. Scientific discussion

2.1. Introduction

Several large and comprehensive diabetes outcome studies have clearly demonstrated the importance of tight glycaemic control in order to avoid comorbidities, but the majority of subjects with type 2 diabetes mellitus (T2DM) nevertheless fail to meet the recommended levels of glycaemic control required to reduce long-term microvascular and macrovascular complications.

With progressing disease, patients become insulin deficient and thus require insulin therapy to obtain adequate glycaemic control. With insulin treatment, hypoglycaemia and the fear of hypoglycaemia are major limiting factors for achieving target levels of glucose control and are also barriers for timely initiation of insulin. The tendency towards weight gain with insulin treatment is an additional potential treatment barrier in patients with T2DM. When considering treatment modalities for the management of T2DM it is furthermore important to bear in mind that T2DM is a multi-organ disease, which in addition to peripheral insulin resistance and progressing relative insulin deficiency is characterised by defective secretion and/or action of incretin hormones including glucagon-like peptide-1 (GLP-1). Optimal glycaemic control therefore relies on a multi-faceted treatment approach, which often cannot be achieved by insulin treatment alone.

The combination product insulin degludec/liraglutide (IDegLira) was being developed to provide the combined benefits of insulin degludec (a long-acting basal insulin) and liraglutide (a GLP-1 receptor agonist) in a single daily injection. It was anticipated that the complementary modes of action of these two compounds would result in clinically important improvements in glycaemic control at a low risk of hypoglycaemia and weight gain in patients with T2DM. In addition, the convenience of administering both components in a single daily injection is expected to facilitate treatment compliance for patients.

Liraglutide

Liraglutide is a GLP-1 analogue with 97% sequence homology to human GLP-1. Liraglutide is the active substance of Victoza (EMEA/H/C/001026), licensed on 30/6/09. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a profile suitable for once daily administration. Liraglutide stimulates insulin secretion and lowers inappropriately high glucagon secretion, in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a delay in gastric emptying, and a modest reduction in body weight and body fat mass.

Insulin degludec

Insulin degludec is long-acting (basal) insulin given once daily, and the active substance of Tresiba (EMEA/H/C/0024980) licensed on 21/1/13. It binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin. The blood glucose-lowering effect of insulin is due to the facilitated uptake of glucose following the binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Insulin degludec/liraglutide (Xultophy)

Xultophy is a combination of liraglutide and insulin degludec. It is presented in a single-chamber 3 ml pre-filled pen containing insulin degludec 100 units per mL and liraglutide 3.6 mg per mL, to which a disposable subcutaneous needle should be attached. As the dose of Xultophy is increased or decreased, the ratio between the doses of the two components does not change.

The combination of 2 parenteral products in this way is entirely novel in the treatment of diabetes.

Proposed indication and posology

The proposed indication was as follows

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

Proposed posology

Exactly as the 2 component products, the route of administration is subcutaneous injection, administered once daily at any time of the day, preferably at the same time of the day.

Xultophy is to be initiated and titrated according to glycaemic control (FPG levels). The dosing unit of Xultophy is defined as a "dose step". One dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide. The pre-filled pen provides up to 50 dose steps (50 units of insulin degludec and 1.8 mg liraglutide) in one injection in increments of one dose step. The recommended daily starting dose of Xultophy in patients not previously on insulin is 10 dose steps (10 U insulin degludec/0.36 mg liraglutide). In patients transferring from basal insulin therapy, the starting dose of Xultophy may be increased to 16 dose steps (16 U insulin degludec/0.6 mg liraglutide)

The maximum dose range proposed is within the licensed dose range for the liraglutide mono-component; however a starting dose incorporating only 0.36 mg liraglutide is less than the licensed starting dose (0.6 mg) for liraglutide, although in Xultophy given with 10 units of insulin.

Xultophy is proposed to be not recommended for use in patients with severe renal impairment, any degree of hepatic impairment, or in patients under 18 years of age.

The development programme

The clinical development strategy for IDegLira builds upon the knowledge obtained in the individual development programmes for IDeg (Tresiba) and liraglutide (Victoza). The completed clinical development programme for the IDeg/liraglutide ratio intended for the market comprises one single-dose clinical pharmacology trial as well as two therapeutic confirmatory trials.

The single-dose, clinical pharmacology trial (Trial 3632) was conducted to investigate to what extent the pharmacokinetic characteristics of the individual components of IDegLira were affected when compared with the mono-components. The two therapeutic confirmatory trials were conducted in subjects with T2DM to demonstrate the benefits of IDegLira relative to IDeg and liraglutide in terms of glycaemic control and to enable an evaluation of the clinical benefit-risk profile of IDegLira, including an evaluation of any additional effects of IDegLira relative to IDeg and liraglutide on key efficacy outcomes. More than 2000 subjects were exposed to trial drug in these trials, of which more than 1000 received IDegLira.

The clinical development was conducted in compliance with the EMA guideline on fixed combinations (CHMP/EWP/240/95 Rev. 1) and the EMA Guideline on the development of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing a fixed combination of 100 units/ml insulin degludec and 3.6 mg/ml liraglutide. Other ingredients are: glycerol, phenol, zinc acetate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

Xultophy is comprised of a 3 ml solution of the finished product in a cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene). The cartridge is contained in a pre-filled multidose disposable pen made of polypropylene, polycarbonate and acrylonitrile butadiene styrene, to which a disposable subcutaneous needle is to be attached.

Pack sizes of 1, 3, 5 and a multipack containing 10 (2 packs of 5) pre-filled pens have been authorised.

2.2.2. Active Substance

Insulin degludec

General information

Insulin degludec is an analogue of human insulin where threonine in position B30 has been omitted and the ε-amino group of lysine B29 has been coupled with hexadecanedioic acid via a γ-glutamic acid spacer. Insulin degludec is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and subsequent chemical modification. The structural formula of insulin degludec is given in the Figure below.

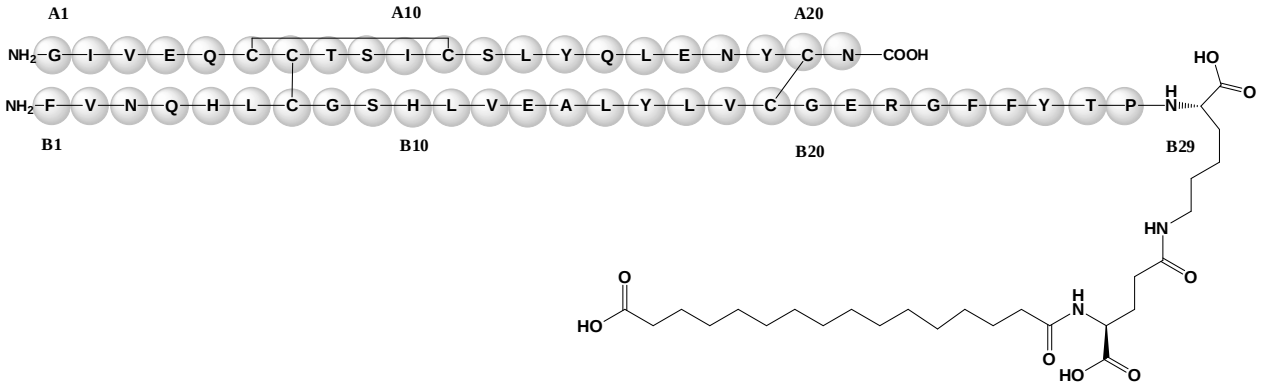


Figure: Structural formula of insulin degludec

Reference has been made to a current marketing authorization, already held by Novo Nordisk, for the insulin degludec active substance: Tresiba (EMEA/H/C/002498, date of EU-approval: 21 January 2013), Consequently, there has been no re-assessment of this drug substance in this report.

Manufacture, characterisation and process controls

The production process includes fermentation of yeast cells, recovery and purification. The fermentation produces a precursor-insulin which is cleaved to produce des-B30-insulin. This is then purified and chemically modified to insulin degludec by inserting a hexadecandioyl-γ-L-glutamate group in position B29. After further purification, the drug substance is stored at long term storage conditions according to the approved shelf-life. Satisfactory information on filling, storage and shipping has been documented.

The 'manufacture' section of the file adequately describes the control of materials including the generation of the *S. cerevisiae* production strain which produces the insulin precursor, the subsequent cell banking system and demonstration of stability of these cell banks.

Many of the raw materials used are compendial and the control of all non-compendial materials has been verified Both the critical operational parameters and critical in-process tests have been accepted and authorised for Tresiba.

The process validation has been satisfactorily performed. Potential process related impurities including host cell proteins, DNA, reagents, solvents and buffers, microbial impurities, endotoxin and other impurities along with their control are described.

Product related impurities are impurities structurally related to insulin degludec. They are generated during fermentation or downstream processing or storage. Reduction factors for each of the product related impurities are estimated from laboratory scale experiments or from process validation.. Process validation has demonstrated that the authorised manufacturing process effectively removes both product (drug substance) and process related impurities to acceptable levels.

The manufacturing process development also details the development genetics of the production strain and the development of the insulin degludec manufacturing process. The comparability of drug substance produced during development has been demonstrated and furthermore, batch data on material used in clinical trials have been provided.

Specification

The active substance specification contains parameters defining identity, content, potency and purity of insulin degludec.

No international or compendial reference material for insulin degludec exists and therefore an assignment of content in terms of international units is not applicable.

Structural and functional characterisation has been performed using state of the art techniques using drug substance batches representative of the manufacturing process used for phase 3 clinical trials and intended for the marketed product. Separation of the main product derived substances and impurities from the main substance have been described and the bioactivity of the various fractions have been characterised by a bioactivity assay which correlates well with biological activity. The authorised specifications and methods have been shown to be suitable for the control of insulin degludec. An overview of the analytical data for relevant insulin degludec drug substance batches has been presented and is acceptable. The batches have been used for non-clinical studies, clinical studies, stability studies, reference material, process validation and setting of specifications.

Stability

Stability data from primary stability studies of drug substance production scale batches and stability studies of insulin degludec drug substance Process Validation (PV) batches have been submitted. In addition, stability data for the supportive stability studies of insulin degludec drug substance pilot scale batches have been completed and are included in the application.

Stability studies at long-term storage conditions and accelerated storage conditions for the supportive, primary, and process validation batches have been performed to support the proposed shelf-life when stored at long-term storage conditions. The stability studies have been performed according to the study protocols and to current ICH stability guidelines.

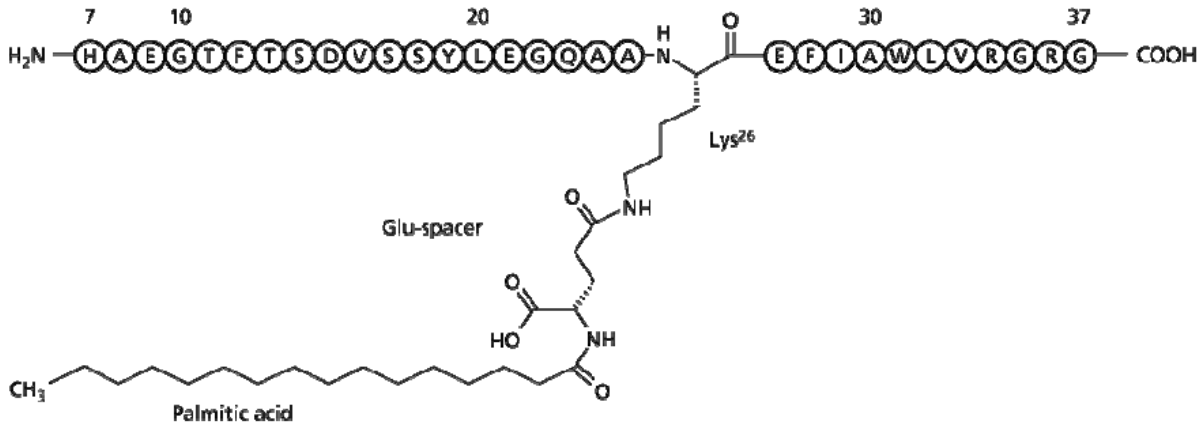
The primary and the process validation stability batches of insulin degludec drug substance show a comparable stability profile to the supportive stability batches. The stability results indicate that the drug substance is sufficiently stable.The studies conducted on supportive stability batches, primary stability batches and process validation batches can be used in establishing the proposed shelf-life for insulin degludec drug substance.

Liraglutide

General information

Liraglutide is a long acting analogue of the naturally occurring human Glucagon-Like-Peptide-1 sequence position 7-37 (GLP-1(7-37)).

The structural formula of liraglutide is shown in the figure below:



Liraglutide has a substitution of the naturally occurring amino acid residue in position 34 (Lys) by Arg and addition of a Glu-spaced palmitic acid to the ε-amino group of lysine in position 26. The analogue is produced as the polypeptide precursor by r-DNA technology with *Saccharomyces cerevisiae* as the production strain. Substitution with the side chain is performed during down-stream processing.

Reference has been made to a current marketing authorization, already held by Novo Nordisk, for the active substance liraglutide: Victoza (EMEA/H/C/001026, date of EU-approval: 30/06/2009). Consequently, there has been no re-assessment of the drug substance in this report, except for the updated documentation on reference standards of materials.

Manufacture, characterisation and process controls

The production process includes fermentation of yeast cells, recovery and purification of liraglutide precursor, acylation of the precursor and further purification of liraglutide to drug substance. The 'manufacture' section of the file adequately describes control of materials, control of critical steps and intermediates, process validation and/or evaluation and manufacturing process development. Filling, storage and transportation (shipping) procedures have been satisfactorily documented.

The generation of the Saccharomyces cerevisiae strain producing liraglutide precursor, the cell banking system and stability of the cell banks has been adequately described in the 'control of materials' section. Critical operational parameters and critical in-process tests have been defined. The purpose of the set acceptance criteria for these critical in-process tests is to control the process and to ensure that the drug substance consistently complies with the specifications. Other steps are also controlled by in process controls.

The process has been satisfactorily validated. Data was collected for critical in-process controls, specification tests on liraglutide drug substance and additional analyses. Potential process related impurities including host cell proteins, DNA, reagents, solvents and buffers, microbial impurities, endotoxin and other impurities, along with their control, are described. All acceptance criteria for the critical operational parameters and similarly acceptance criteria for the in-process tests were fulfilled.

The manufacturing process development also details the development of the liraglutide manufacturing process. The comparability of drug substance produced during development has been demonstrated and furthermore, batch data on material used in clinical trials has been provided.

Specification

No international or compendial reference material for liraglutide exists and therefore an assignment of content in terms of international units is not applicable. The specification and control of the drug substance is acceptable.

Structural and functional characterisation has been performed using state of the art techniques. Separation of product derived substances and impurities from the main substances has been described and the bioactivity of the main fractions have been characterised by a bioactivity assay.

All the analytical procedures are described. The non-pharmacopoeial methods have been validated according to the ICH Q2 (R1) guideline and brief summaries of the validations are provided.

An overview of the analytical results for relevant liraglutide drug substance batches is presented. The batches have been used for non-clinical studies, clinical studies, stability studies, reference material, process validation and setting of specifications.Product related impurities are impurities structurally related to liraglutide. Related impurities associated with liraglutide and potential degradation products have been identified. The product related impurities having biological activity are controlled. Process validation has demonstrated that the authorised manufacturing process effectively removes both product (drug substance) and process related impurities

Stability

Stability data from primary stability studies of drug substance production scale batches and stability studies of drug substance pilot scale batches have been submitted. In addition, stability data for the supportive stability studies of liraglutide drug substance pilot scale batches have been completed and are included in the application.

Stability studies at long-term storage conditions and accelerated storage conditions for the supportive, primary, and process validation batches have been performed to establish the proposed shelf-life when

stored at long term storage. Sufficient stability data has been provided to support the proposed shelf life of specified intermediates. The stability studies have been performed according to the study protocols and to current ICH stability guidelines.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

In addition to the active ingredients, the drug product contains the following excipients: phenol (preservative), glycerol (for isotonicity), zinc acetate (stabilising agent) and water. Hydrochloric acid and sodium hydroxide are used to adjust the pH of the final drug product. The insulin degludec/liraglutide (100 U/3.6 mg/ml) formulation used in phase 3 studies is identical to the intended commercial formulation.

The primary packaging is a 3 ml cartridge. The cartridge is made of clear, colourless type I glass. Closures comply with Ph.Eur. The 3 ml cartridge is assembled into a pre-filled disposable device., the PDS290 pen-injector. The pre-filled PDS290 pen-injector has been approved with other Novo Nordisk insulin drug products (Tresiba).The drug substances used for the insulin degludec/liraglutide formulations from Phase 3 and onwards are identical to the drug substances used for the approved formulations of Victoza® and Tresiba®.

Phenol is added as a preservative agent since the product is intended for multiple dosing.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Development and understanding of the drug product has been based on prior knowledge from insulin degludec (Tresiba) and liraglutide (Victoza).

During development, minor changes to optimise the manufacturing process were introduced. The manufacturing process development has been adequately described. The drug product formulation and manufacturing process tested in phase 3 clinical trials are identical to the formulation and manufacturing process intended for commercial use.

The primary packaging is described above. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by data and has been found adequate for the intended use of the product. The function and the dose accuracy of the insulin degludec/liraglutide drug product in the pen-injector has been tested and verified according to ISO standards.

Manufacture of the product and process controls

Overall, the manufacturing process for Xultophy has been sufficiently described and validated. Critical steps in the production have been adequately identified and are monitored by in-process controls.

Product specification

In general, appropriate drug product specifications have been set and justified. The release specification for Xultophy contains parameters defining identify, content, potency and purity of the product. Non-pharmacopoeial methods were validated in accordance with ICH guidelines.

Specifications and acceptable control of the impurity profile have been demonstrated and justified.

As concerns the primary packaging i.e. a 3 ml cartridge, the compatibility with the drug, the assessment of extractables and of leachables have been considered acceptably demonstrated. The description of the autoinjector design and the conformance to the relevant standards are also considered acceptable.

Stability of the product

A stability study has been performed at long term (5°C ± 3°C) and accelerated conditions on primary batches in order to establish the proposed shelf life of 24 months at 5°C. The primary batches were manufactured with a formulation and drug product manufacturing process identical to the drug product intended for the market. A stability study has also been initiated on process performance qualification (PPQ) batches in order to confirm the shelf life and show comparability between primary stability batches and PPQ batches. The parameters tested are stability indicating.

In-use stability has been performed on cartridges to establish the proposed in-use period of 21 days at a maximum temperature of 25°C.

The primary stability data and the data from the PPQ batches complied with the drug product shelf life specification. All results complied with the drug product shelf life specification.

Based on the stability studies conducted, a shelf-life period of 24 months is considered justified for drug product when stored at 5°C. An in-use period of 21 days at up to 25°C is considered justified for this product as stated in the SmPC. The photostability study concludes that the secondary packaging intended for the market (pen-injector with the cap on) provides adequate protection against light.

Adventitious agents

The manufacturing process for a raw material used in the manufacture of insulin degludec uses two bovine milk products. By reference to a current marketing authorization, already held by Novo Nordisk, these materials have already been deemed acceptable.

No animal derived raw materials or excipients are used in the production of liraglutide.

The manufacturing and formulation of insulin degludec/liraglutide drug product does not include any additional animal derived raw materials or excipients. The overall conclusion of the adventitious agents safety evaluation is that the insulin degludec/liraglutide drug product is safe with regards to both viral and TSE agents.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

This is a fixed combination of the two approved active substances insulin degludec and liraglutide. The applicant has submitted summaries on the pharmacology, pharmacokinetics and toxicology of the individual components. For the pharmacology and toxicology of the combination the applicant has submitted novel data with this application.

A detailed assessment of the pharmacology, pharmacokinetics and toxicology of the individual components is included in the European Public Assessment Report (EPAR) for Tresiba (insulin degludec; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002498/WC500139010.pdf) and Victoza (liraglutide; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001026/WC500050013.pdf), respectively.

GLP

The pivotal repeat-dose toxicity studies in rats were performed in accordance with GLP regulations.

2.3.2. Pharmacology

Insulin degludec

Insulin degludec is a long-acting insulin analogue. A series of *in vitro* and *in vivo* studies showed that insulin degludec's mode of action and metabolic effects are the same as that of naturally occurring human insulin. Due to the molecular modifications made to IDeg, its insulin receptor binding is slightly lower than that of human insulin, but the efficacy at the receptor is the same.

The ratio between IGF-1 and insulin receptor affinities for insulin degludec relative to human insulin was consistently <1 in all species and assay systems. Studies on insulin receptor activation, and cellular and mitogenic responses showed no relevant differences from human insulin.

Safety pharmacology studies in rats and dogs showed no findings except those associated with hypoglycaemia at the highest dose.

Liraglutide

Liraglutide is a recombinant analogue of GLP-1 acting as a selective agonist on the GLP-1 receptor. *In vitro* studies showed stimulation of insulin secretion and beta-cell proliferation and inhibition of beta-cell apoptosis. *In vivo* studies showed lowered blood glucose and body weight in a number of animal disease models.

In safety pharmacology studies effects were confined to the rat and these were known GLP-1 mediated effects in rodents on the cardiovascular system and kidney function.

Insulin degludec and liraglutide

Pimary pharmacodynamic studies
The acute pharmacodynamic effects of a single dose of IDegLira with a ratio of IDeg and liraglutide of 600 nmol/ml IDeg and 1600 nmol/ml liraglutide were evaluated in male Wistar rats. The effects were compared to the individual effects of IDeg and liraglutide when given alone. The pharmacodynamic effects of IDegLira on blood glucose, food and water consumption and change in body weight were as expected based on the known effects of IDeg and liraglutide tested as individual components.

Secondary pharmacodynamic studies and Safety pharmacology programme
No studies on secondary pharmacodynamics or safety pharmacology were performed.

2.3.3. Pharmacokinetics

Insulin degludec

Insulin degludec has a prolonged pharmacokinetic profile due to slow and continuous delivery of insulin degludec from a subcutaneous injection site into the systemic circulation. Tissue uptake was low with the highest tissue concentrations in kidney and liver, known to be involved in receptor mediated uptake and degradation of insulin. Metabolism and clearance is similar to clearance of human insulin.

Liraglutide

Liraglutide is a human GLP-1 analogue with a prolonged pharmacokinetic profile based on high binding to plasma proteins and stabilisation against metabolic degradation by the peptidases (DPP-IV and NEP) known to be involved in the clearance of native GLP-1. The distribution volume is low, in agreement with high protein binding. The metabolic and excretion pattern were highly similar across species with liraglutide being fully metabolised in the body by sequential cleavage.

Insulin degludec and liraglutide

The pharmacokinetics of IDegLira was evaluated by investing the PK of the two components following subcutaneous administration, as part of the general toxicity evaluation in rats. Additional evaluation was performed in pigs as part of the formulation development.

The PK of IDeg and liraglutide following s.c. administration was similar to what was observed for the mono-components. In single dose studies in pigs a tendency towards lower C_{max} was observed for liraglutide. Furthermore, the addition of zinc to a formulation of liraglutide alone resulted in a reduction in liraglutide AUC and C_{max}. This may explain the lower liraglutide exposures observed in IDegLira clinical pharmacology trials.

2.3.4. Toxicology

Insulin degludec

General toxicity was studied in rats (up to 52 weeks including carcinogenicity assessment) and dogs (up to 26 weeks). Only effects related to the pharmacological effects of insulin were observed, similar in nature and magnitude to those induced by NPH insulin.

Insulin showed no carcinogenic potential in a 52-week toxicity study in Sprague Dawley rats. No treatment related changes in the female mammary gland proliferation were found using BrdU incorporation.

In reproductive and developmental toxicity studies, decreased maternal food consumption and body weight, periparturient maternal hypoglycaemia-related mortality, lowered live birth index and viability index, lower offspring body weight and viability, skeletal changes in the offspring and delayed balano preputial separation are all considered secondary changes to the expected pharmacological effect on lowering the maternal blood glucose levels. Similar effects were seen following dosing with NPH insulin, albeit some effects were more pronounced in rats receiving insulin degludec, which is related to the higher dose and prolonged pharmacological effect observed following insulin degludec dosing compared to NPH insulin.

Liraglutide

The general toxicity of liraglutide was assessed after subcutaneous repeat-dose administration in mice, rats and monkeys for up to 3,6 and 12 months, respectively. Expected pharmacological effects on food consumption and body weight were seen in all species. These effects were the dose-limiting factor in all species tested. Thyroid C-cell hyperplasia was seen in mice after 3 months of dosing. No other target organ of systemic toxicity was identified.

Liraglutide was tested for carcinogenic potential in 104-week studies in mice and rats. In mice, a treatment-related increase in thyroid C-cell adenomas was seen in two highest dose-groups and thyroid C-cell carcinomas were seen in the highest dose group. In rats, a treatment-related increase in thyroid C-cell adenomas was seen in males in the two highest dose groups and at all doses in females. An increase in thyroid C-cell carcinomas was observed in all groups of males and in females at the two highest doses.

Based on published literature and further substantiated with experimental data, the mode-of-action behind the C-cell findings is proposed to due to the following sequential key events:

1) Circulating liraglutide binds to and activates GLP-1 receptors on C-cells.
2) GLP-1 receptor activation on C-cells induces calcium release.
3) Persistent GLP-1 receptor stimulation of the C-cells leads to C-cell hyperplasia in rodents.

In a combined fertility and embryo-foetal development study in rats, an increase in early embryonic deaths and an increased incidence of foetuses with minimally kinked ribs were seen at the highest dose level, corresponding to 11-fold the MRHD based on $AUC_{(0\text{-}24h)}$. At this dose level maternal clinical signs of adverse reactions, decreased food consumption and body weight were observed. In the rabbit developmental study foetal effects were reduced foetal weight, an increase in skeletal variations and a slight increase in the number of gall bladder abnormalities. In the pre- and post-natal development study in rats, pharmacologically mediated effects on body weight and food consumption in F0 animals and a decreased body weight gain in F1 animals was observed at all doses.

Insulin degludec and liraglutide

The general toxicity of IDegLira was assessed in two pivotal toxicity studies in rats after s.c. repeated dose administration for up to 13 weeks duration. Effects related to the pharmacological effects of insulin and GLP-1 analogues were seen. These were mainly episodes of lowered blood glucose/hypoglycaemia, reduced food consumption and reduced body weight gain. Histological effects were observed in the adrenal gland, liver and testis. Such effects have been reported earlier with insulin alone or were similar to effects of reduced food consumption reflecting the known pharmacology of insulin and GLP-1 analogues.

The Applicant conducted a study to investigate the effect of liraglutide and insulin on the proliferation of the mouse pancreatic beta cell line INS-1. When administered separately, insulin and liraglutide caused a concentration-dependent increase in the observed levels of mitochondrial dehydrogenase activity

(considered to be directly proportional to the number of viable INS-1 cells). Liraglutide was shown to have an additive effect on the response to insulin as opposed to a synergistic effect as there was no change in the observed EC_{50}. With the aid of COLO-205 human colon adenocarcinoma cells, the Applicant has also investigated the effects of liraglutide on the proliferative response of insulin and shown that liraglutide at up to 500 nM (which is substantially higher than the proposed C_{max} for liraglutide, ~14 nM) has no effect on the proliferative response afforded by insulin.

Local tolerance was assessed in two separate studies in pigs and rabbits. The local tissue reaction was mild and comparable to that of the vehicle.

No further toxicity studies were performed.

2.3.5. Ecotoxicity/environmental risk assessment

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

2.3.6. Discussion on non-clinical aspects

This is a fixed combination of the two approved active substances insulin degludec and liraglutide. The applicant has submitted summaries on the pharmacology, pharmacokinetics and toxicology of the individual components, a detailed assessment of which is included in the EPAR of Tresiba (insulin degludec) and Victoza (liraglutide), respectively.

The novel data submitted with this application has shown that the pharmacology and toxicology of the combination does not show any meaningful differences from what would be expected based on the knowledge of the individual components.

An area of possible concern is carcinogenicity. Liraglutide, as well as a number of other GLP-1 receptor agonists, are associated with thyroid C-cell tumours in rodents. This issue has been addressed in depth and it is agreed that while a clinical relevance cannot be fully excluded, rodents are particularly sensitive to this effect and there are no data showing an increased risk in humans. In nonclinical *in vitro* and *in vivo* models insulin degludec was not associated with an increased carcinogenic potential when compared to human insulin. However, insulin has growth-promoting activity and a theoretical risk for enhancing the carcinogenic potential of the GLP-1 receptor agonist could be depicted. Additive effects (of a small magnitude) on cell proliferation have been observed in a mouse pancreatic beta cell line and the clinical relevance of the observed magnitude of the additive effect *in vitro* and how it would translate to the *in vivo* situation is unclear. Nevertheless, it is agreed that this additive effect would occur in a small number of cells in humans which would express both the GLP-1 and the insulin receptor and would most likely affect the pancreas. Pancreatic cancer has been included as a potential risk within the risk management plan.

It is evident that when administered as individual components both insulin degludec and liraglutide can potentially affect embryofoetal development and for this reason, the SmPC currently states that Xultophy should not be used in pregnant women. Given the magnitude of the safety margins for insulin degludec, it is agreed that the potential for significant additive or synergistic effects of the fetus following treatment with IDegLira (if used as proposed) are low. The proposed wording in Sections 4.6 and 5.3 of the SmPC (which is in line with the current wording used for liraglutide) was therefore considered to be acceptable by CHMP.

2.3.7. Conclusion on the non-clinical aspects

There are no objections to the approval of the product from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Overview of clinical studies

The safety and efficacy of IDegLira has been evaluated in two therapeutic confirmatory trials (Trials 3697 and 3912). An overview of the two trials is displayed in Table 1. In addition, supportive data from study 3948 have been submitted (Table 2). Further to this, data for trial 3951 was submitted during the procedure (Figure 1).

Figure 1 Overview of trials in the IDegLira development programme

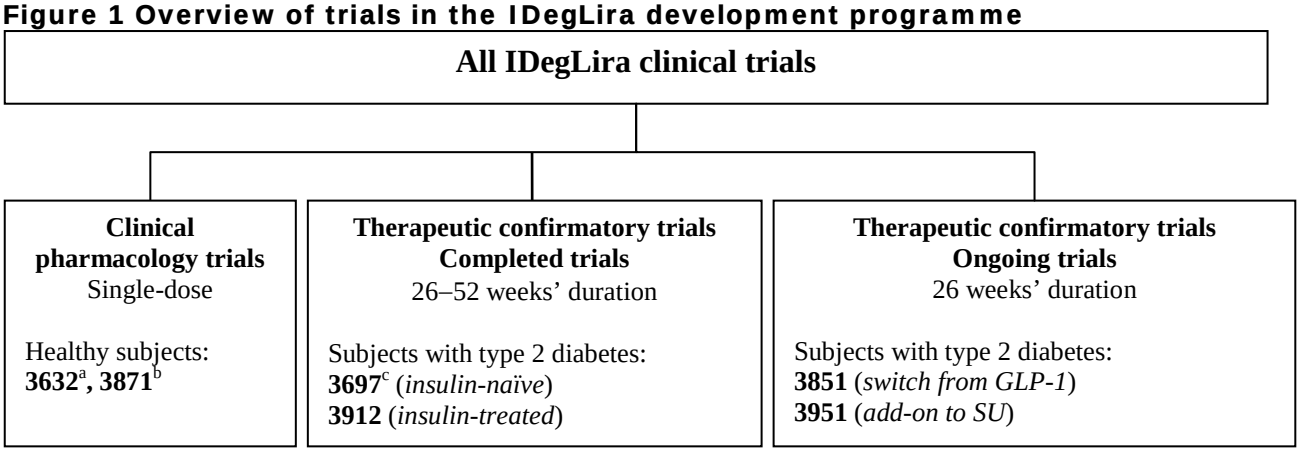


Table 1 Confirmatory therapeutic trials

Trial	Trial description and treatment	Subject population	Antidiabetic therapy at screening	Rando-mised IDegLira: comp.	No. of subjects eligible for analysis*	Endpoints/assessments

Trial	Trial description and treatment	Subject population	Antidiabetic therapy at screening	Rando-mised IDegLira: comp.	No. of subjects eligible for analysis*	Endpoints/assessments
3697 26 weeks + 26 weeks exten-sion	IDegLira versus IDeg and liraglutide in separate, parallel treatment arms (open-label). All three treatments as add-on to metformin ± pioglitazone. IDegLira and IDeg[a]: starting dose of 10 dose steps and 10 units, respectively, dosed once daily and titrated twice weekly to a FPG target of 4.0-5.0 mmol/L (72-90 mg/dL) Maximum IDegLira dose of 50 dose steps. Liraglutide[b]: Weekly dose increase of 0.6 mg/day until reaching the target dose of 1.8 mg/day Metformin: ≥ 1500 mg/day or maximum tolerated dose Pioglitazone: ≥ 30 mg/day	T2DM subjects inadequately controlled on metformin ± pioglitazone (screening HbA1c 7.0-10.0%, both inclusive). BMI ≤ 40 kg/m^2	Metformin ± pioglitazone	2:1:1	IDegLira: 833 IDeg: 413 Liraglutide: 414	• HbA1c (primary) • Responders for HbA1c targets • Insulin dose (confirmatory secondary) • Fasting plasma glucose • Prandial AUC increment based on meal test (confirmatory secondary) • 9-point SMPG profiles • CGM measurements • Hypoglycaemic episodes (confirmatory secondary) • Body weight (confirmatory secondary) • Waist circumference • Blood pressure • Cardiovascular biomarkers • Fasting lipid profile • Beta cell function • Safety
3912 26 weeks	IDegLira vs. IDeg (double-blinded), both in combination with metformin. IDegLira and IDeg: starting dose of 16 dose steps of IDegLira and 16 units of IDeg, both dosed once daily and titrated twice weekly to a FPG target of 4.0 -5.0 mmol/L (72 -90 mg/dL). Maximum IDegLira dose of 50 dose steps and IDeg dose of 50 units. Metformin: ≥ 1500 mg/day or max tolerated dose.	T2DM subjects inadequately controlled on basal insulin + metformin ± SU or glinides (screening HbA1c 7.5-10.0%, both inclusive). BMI ≥ 27 kg/m^2	Basal insulin + metformin ± SU/glinides. Basal insulin: 20-40 units/ day. SU and glinides: ≥ half of max approved dose according to local label	1:1	IDegLira: 199 IDeg: 199	• HbA1c (primary) • Responders for HbA1c targets • Insulin dose • Fasting plasma glucose • 9-point SMPG profiles • Body weight • Waist circumference • Blood pressure • Cardiovascular biomarkers • Fasting lipid profile • Withdrawal due to ineffective therapy • Beta cell function • Safety
3951 26 weeks	IDegLira vs. placebo (double-blinded), both in combination with SU ± metformin.	T2DM inadequately controlled on their current OAD regimen of SU ±	SU ± metformin.	2:1	IDegLira: 288 Placebo: 146	• HbA1c (primary) • Responders for HbA1c targets • Withdrawal due to ineffective therapy • Fasting plasma glucose

Trial	Trial description and treatment	Subject population	Antidiabetic therapy at screening	Rando-mised IDegLira: comp.	No. of subjects eligible for analysis*	Endpoints / assessments
	IDegLira: starting dose of 10 dose steps of IDegLira, dosed once daily and titrated twice weekly to a FPG target of 4.0 -6.0 mmol/L (72 -108 mg/dL) Maximum IDegLira dose of 50 dose steps. SU: ≥ half of the maximum approved dose according to local label. Metformin: ≥ 1500 mg/day or max tolerated dose.	metformin (screening HbA1c 7.5-9.0%, both inclusive). BMI ≤ 40 kg/m^2				• 9-point SMPG profiles • Fasting insulin • Fasting C-peptide • Fasting glucagon • Body weight • Waist circumference • Fasting lipid profile • Blood pressure • Safety

[a] One dose step of IDegLira is equivalent to 1 unit IDeg and 0.036 mg liraglutide.
[b] Liraglutide was started with 0.6 mg/day and subsequent 0.6 mg weekly dose escalation to a maximum dose of 1.8 mg/day, where after it should remain unchanged.
* 18 subjects (3 from Trial 3697 and 15 from Trial 3912) were excluded from analysis
Abbreviations: BMI = Body mass index; glin = glinide; IDeg = insulin degludec; IDegLira = insulin degludec/liraglutide; met = metformin; pio = pioglitazone; SU = sulphonylurea; T2DM = type 2 diabetes mellitus.

Table 2

Trial ID Country	Type of study	Trial design and type of control	Test drugs and route of administration	Number of subjects in full analysis set (male (M)/female (F))	Healthy or T2DM	Duration of treatment	Study status Type of report Location
NN1250-3948 AT, BE, CA, CZ, DE, DK, ES, FI, FR, NO, RS, US	Efficacy and safety	Multi-centre, multi-national randomised (1:1), open-label, two-arm, parallel group, treat-to-target trial comparing liraglutide to insulin aspart (IAsp), both as add-on to IDeg + metformin in subjects with T2DM who had completed approximately 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643, and with an end-of-treatment HbA1c ≥7.0% thus qualifying for further treatment intensification	Liraglutide OD s.c. IAsp OD s.c. Both as add-on to IDeg (OD, s.c.) + metformin (oral) **Liraglutide:** Starting dose of 0.6 mg/day, increased to 1.2 mg/day after 1 week, and then maintained at 1.2 mg; further increased to 1.8 mg after week 5 if needed based on FPG **IAsp:** 4 units with the main meal of the day **IDeg:** Starting dose based on individual end-of-treatment dose in Trial NN1250-3643, hereafter titration of dose according to titration guideline **Metformin:** Continued at pre-trial dose level	IDeg + liraglutide: 88 (M: 63/F: 25) IDeg + IAsp: 89 (M: 53/F: 36)	T2DM	26 weeks	Completed Full report Module 5.3.5.4

IDegLira: Insulin degludec/liraglutide; IDeg Insulin degludec; IAsp: Insulin aspart; OD: once-daily; s.c. subcutaneous; M: male; F: female; T2DM: type 2 diabetes mellitus

2.4.2. Pharmacokinetics

The application of IDegLira is referring to the data from the mono-components, a detailed assessment of which is included in the EPAR of Tresiba (insulin degludec) and Victoza (liraglutide), respectively.

The following trials contribute to characterize the clinical pharmacology properties of the combination:

NN9068-3632 was a single dose trial in healthy subjects comparing the bioavailability of IDegLira with the mono-components given separately or concomitantly. This study used the dose 17U/0.6 mg, which is the IDeg/Lira ratio intended for the market (100 U/3.6 mg). The study included 24 healthy male volunteers, and each subject was dosed on 4 occasions with 7-15 days wash-out. All doses were administered s c in the thigh, with PK sampling for 72 hours for Lira and 96 hours for IDeg. The planned analysis of bioavailability was based on a two-sided statistical test at 95% significance level instead of an equivalence test. The ratios of AUC and Cmax with 90% CI were evaluated in a post-hoc analysis, and are presented in the assessment.

NN9068-3697 was a 26-week randomised, parallel, three-arm, open-label, multi-centre, treat-to-target trial comparing fixed ratio combination of insulin degludec and liraglutide versus insulin degludec or liraglutide alone, in subjects with type 2 diabetes treated with 1-2 oral anti-diabetic drugs with a 26-week extension. A total of 1660 patients with type 2 diabetes out of 1663 patients randomised were included in the FAS data. The PK, including dose-proportionality and selected covariate effects, of IDeg and liraglutide was assessed using a population approach.

In addition, study **NN9068-3871** was a relative bioavailability study on an early formulation of IDegLira, with another ratio between the agents (100 U/6 mg). This formulation has not been further developed, and the study has not been assessed.

Bioassays

IDeg was assayed using a specific sandwich ELISA. The assay has previously been assessed in the approval of Tresiba, and found to be acceptable. Liraglutide was quantified by an ELISA with two monoclonal antibodies directed against different epitopes of liraglutide. The validation was acceptable, and conventional acceptance criteria were used.

Results

NN9068-3632 The combination product IDegLira resulted in an IDeg exposure very similar to that of mono-component IDeg, whereas the bioavailability of Lira was somewhat (11%) lower with 23% lower Cmax when given in the combination product. A 12% higher Cmax was observed for IDeg when given in the combination product. Possible reasons for, or clinical implications of, the observed differences are not discussed by the applicant.

NN9068-3697 The evaluation of PK in the patient population and anticipated special populations was essentially adequate. Results show that weight and gender were found to be significant covariates for liraglutide and only weight for insulin. However, as Xultophy is dosed using individual titration, dose-adjustments based on body weight would be redundant. The PK data is limited for the very elderly and patients with moderate renal impairment.

Absorption
The overall exposure of insulin degludec was equivalent following administration of Xultophy versus insulin degludec alone while the C_{max} was higher by 12%. The overall exposure of liraglutide was equivalent following administration of Xultophy versus liraglutide alone while C_{max} was lower by 23%.

Distribution
Insulin degludec and liraglutide are extensively bound to plasma proteins (> 99% and > 98%, respectively).

Elimination
The half-life of insulin degludec is approximately 25 hours and the half-life of liraglutide is approximately 13 hours.

2.4.3. Pharmacodynamics

Mechanism of action

Xultophy is a combination product consisting of insulin degludec and liraglutide having complementary mechanisms of action. Insulin degludec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin. Liraglutide is a Glucagon-Like Peptide-1 (GLP-1) analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor. Liraglutide stimulates insulin secretion and lowers inappropriately high glucagon secretion in a glucose-dependent manner.

Primary and Secondary pharmacology

Insulin degludec (IDeg) is a basal insulin with a glucose-lowering effect which extends beyond 42 hours. Steady state is achieved following 2-3 days of once-daily dosing with no further increase in exposure thereafter.

The day-to-day variability in glucose-lowering effect, as assessed by the glucose infusion rate during euglycaemic clamps, is lower with IDeg compared to insulin glargine. IDeg can be administered subcutaneously in the abdomen, deltoid or thigh with equal effect.

The long pharmacodynamic properties of IDeg are preserved in all populations investigated. There are no differences in the pharmacodynamic properties of IDeg between geriatric and younger adult subjects, between subjects with or without hepatic or renal impairment, or between subjects of different race and ethnicity. There is no difference in pharmacokinetic properties between women and men, whereas glucose-lowering effect is greater in women compared to men, consistent with the greater insulin sensitivity in women.

Liraglutide is a human analogue of the naturally occurring hormone GLP-1. Following subcutaneous administration, the protracted action profile is based on self-association, which results in slow absorption, binding to albumin, and higher enzymatic stability towards the dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidase (NEP) enzymes.

Liraglutide has a 4-hour duration of action and improves glycaemic control by stimulating insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner when plasma glucose levels are above normal. Liraglutide also reduces body weight through mechanisms involving decreased hunger and lowered energy intake.

In trial 3632, the pharmacodynamics of IDegLira was investigated in healthy volunteers by comparing the Glucose Infusion Rates (GIR) of the four treatment groups; IDeg, liraglutide, IDegLira and separate simultaneous administration of IDeg and liraglutide. Some additional pharmacodynamic response was observed for the combination of IDeg and liraglutide compared to IDeg alone, however no clear difference is observed between the combination and liraglutide alone. Comparable results were observed for IDegLira (fixed combination) vs the free combination. No synergistic effect was observed. When interpreting the data it should be taken into consideration that the euglycaemic clamp situation does not reflect the clinical setting.

The pharmacodynamics of IDegLira was further investigated in a sub-population in trial 3697 after a standardised liquid meal. The effect on postprandial glucose levels are further discussed in the efficacy section of this report. The data on serum insulin, serum C-peptide AUC_{0-4h} and plasma glucagon AUC_{0-4h} indicate that the liraglutide effect on these parameters is maintained when given in the fixed combination.

Over the 26 week treatment period, the insulin secretion rate was comparable for IDegLira and liraglutide alone, whereas a lower insulin secretion rate was observed for IDeg. Corresponding findings were observed when beta-cell function was estimated.

The relationship between dose/exposure and effect was investigated in study 3697 and the data show that both components contribute to the glucose lowering effect. This could in part justify the use of liraglutide doses lower than the 0.6 mg dose shown efficient in the liraglutide file.

2.4.4. Discussion on clinical pharmacology

The applicant bridged his application to the clinical pharmacology data for the mono-components, based on showing similar exposure to the mono-components given separately or concomitantly. This was found to be acceptable by CHMP, given that dose proportionality was shown, meaning that bioavailability data from one dose level can be extrapolated over the full dose range. The study designs and bioanalysis methods used were considered acceptable. The use of PopPK is appropriate.

Performing study 3632 as a comparative bioavailability study instead of a bioequivalence study was found to be acceptable, as the aim was only to show similar exposure to be able to bridge to pharmacokinetic data for the mono-components, and not to enable patients to transfer from mono-components to the combination.

The modest differences in bioavailability and absorption rate observed between mono-components and the IDegLira formulation do not prevent bridging to clinical pharmacology data for the mono-components. The product IDegLira is to be used as a titration product in itself, and it is not foreseen for patients to be able to change between the individual components and the combination just by using identical dosages of the 2 components, respectively, but rather to adjust the dose of Xultophy by titration; thus it is not necessary to show strict bioequivalence. The somewhat higher Cmax of IDeg and lower Cmax and AUC of liraglutide when given in the combination product compared to mono-components are not expected to have clinical significance.

2.4.5. Conclusions on clinical pharmacology

IDegLira is a combination of the basal insulin *insulin degludec* (IDeg, active substance of Tresiba), and the GLP-1 analogue *liraglutide* (active substance of Victoza).

The mechanism of action and pharmacodynamic properties of both components, IDeg and liraglutide, have been well characterised in the development programs of the mono-components supporting their respective MAAs. Both components have a long duration of action and can be given as OD injections.

The bioavailability and dose-linearity of IDeg and liraglutide in the new formulation has been sufficiently characterised, and bridging to clinical pharmacology data of the mono-components was found to be acceptable by CHMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose-response study was performed. The ratio of IDeg and liraglutide in the IDegLira product was chosen such that clinically appropriate doses of both IDeg and liraglutide would be co-administered with the product, taking the starting dose and the maximum approved liraglutide dose of 1.8 mg per day into consideration. Two fixed IDeg/liraglutide ratios were tested in clinical pharmacology trials, and based on

these trials the ratio providing a maximum of 50 units IDeg (i.e., with each of the 50 dose steps containing 1 unit IDeg and 0.036 mg liraglutide) was considered to most adequately cover the treatment requirement of people with type 2 diabetes. This a priori assumption was in accordance with clinical experience with co-administration of basal insulin and GLP-1 analogues.

The dosing unit of IDegLira is defined as a dose step. One dose step provides 1 unit of insulin degludec and 0.036 mg of liraglutide. The pre-filled pen has a dose range of 1 to 50 dose steps in a single injection with dose adjustments of 1 dose step.

2.5.2. Main studies

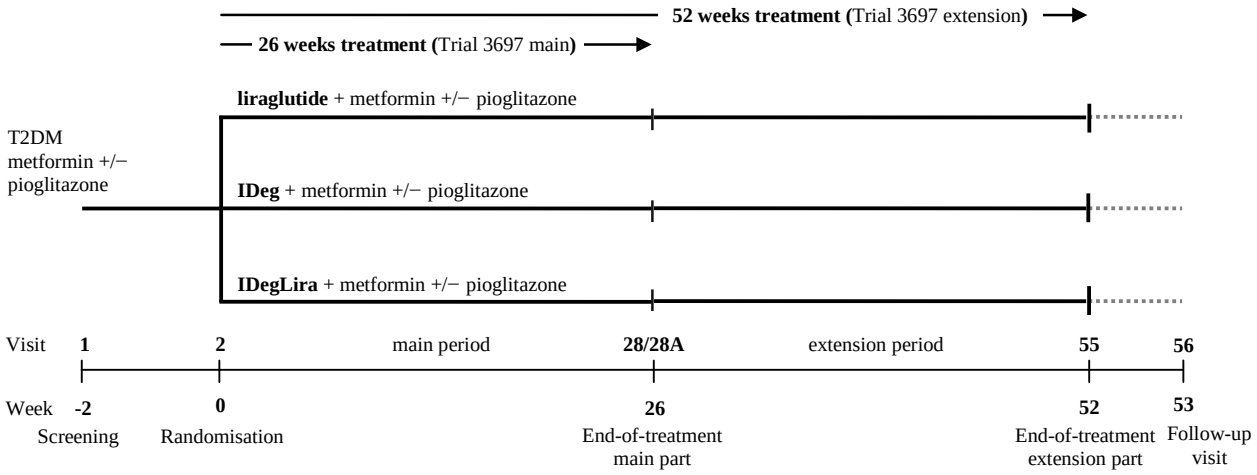
In the following the two pivotal studies and study 3951 are described in parallel.

Methods

Trial 3697

Trial 3697 was a randomised, controlled, parallel three-arm, multicentre, multinational treat-to-target trial with a 26-week main phase, which was followed by a 26-week extension phase to provide evidence of persistence of efficacy and safety during long-term exposure (Figure 2). The trial included subjects with type 2 diabetes inadequately controlled on metformin or metformin + pioglitazone, defined as HbA1c level of 7.0−10.0% (both inclusive). Subjects continued on their pre-trial OAD regimen throughout the duration of the trial.

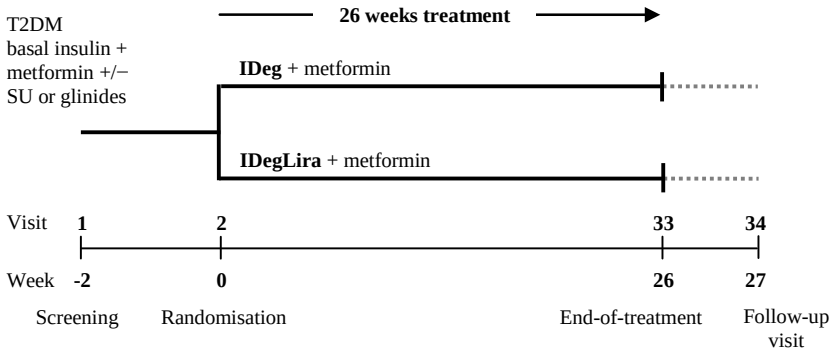
Figure 2 Design of Trial 3697



Trial 3912

Trial 3912 was a randomised, controlled, double-blind, parallel two-arm, multicentre, multinational, treat-to-target trial of 26 weeks duration (Figure 3). The trial included patients inadequately controlled on 20-40 units of basal insulin and 1-2 OADs (metformin, or metformin and sulfonylurea/glinides), defined as HbA1c of 7.5–10.0% (both inclusive).

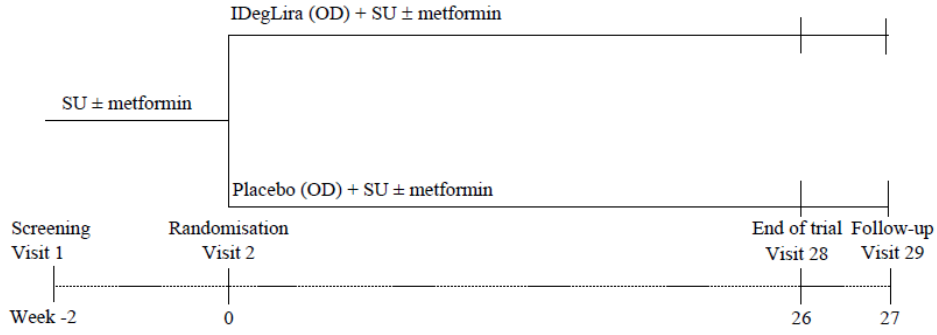
Figure 3 Design of Trial 3912



Trial 3951

Trial 3951 was a 26-week, multinational, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, treat-to-target trial in subjects with T2DM inadequately controlled on their current oral antidiabetic drug (OAD) regimen consisting of sulphonylurea (SU) with or without metformin (Figure 4). The trial compared the efficacy and safety of IDegLira once daily with placebo once daily, both added on to current SU ± metformin. Inadequately controlled T2DM was defined as an HbA1c level of 7.0–9.0% (both inclusive).

Figure 4 Design of Trial 3951



OD: once daily; SU: sulphonylurea

Objectives

Primary objective of Trial 3912

To confirm superiority of IDegLira vs. IDeg in controlling glycaemia in subjects with type 2 diabetes. The maximum insulin dose in the IDeg treatment arm was 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.

Secondary objective of Trial 3912

- To compare general efficacy and safety parameters of IDegLira and IDeg after 26 weeks of treatment.

Primary objective of Trial 3697

To confirm the efficacy of IDegLira in controlling glycaemia in subjects with type 2 diabetes. This was done by determining if 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.

Secondary objectives of Trial 3697

- To confirm superiority of IDegLira vs. IDeg after 26 weeks of treatment on either weight control, hypoglycaemic episodes, glycaemic control in relation to a meal, or glycaemic control as indirectly measured by daily dose of IDeg
- To confirm the efficacy of IDegLira in controlling glycaemia in subjects with type 2 diabetes after 52 weeks of treatment
- To compare general efficacy and safety of IDegLira, IDeg and liraglutide after 26 and 52 weeks of treatment

Primary objective of Trial 3951

To confirm superiority of insulin degludec/liraglutide compared to placebo in controlling glycaemia as add-on treatment in insulin-naïve subjects with T2DM inadequately controlled on SU with or without metformin therapy after 26 weeks of treatment.

Secondary objective of Trial 3951

To compare general efficacy and safety of the addition of insulin degludec/liraglutide and insulin degludec/liraglutide placebo in insulin-naïve subjects with T2DM inadequately controlled on SU with or without metformin therapy after 26 weeks of treatment.

Statistical methods

The statistical evaluations were based on pre-specified analyses for each trial individually, using the common statistical principles implemented across the IDegLira clinical development trial programme. The primary statistical evaluation of efficacy was based on the full analysis set (FAS) adhering to the intention-to-treat principle. Missing values were imputed using the last observation carried forward (LOCF) approach.

Continuous endpoints (including the primary endpoint) were analysed using a pre-specified standard analysis of covariance (ANCOVA) method including treatment, all stratification factors and country as fixed effects and the baseline value of the response as covariate. Log-transformation was applied for a number of pre-specified endpoints. Binary endpoints were analysed using a pre-specified standard logistic regression model with treatment, all stratification factors and country as fixed factors and the applicable baseline value as covariate. Counting endpoints (including hypoglycaemic episodes) were analysed using a pre-specified standard negative binomial regression model with a log-link function, and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset (or relevant exposure time for other endpoints). The model included treatment, all stratification factors and country/region as fixed factors. Stratification varied between trials. As pre-specified in the respective statistical analysis plans, country was exchanged with region in the analysis of binary and counting endpoints of Trial 3697 (full 52-week trial period) and Trial 3912 in order to avoid potential analysis issues caused by a low number of subjects in some countries.

Confirmatory statistical testing strategy

For the primary endpoint of change in HbA1c, non-inferiority was confirmed for the comparison of IDegLira relative to IDeg in Trial 3697 if the 95% confidence interval for the estimated mean treatment difference was entirely below the non-inferiority margin of 0.3%. Superiority of IDegLira on the primary endpoint was tested against liraglutide in Trial 3697, against IDeg in Trial 3912 and against placebo in Trial 3951. For all three comparisons, superiority was confirmed if the 95% confidence interval for the estimated mean treatment difference was entirely below 0%, equivalent to a one-sided test with a significance level of 2.5%.

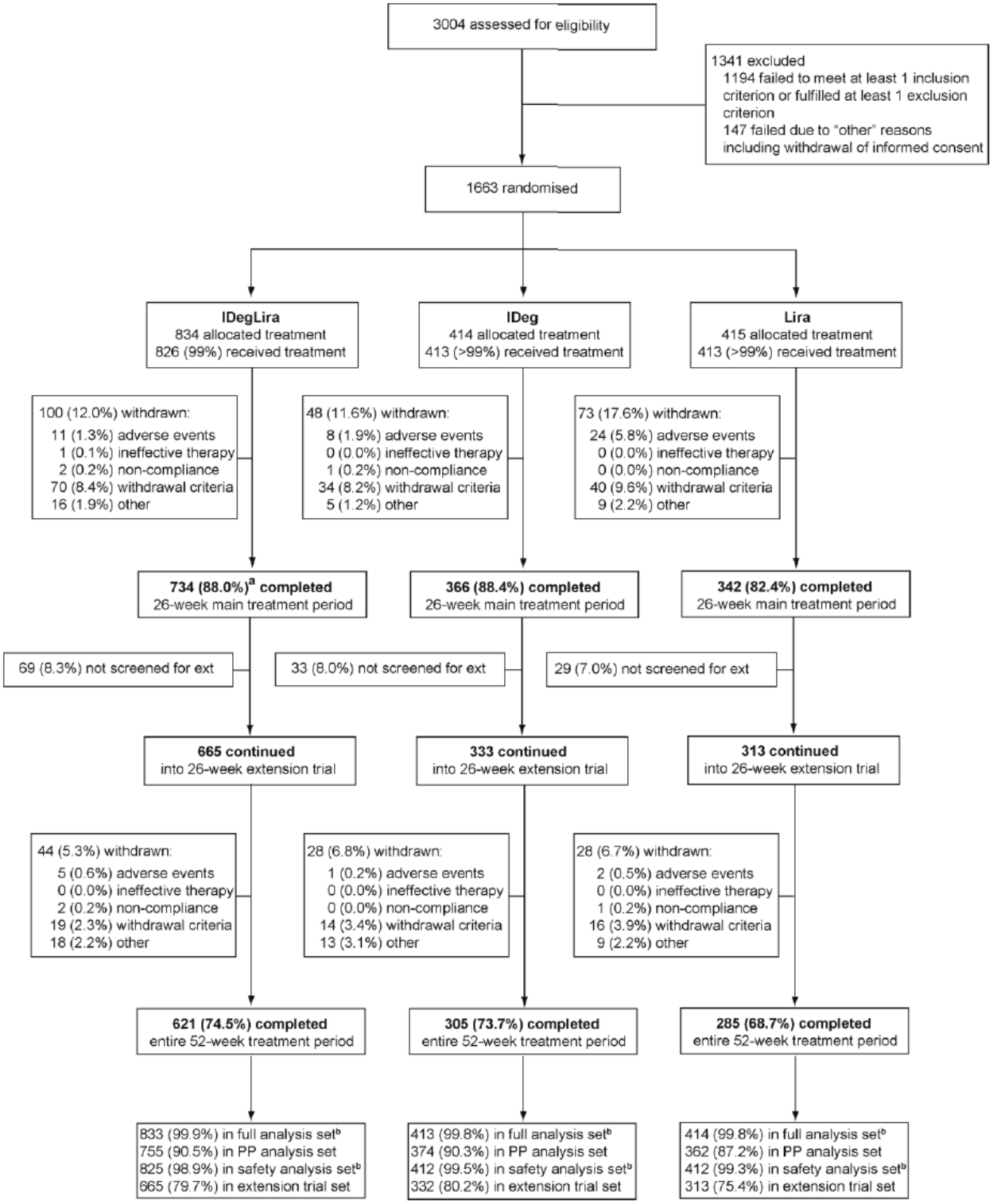
In order to ensure that the overall type I error rate was not inflated, the four confirmatory secondary endpoints of Trial 3697 were only to be tested for superiority (IDegLira versus IDeg) if the primary objective was confirmed. In addition, the family-wise type I error rate for testing the four confirmatory secondary endpoints was controlled at a 2.5% level in the strong sense using the Holm-Bonferroni method. Overall, this pre-specified confirmatory statistical testing strategy controlled the type I error rate at a 2.5% level in the strong sense with respect to testing both the primary objective and the secondary objectives.

Results

Trial 3697

Subject disposition for Trial 3697 is summarised in Figure 5. The proportion of randomised subjects who withdrew or were withdrawn before exposure to trial drug was 1.0% in the IDegLira group versus 0.2% and 0.5% in the IDeg and liraglutide groups, respectively.

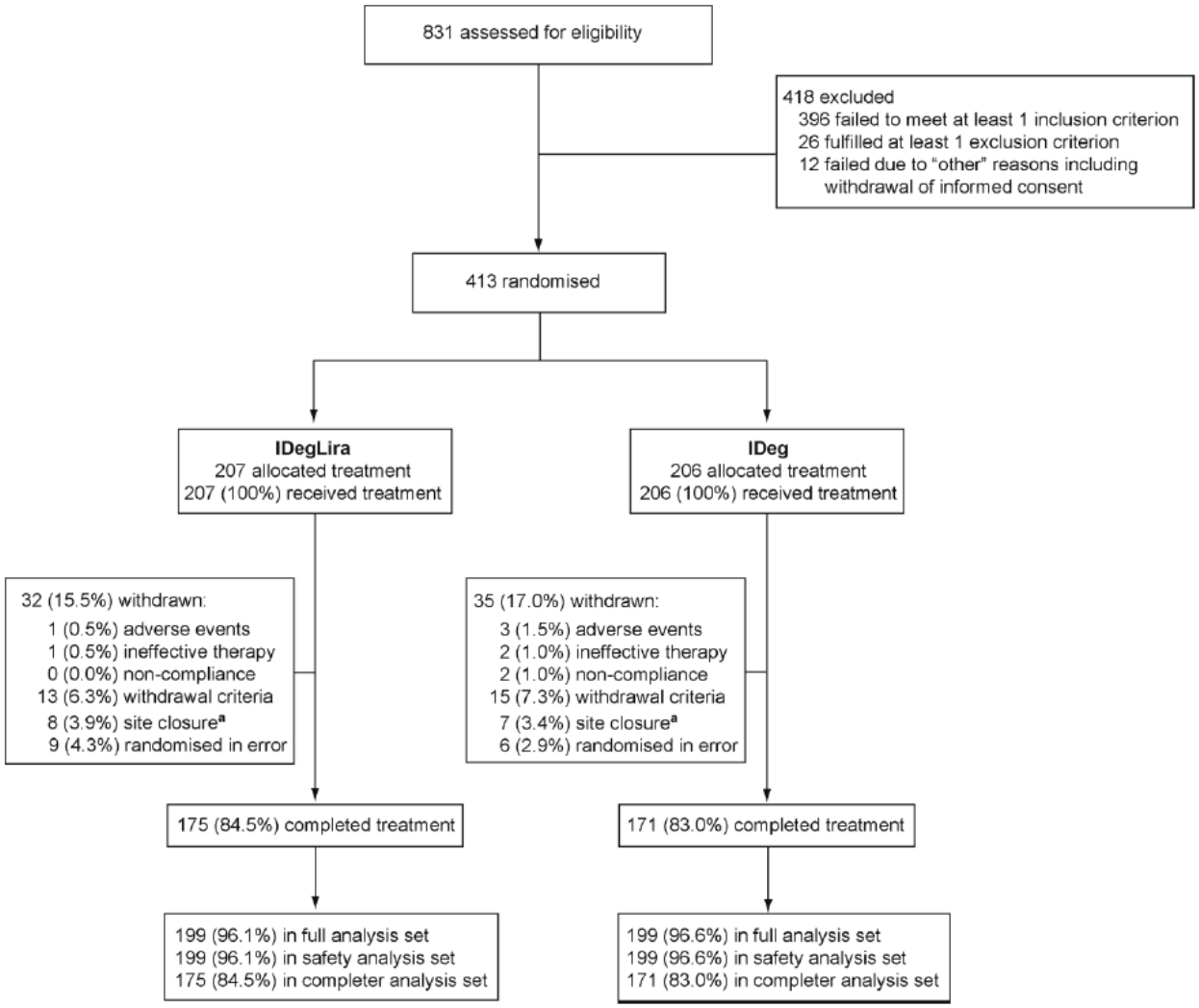
Figure 5 Subject disposition – Trial 3697



Trial 3912

In Trial 3912, the withdrawal pattern was similar between the IDegLira and IDeg treatment groups Figure 6.

Figure 6 Subject disposition – Trial 3912



Trial 3951

In Trial 3951, the withdrawal rate was higher in the placebo group. More patients in the placebo groups fulfilled withdrawal criteria and more patients in this group withdrew due to other reasons. Withdrawal due to adverse events was low (1.4 % and 3.1 % in the placebo- and IDegLira-treated groups, respectively) (Table 3).

Table 3 Subject disposition – Trial 3951

	IDegLira N (%)	Placebo N (%)	Total N (%)
Screened			760
Screening Failures			325
Withdrawn before Randomisation			0
Randomised	289 (100.0)	146 (100.0)	435 (100.0)
Exposed	288 (99.7)	146 (100.0)	434 (99.8)
Withdrawn at/after Randomisation	38 (13.1)	35 (24.0)	73 (16.8)
Adverse Event	9 (3.1)	2 (1.4)	11 (2.5)
Non-Compliance With Protocol	13 (4.5)	10 (6.8)	23 (5.3)
Withdrawal Criteria	2 (0.7)	10 (6.8)	12 (2.8)
Other	14 (4.8)	13 (8.9)	27 (6.2)
Completed	251 (86.9)	111 (76.0)	362 (83.2)
full analysis set	289 (100.0)	146 (100.0)	435 (100.0)
PP analysis set	266 (92.0)	126 (86.3)	392 (90.1)
safety analysis set	288 (99.7)	146 (100.0)	434 (99.8)

N: Number of subjects
%: Proportion of randomised subjects

Baseline data

Trial 3697

Subjects in Trial 3697 were representative of insulin-naïve subjects with type 2 diabetes, with respect to both demographic characteristics (Table 4) and other key baseline characteristics (Table 5). The three treatment groups were similar with respect to baseline characteristics. The mean age was 55.0 years, and the gender distribution was even. The racial distribution reflected the international trial design, with 61.9% of subjects being White, 21.7% being Asian Indian and 7.4% being Black or African American.

Table 4 Demographic characteristics at baseline – Trial 3697 – FAS

	IDegLira	IDeg	Lira	Total
Number of Subjects	833	413	414	1660
Age (years)				
N	833	413	413	1659
Mean (SD)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	55.0 (9.9)
Median	55.7	55.0	55.3	55.4
Min ; Max	27.8 ; 83.8	24.0 ; 79.1	24.4 ; 81.6	24.0 ; 83.8
Sex; N (%)				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Female	398 (47.8)	213 (51.6)	206 (49.8)	817 (49.2)
Male	435 (52.2)	200 (48.4)	208 (50.2)	843 (50.8)
Ethnicity; N (%)				
N	833 (100.0)	412 (100.0)	413 (100.0)	1658 (100.0)
Hispanic or Latino	127 (15.2)	67 (16.3)	56 (13.6)	250 (15.1)
Not Hispanic or Latino	706 (84.8)	345 (83.7)	357 (86.4)	1408 (84.9)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race; N (%)				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
White	513 (61.6)	257 (62.2)	258 (62.3)	1028 (61.9)
Black or African American	72 (8.6)	23 (5.6)	28 (6.8)	123 (7.4)
Asian Indian	176 (21.1)	97 (23.5)	88 (21.3)	361 (21.7)
Asian non-Indian	52 (6.2)	23 (5.6)	28 (6.8)	103 (6.2)
American Indian or Alaska Native	2 (0.2)	2 (0.5)	0 (0.0)	4 (0.2)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	18 (2.2)	11 (2.7)	11 (2.7)	40 (2.4)
BMI (kg/m^2)				
N	833	413	414	1660
Mean (SD)	31.3 (5.1)	31.2 (5.2)	31.4 (4.8)	31.3 (5.1)
Median	31.2	31.1	31.3	31.2
Min ; Max	17.3 ; 43.5	16.5 ; 40.0	20.0 ; 40.0	16.5 ; 43.5

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, %= Percentages based on N

Consistent with the subject inclusion criteria all subjects were on metformin therapy at screening, with 17.3% of subjects receiving pioglitazone concomitantly. One subject in the liraglutide treatment group was on a regimen of metformin and glimepiride at screening. This subject was randomised in error and was withdrawn at Visit 3. The subject is included in the FAS.

Table 5 Key baseline characteristics – Trial 3697 – FAS

	IDegLira	IDeg	Lira	Total
Number of Subjects	833	413	414	1660
HbA1c (%)				
N	833	413	414	1660
Mean (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)
Median	8.2	8.2	8.2	8.2
Min ; Max	6.0 ; 11.0	6.6 ; 11.3	6.4 ; 12.6	6.0 ; 12.6
FPG (mmol/L)				
N	809	409	409	1627
Mean (SD)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	9.2 (2.5)
Median	8.8	8.7	8.4	8.7
Min ; Max	2.7 ; 18.5	4.7 ; 19.4	3.1 ; 23.4	2.7 ; 23.4
Duration of diabetes (yrs)				
N	833	413	413	1659
Mean (SD)	6.6 (5.1)	7.0 (5.3)	7.2 (6.1)	6.8 (5.4)
Median	5.2	5.5	5.6	5.4
Min; Max	<0.1 ; 35.1	<0.1 ; 32.3	<0.1 ; 53.9	<0.1 ; 53.9
OAD at Screening; N (%)				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Metformin	691 (83.0)	343 (83.1)	338 (81.6)	1372 (82.7)
Metformin+Pioglitazone	142 (17.0)	70 (16.9)	75 (18.1)	287 (17.3)
Metformin+Glimepiride	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose, OAD= Oral Anti-diabetic Drug, %= Percentages based on N

Trial 3912

Subjects in Trial 3912 were representative of insulin-using subjects with type 2 diabetes, with respect to both demographic characteristics (Table 6) and other key baseline characteristics (Table 7). The two treatment groups were overall well matched with respect to demographics and baseline characteristics.

Table 6 Demographic characteristics at baseline – Trial 3912 – FAS

	IDegLira	IDeg	Total
Number of Subjects	199	199	398
Age (years)			
N	199	199	398
Mean (SD)	56.8 (8.9)	57.5 (10.5)	57.2 (9.7)
Median	56.2	58.2	57.4
Min ; Max	31.4 ; 76.9	29.5 ; 85.8	29.5 ; 85.8
Sex; N (%)			
N	199 (100.0)	199 (100.0)	398 (100.0)
Female	87 (43.7)	93 (46.7)	180 (45.2)
Male	112 (56.3)	106 (53.3)	218 (54.8)
Ethnicity; N (%)			
N	199 (100.0)	199 (100.0)	398 (100.0)
Hispanic or Latino	16 (8.0)	24 (12.1)	40 (10.1)
Not Hispanic or Latino	183 (92.0)	175 (87.9)	358 (89.9)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Race; N (%)			
N	199 (100.0)	199 (100.0)	398 (100.0)
White	157 (78.9)	151 (75.9)	308 (77.4)
Black or African American	9 (4.5)	10 (5.0)	19 (4.8)
Asian Indian	31 (15.6)	34 (17.1)	65 (16.3)
Asian non-Indian	2 (1.0)	2 (1.0)	4 (1.0)
Native Hawaiian or Oth. Pacific Island		1 (0.5)	1 (0.3)
Other		1 (0.5)	1 (0.3)
BMI (kg/m^2)			
N	199	199	398
Mean (SD)	33.6 (5.7)	33.8 (5.6)	33.7 (5.7)
Median	32.3	32.8	32.6
Min ; Max	26.5 ; 56.5	25.8 ; 54.7	25.8 ; 56.5

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, %= Percentages based on N

The results for baseline characteristics were indicative of a relatively more advanced stage of T2DM compared to subjects in Trial 3697 (higher HbA1c and FPG and a longer duration of diabetes). This is in accordance with the subject selection criteria for the two trials. The time lack from screening to baseline is a contributing factor with respect to the observation that a minority of patients deviated slightly from subject selection criteria.

Table 7 Key baseline characteristics – Trial 3912 – FAS

	IDegLira	IDeg	Total
Number of Subjects	199	199	398
HbA1c (%)			
N	199	199	398
Mean (SD)	8.7 (0.7)	8.8 (0.7)	8.8 (0.7)
Median	8.6	8.9	8.7
Min ; Max	7.2 ; 12.3	7.3 ; 10.9	7.2 ; 12.3
FPG (mmol/L)			
N	198	199	397
Mean (SD)	9.7 (2.9)	9.6 (3.1)	9.6 (3.0)
Median	9.5	9.3	9.4
Min ; Max	3.0 ; 19.1	4.2 ; 29.9	3.0 ; 29.9
Duration of Diabetes (years)			
N	199	199	398
Mean (SD)	10.3 (6.0)	10.9 (7.0)	10.6 (6.5)
Median	8.7	9.5	9.1
Min ; Max	0.8 ; 30.4	0.8 ; 40.4	0.8 ; 40.4
OAD at Screening; N (%)			
1 OAD	95 (47.7)	98 (49.2)	193 (48.5)
Metformin	95 (47.7)	98 (49.2)	193 (48.5)
2 OADs	104 (52.3)	101 (50.8)	205 (51.5)
Metformin + Glinide	4 (2.0)	2 (1.0)	6 (1.5)
Metformin + Sulphonylurea	99 (49.7)	98 (49.2)	197 (49.5)
Metformin + SU or Glinides	1 (0.5)	1 (0.5)	2 (0.5)

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose, OAD= Oral Anti-diabetic Drug, SU = sulphonylurea, %= Percentages based on N

At screening, the following basal insulins were used: insulin detemir (n=67), insulin glargine (n=174), insulin NPH (n=174) and other/unknown (n=7).

Trial 3951

The treatment groups were overall well matched with respect to demographics and baseline characteristics. The mean age was 59.8 years (29% were >65 years old), mean BMI was 31.5 kg/m2 (31.2 kg/m2 in the Xultophy group and 32.0 kg/m2 in the placebo group), and the gender distribution was even. The racial distribution reflected the international trial conduct, with 75.4% of subjects being White, 16.6% being Asian and 6.7% being Black or African American. The HbA1c inclusion criterion was 7.0−9.0%, resulting in a mean baseline HbA1c of 7.9% in both treatment groups. Mean duration of diabetes was 9.1 years. All subjects were on SU therapy at screening, with 89.2% of subjects using metformin concomitantly. Mean HbA1c at baseline was 7.9% in both treatment groups.

Outcomes and estimation

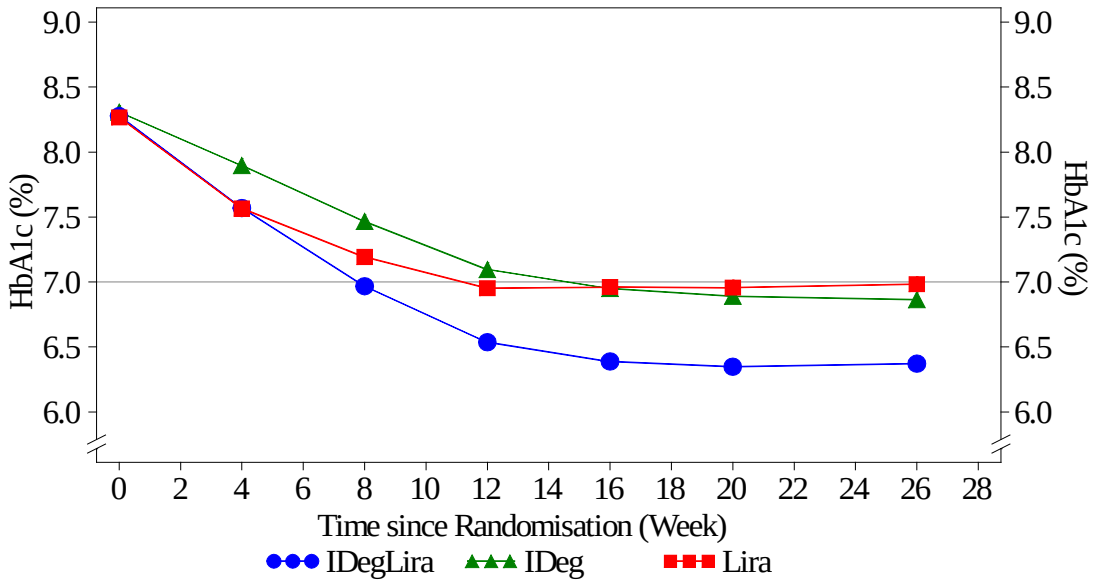
Trial 3697

Change in HbA1c (primary endpoint)

Mean HbA1c levels throughout the duration of the trial are depicted by treatment group in Figure 7. Mean HbA1c at baseline was 8.3% in all three treatment groups. After 26 weeks of treatment, HbA1c had on average decreased by 1.91%-point to 6.4% with IDegLira, by 1.44%-point to 6.9% with IDeg and by

1.28%-point to 7.0% with liraglutide. The reduction in HbA1c occurred during the initial 3 months of treatment in all treatment groups.

Figure 7 HbA1c (%) by treatment week - Trial 3697 - FAS



FAS; LOCF imputed data
Error bars: +- Standard Error (Mean)
/nn9068/nn9068-exploratory/lsuegc005
30APR2013:12:21:50 - fmean_numfind_v03.sas/e_hba1c_abs_mean_locf_3697_fas.cgm

The reduction in HbA1c was statistically significantly greater with IDegLira compared with IDeg (estimated treatment difference: -0.47 [-0.58; -0.36]$_{95\%CI}$; p<0.0001), confirming the pre-specified test for non-inferiority for this comparison. Additionally, superiority of IDegLira over liraglutide in terms of change in HbA1c was confirmed (estimated treatment difference: -0.64 [-0.75; -0.53]$_{95\%CI}$; p<0.0001).

HbA1c target responder analyses

Subjects achieving HbA1c targets

For Trial 3697, the proportion of subjects reaching the pre-defined HbA1c targets at the end of the 26-week treatment period was consistently greater with IDegLira than with comparator treatments. The American Diabetes Association (ADA) target of HbA1c <7.0% was reached by 80.6% of subjects receiving IDegLira versus 65.1% and 60.4% of subjects receiving IDeg and liraglutide, respectively. Similarly, the proportion of subjects reaching the International Diabetes Federation (IDF) target of HbA1c ≤6.5% was 69.7% with IDegLira versus 47.5% and 41.1% with IDeg and liraglutide, respectively.

Logistic regression analysis showed that the estimated odds of achieving these HbA1c targets after 26 weeks of treatment were statistically significantly greater for subjects of the IDegLira treatment group compared to those of the IDeg and liraglutide treatment groups.

Subjects achieving HbA1c targets without gaining weight

For Trial 3697, the proportion of subjects reaching the ADA target of HbA1c <7.0% without gaining weight was 46.2% with IDegLira versus 21.1% with IDeg and 54.3% with liraglutide. The proportion of subjects of Trial 3697 reaching the more ambitious IDF target of HbA1c ≤6.5% without gaining weight was 41.9% with IDegLira versus 14.5% with IDeg and 39.1% with liraglutide.

Subjects achieving HbA1c targets without confirmed hypoglycaemia

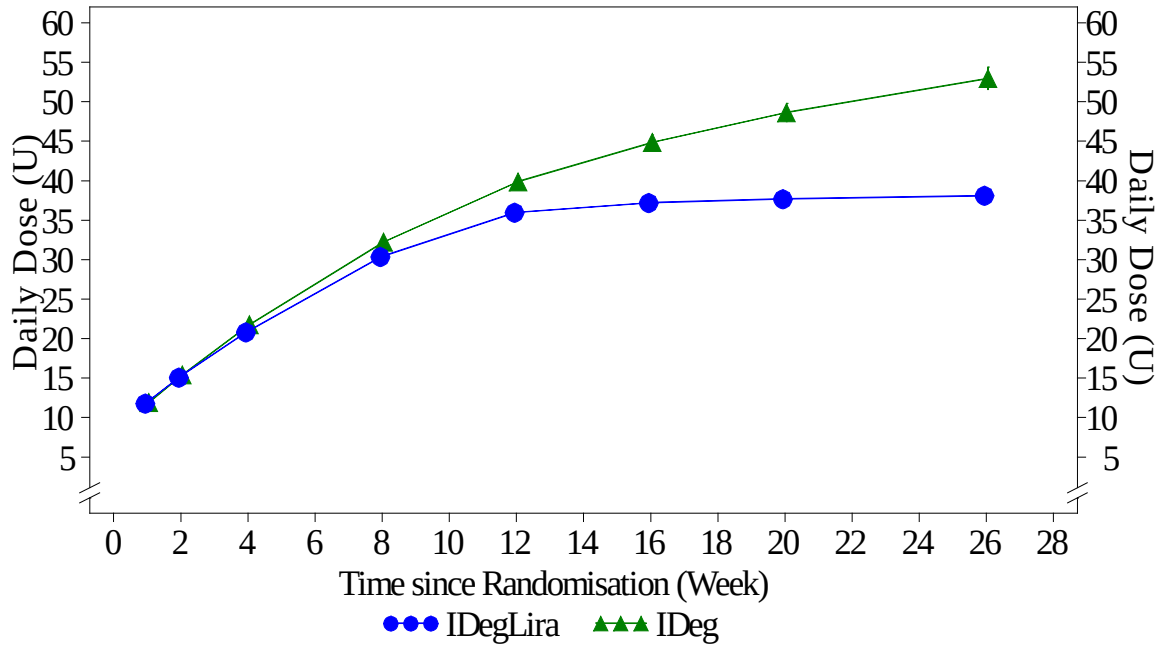
For Trial 3697 the proportion of subjects reaching the ADA target of HbA1c <7.0% without experiencing any episodes of confirmed hypoglycaemia (defined as severe hypoglycaemia according to ADA criteria or episodes of hypoglycaemia confirmed with a PG < 3.1 mmol/L (56 mg/dL) irrespective of symptoms) was 60.4% with IDegLira versus 40.9% with IDeg and 57.7% with liraglutide, i.e., with a higher responder rate for IDegLira than IDeg, and no major difference in responder rate between the IDegLira and liraglutide groups. The proportion of subjects in Trial 3697 reaching the more ambitious IDF target of HbA1c ≤6.5% without confirmed hypoglycaemia was 52.2% with IDegLira versus 27.4% with IDeg and 39.6% with liraglutide.

Insulin dose

A 'treat-to-target' approach was applied for IDegLira and IDeg treatment in both therapeutic confirmatory trials, aiming for predefined fasting plasma glucose of 4.0–5.0 mmol/L (72–90 mg/dL) in order to achieve glycaemic control, as recommended by current treatment guidelines. IDegLira and IDeg doses were titrated twice weekly in adjustments of 2 dose steps for IDegLira and 2 units for IDeg according to the average fasting mean SMPG from the preceding three daily measurements.

Actual daily insulin dose by week in Trial 3697 is presented in Figure 8. At Week 1, the mean insulin dose was 12 units in both the IDegLira group and the IDeg group. The mean insulin dose steadily increased during the first weeks of the trial in both treatment arms. After 12 weeks of treatment the insulin dose in the IDegLira treatment group remained relatively stable, whereas the insulin dose continued to increase in the IDeg treatment group (Figure 8). At the end of the main trial period at Week 26, the mean daily insulin dose was 38 units with IDegLira and 53 units with IDeg.

Figure 8 Daily insulin dose (actual) in units by treatment week – Trial 3697 – SAS



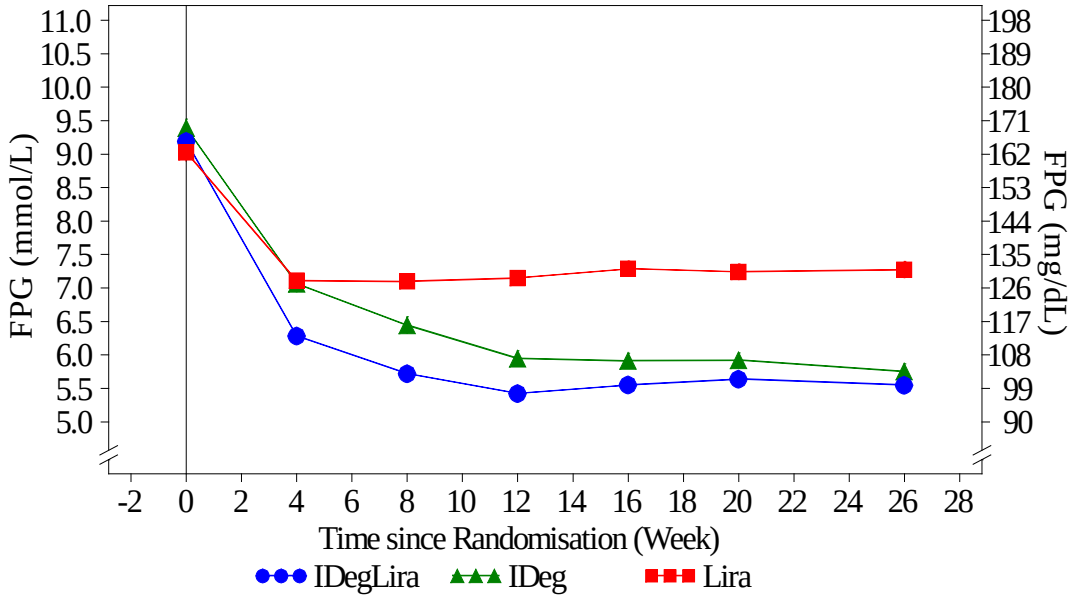
SAFETY; LOCF imputed data
Error bars: +- Standard Error (Mean)

The daily insulin dose after 26 weeks of treatment was a confirmatory secondary endpoint for Trial 3697. Results of the statistical analysis showed a statistically significantly lower insulin dose of 14.9 units with IDegLira relative to IDeg (estimated treatment difference: -14.90 units [-17.14; -12.66]$_{95\%CI}$; p<0.0001).

Fasting plasma glucose

For Trial 3697, mean FPG levels throughout the duration of the trial are depicted by treatment group in Figure 9.

Figure 9 Fasting plasma glucose by treatment week - Trial 3697 - FAS



FAS; LOCF imputed data

Error bars: +- Standard Error (Mean)

No statistically significant difference between IDegLira and IDeg was found, whereas the reduction in FPG was significantly greater for IDegLira relative to liraglutide (estimated treatment difference: −1.76 mmol/L $[-2.00;-1.53]_{95\%CI}$, $p < 0.0001$).

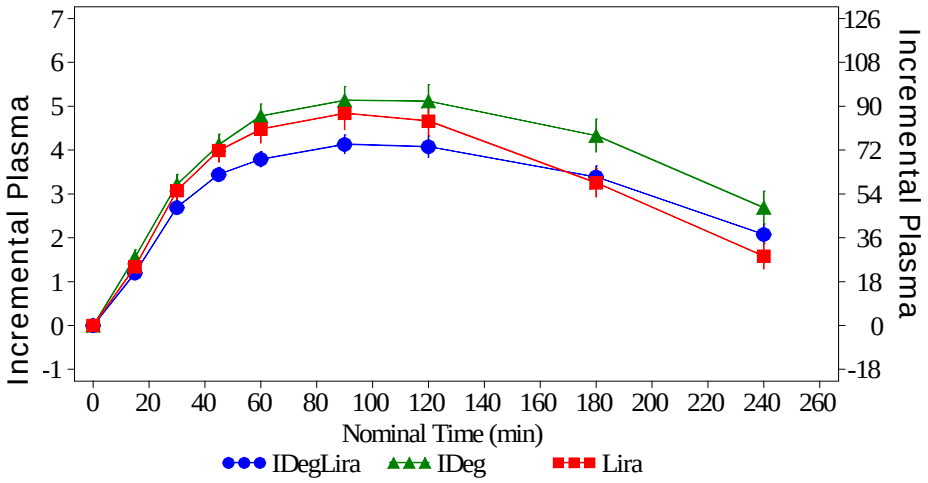
Prandial glucose control

Incremental mean plasma curves after 26 weeks of treatment are depicted in Figure 10.

Baseline normalised $iAUC_{0-4h}$ for glucose was similar across treatment groups (IDegLira: 4.11 mmol/L [74.1 mg/dL], IDeg: 4.12 mmol/L [74.2 mg/dL], and liraglutide: 4.12 mmol/L [74.1 mg/dL]).

After 26 weeks of treatment, $iAUC_{0-4h}$ had decreased by 0.87 mmol/L [15.7 mg/dL] with IDegLira, by 0.16 mmol/L [3.1 mg/dL] with IDeg and by 0.78 mmol/L [14.2 mg/dL] with liraglutide.

Figure 10 Incremental mean plot of plasma glucose after 26 weeks of treatment – Trial 3697 - FAS

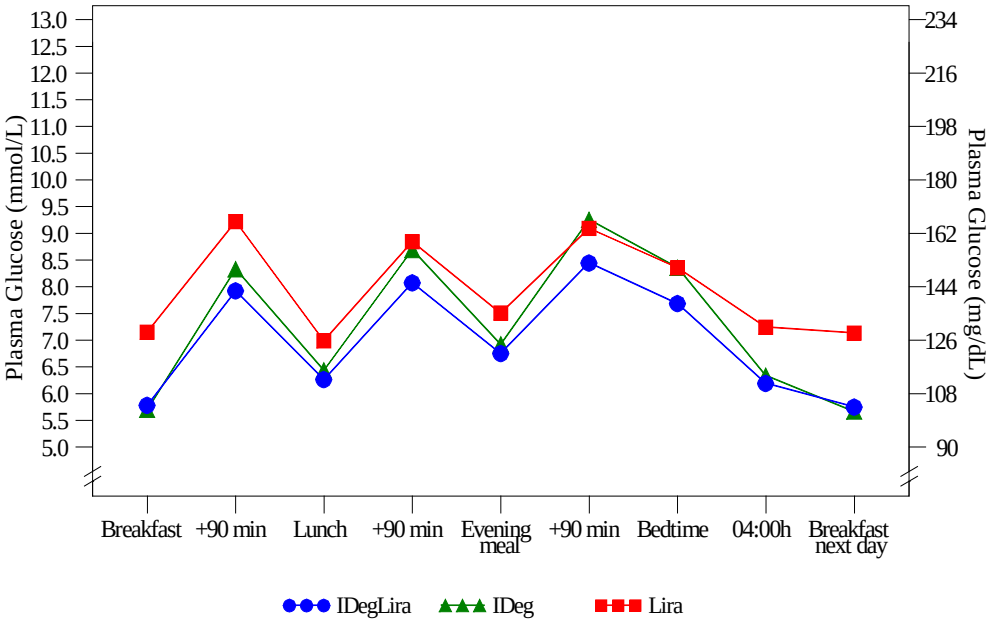


Missing profiles are imputed from Week 0
Error bars: +- Standard Error (Mean)

The reduction in prandial increment was statistically significantly greater with IDegLira than with IDeg (estimated treatment difference: -0.71 mmol/L [-1.17; -0.26]$_{95\%\ CI}$; p = 0.0023) confirming superiority, whereas no significant difference between IDegLira and liraglutide was observed for change in prandial increment.

The results on incremental AUC described above are in alignment with the results on self-measured plasma glucose (SMPG) profiles for the full trial population as illustrated in Figure 11. In addition to a statistically significantly greater reduction in mean of 9-point SMPG profile with IDegLira compared to IDeg (estimated treatment difference -0.30 mmol/L [-0.50; -0.09]95%CI, p = 0.0040) and liraglutide (estimated treatment difference -0.93 mmol/L [-1.13; -0.73]95%CI, p < 0.0001), there was a lower mean prandial increment across all meals with IDegLira compared to IDeg (1.9 mmol/L [34 mg/dL] vs. 2.4 mmol/L [43 mg/dL]). The increment observed with liraglutide (1.9 mmol/L [34 mg/dL]) was similar to that of IDegLira.

Figure 11 Mean 9-point SMPG profile at Week 26 – Trial 3697 – FAS



LOCF imputed data for all time points

Hypoglycaemia

Confirmed hypoglycaemia

Confirmed hypoglycaemia (defined as either severe hypoglycaemia according to ADA criteria or episodes of hypoglycaemia confirmed with a PG < 3.1 mmol/L (56 mg/dL) irrespective of symptoms) was recorded for 31.9% of subjects receiving IDegLira and for 38.6% of subjects receiving IDeg. Corresponding event rates were 180.2 and 256.7 events per 100 patient-years of exposure (PYE). Confirmed hypoglycaemia was a confirmatory secondary endpoint for Trial 3697 and was analysed using a negative binomial regression model. The analysis shows a statistically significant 32% reduction in the rate of confirmed hypoglycaemic episodes with IDegLira relative to IDeg (estimated treatment ratio: 0.68 [0.53; 0.87]$_{95\%CI}$; p= 0.0023).

A significantly lower risk of confirmed hypoglycaemia with liraglutide relative to IDegLira was observed in Trial 3697 (estimated treatment ratio (IDegLira vs. liraglutide): 7.61 [5.17; 11.21]$_{95\%CI}$; p < 0.0001).

A statistically significant reduction of 32% with IDegLira relative to IDeg was also seen for the rate of documented symptomatic hypoglycaemic episodes (as defined by ADA), thus confirming the results obtained for confirmed hypoglycaemia. The estimated event rates of documented symptomatic hypoglycaemic episodes were 375.85 and 554.54 events per 100 patient-years of exposure (PYE) for IDegLira and IDeg, respectively; estimated rate ratio 0.68 [0.52; 0.89]$_{95\%CI}$; p = 0.0049.

Body weight

Mean body weight at baseline was similar across treatments (IDegLira: 87.2 kg, IDeg: 87.4 kg, and liraglutide: 87.4 kg). After 26 weeks of treatment, mean body weight had decreased by 0.5 kg with IDegLira, increased by 1.6 kg with IDeg and decreased by 3.0 kg with liraglutide.

The estimated treatment difference between IDegLira and IDeg of -2.22 kg [-2.64; -1.80]95%CI as well as the estimated treatment difference between IDegLira and liraglutide of 2.44 kg [2.02; 2.86]95%CI

were both statistically significant (p< 0.0001 for both comparisons). Results for change in BMI as well as change in waist and hip circumference were in alignment with the above results on weight change.

Efficacy results after 52 weeks exposure

A total of 1311 patients (78.8 % of patients randomised to the core phase) were included in the extension phase of trial 3697 (IDegLira 665 (79.7 %); IDeg 333 (80.4 %); Lira 313 (75.4 %)). Out of these, 1211 patients (72.8 %) completed the study (IDegLira 621 (74.5 %); IDeg 305 (73.7 %); Lira 285 (68.7 %).

Key efficacy results pertaining to the extended 52-week treatment period of Trial 3697 are compared against the corresponding results for the 26-week treatment period in Table 8.

Table 8 Key efficacy results for 26 vs. 52-week treatment period – Trial 3697 – FAS

	26-week results			52-week results		
Endpoints Treatment contrast or ratio	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Change in HbA1c (%-point)						
IDegLira – IDeg	-0.47	[-0.58; -0.36]	<0.0001	-0.46	[-0.57 ; -0.34]	<0.0001
IDegLira – lira	-0.64	[-0.75; -0.53]	<0.0001	-0.65	[-0.76 ; -0.53]	<0.0001
Insulin dose (units/day)						
IDegLira – IDeg	-14.90	[-17.14; -12.66]	<0.0001	-23.38	[-26.44;-20.31]	<0.0001
Change in prandial glucose increment ($iAUC_{0-4h}$; mmol/L)*						
IDegLira – IDeg	-0.71	[-1.17 ; -0.26]	0.0023	-0.64	[-1.11 ; -0.17]	0.0073
IDegLira – lira	-0.09	[-0.56 ; 0.37]	0.7000	0.05	[-0.43 ; 0.53]	0.8417
Confirmed hypoglycaemic episodes						
IDegLira/IDeg	0.68	[0.53 ; 0.87]	0.0023	0.63	[0.50 ; 0.79]	<0.0001
IDegLira/lira	7.61	[5.17 ; 11.21]	<0.0001	8.52	[6.09 ; 11.93]	<0.0001
Change in body weight (kg)						
IDegLira – IDeg	-2.22	[-2.64 ; -1.80]	<0.0001	-2.80	[-3.34 ;-2.27]	<0.0001
IDegLira – lira	2.44	[2.02 ; 2.86]	<0.0001	2.66	[2.13 ; 3.20]	<0.0001

* Calculated for a pre-specified population of 260 subjects of Trial 3697

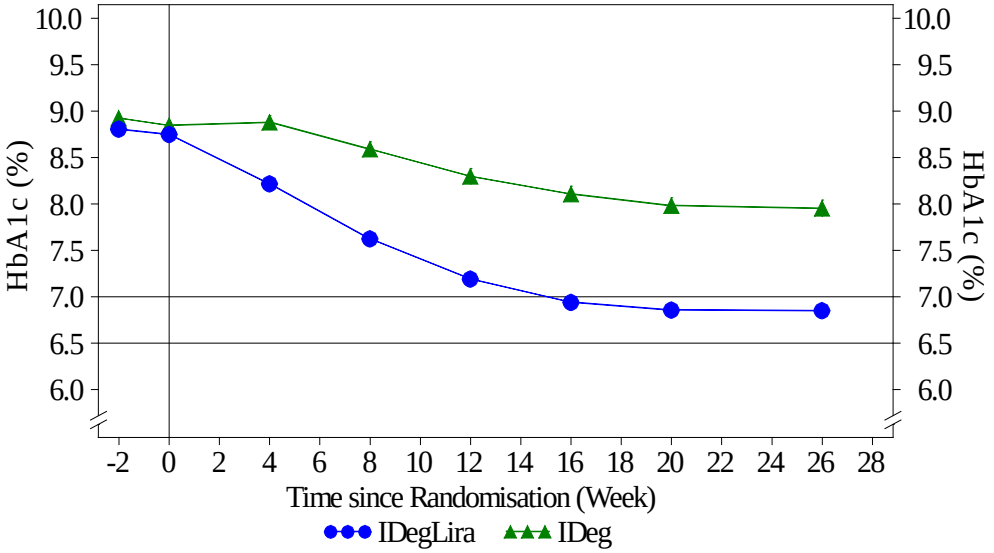
After 12 weeks of treatment, the insulin dose in the IDegLira treatment group remained stable during extended exposure, whereas the insulin dose continued to increase in the IDeg treatment group. At Week 52, mean daily insulin dose was 39 units and 62 units for subjects treated with IDegLira and IDeg, respectively, with a similar proportion of IDegLira treated subjects reaching the maximum dose after 52 weeks as compared to after 26 weeks of treatment. Despite the dose difference at Week 52, the mean fasting SMPG was close to the glycaemic target and similar in both treatment groups after 52 weeks of treatment (IDegLira: 5.6 mmol/L [101 mg/dL] and IDeg: 5.4 mmol/L [97 mg/dL]).

Trial 3912

Change in HbA1c (primary endpoint)

Mean HbA1c levels throughout the duration of the trial are depicted by treatment group in Figure 12. Mean HbA1c at baseline was 8.7% in the IDegLira group and 8.8% in the IDeg group. After 26 weeks of treatment, HbA1c had on average decreased by 1.90 %-point to 6.9% with IDegLira and by 0.89 %-point to 8.0% with IDeg. The reduction in HbA1c was statistically significantly greater with IDegLira compared with IDeg (estimated treatment difference: -1.05 %-point [-1.25; -0.84]95%CI, p < 0.0001).

Figure 12 HbA1c by treatment week - Trial 3912 – FAS



FAS; LOCF imputed data
Error bars: +- Standard Error (Mean)

HbA1c target responder analyses

Starting at an HbA1c of 8.7%, the HbA1c targets of <7% and ≤6.5% were reached by 60.3% and 45.2% of IDegLira-treated subjects, respectively, and a significant proportion of these subjects reached these glycaemic targets without gaining weight or experiencing any events of confirmed hypoglycaemia. In comparison, the HbA1c targets of <7% and ≤6.5% was reached by 23.1% and 13.1% of IDeg-treated subjects, respectively.

Insulin dose

Within the limitation of the allowed maximum doses, a treat-to-target approach and frequent visit schedule were applied during the treatment period to ensure optimal titration of IDegLira and IDeg based on fasting SMPG values to the glycaemic target of 4.0−5.0 mmol/L (72−90 mg/dL).

The mean actual daily insulin dose in Trial 3912 was similar between IDegLira and IDeg throughout the trial. After 26 weeks of treatment, the mean actual daily insulin dose was 45 units with both IDegLira and IDeg. Of the IDegLira treated subjects 65.3% reached a daily dose of 50 dose steps and 67.3% of the IDeg treated subjects reached a daily insulin dose of 50 units.

Fasting plasma glucose

From baseline to Week 26, FPG for subjects on IDegLira and IDeg decreased by 3.46 mmol/L [62.4 mg/dL] to 6.2 mmol/L [112.0 mg/dl] and by 2.58 mmol/L [46.4 mg/dL] to 7.0 mmol/L [125.7 mg/dL], respectively. The estimated treatment difference for IDegLira vs. IDeg was -0.73 mmol/L [-1.19;-0.27]95%CI, p = 0.0019.

Prandial glucose control

At baseline, the SMPG 9-point profiles appeared similar between treatments groups. After 26 weeks of treatment, plasma glucose concentrations had decreased for both treatments, however, the profile for IDegLira showed both lower pre-prandial (i.e. before meals) glucose concentrations as well as lower post-prandial (90 min after meal consumption) glucose concentrations compared with IDeg. The estimated treatment difference in mean SMPG for IDegLira vs. IDeg was -1.07 mmol/L $[-1.44;-0.70]_{95\%CI}$, p < 0.0001.

The mean prandial increments across all meals were 2.2 mmol/L (39.6 mg/dL) with IDegLira and 2.4 mmol/L (43.2 mg/dL) with IDeg after 26 weeks of treatment. Change from baseline in prandial increment after 26 weeks of treatment was greater with IDegLira than with IDeg, estimated treatment difference between IDegLira and IDeg for all meals was -0.37 mmol/L $[-0.69;-0.04]_{95\%CI}$, p = 0.0260.

Hypoglycaemia

The improvements in glycaemic control with IDegLira in Trial 3912 were obtained at a similar incidence of hypoglycaemia with IDegLira relative to IDeg. The percentage of subjects with confirmed hypoglycaemia was approximately 24% in both treatment arms. The difference in rates (153.4 and 263.3 episodes per 100 PYE for IDegLira and IDeg, respectively) was not statistically significant.

Body weight

For IDegLira treated subjects, body weight decreased, whereas for IDeg treated subjects there was no change in weight. After 26 weeks of treatment, mean body weight was 92.7 kg and 93.5 kg corresponding to a change in body weight from baseline to Week 26 of -2.7 kg and 0.0 kg, for IDegLira and IDeg, respectively; estimated mean treatment difference (IDegLira vs. IDeg) was -2.51 kg $[-3.21; -1.82]_{95\%CI}$, p < 0.0001.

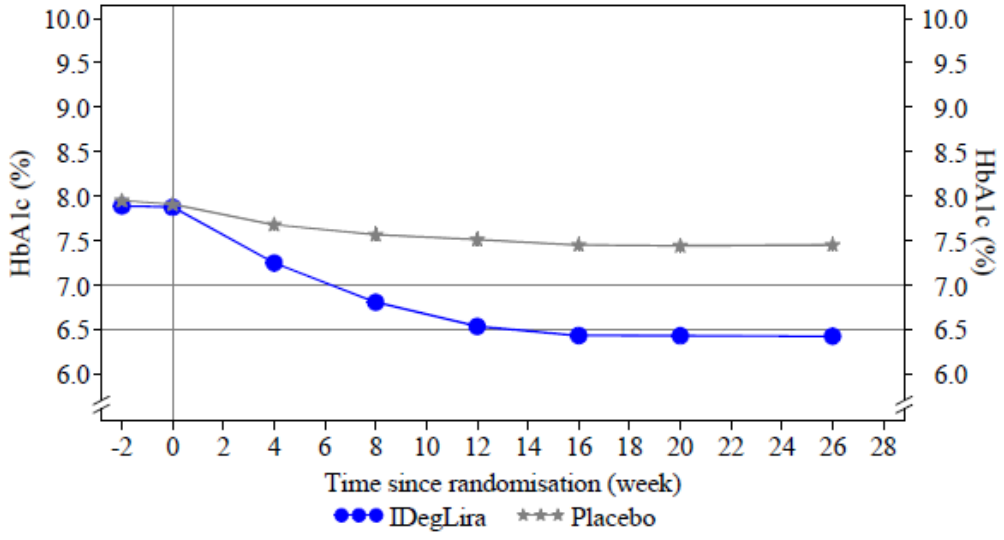
Trial 3951

Change in HbA1c (primary endpoint)

Mean HbA1c and mean change from baseline in HbA1c over time is shown in Figure 13. For the primary endpoint of change in HbA1c after 26 weeks of treatment, HbA1c decreased by 1.45% points to 6.4% in the IDegLira group and by 0.46%-points to 7.4% in the placebo group (estimated mean treatment difference: -1.02 [-1.18-0.87] p<0.001) .

The mean dose of IDegLira at end study was 28 dose steps.

Figure 13 HbA1c (%) by treatment week – Trial 3951 - FAS



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

Responders for HbA1c

After 26 weeks of treatment, the proportion of subjects achieving HbA1c <7% was 79.2% in the IDegLira group and 28.8% in the placebo group. In line with these results, 64.0% of the subjects in the IDegLira group achieved HbA1c ⩽6.5%, compared to 12.3% in the placebo group.

Withdrawal due to ineffective therapy

A total 11 subjects were withdrawn due to ineffective therapy (withdrawal criterion no. 3 or AEs related to hyperglycaemia); 1 subject in the IDegLira group and 10 subjects in the placebo group. In addition to the above 11 cases, 8 subjects were withdrawn from the trial with reasons such as 'high blood glucose levels', 'patient had too high fasting blood values' or similar. All cases were reported by subjects in the placebo group.

Fasting plasma glucose

Mean FPG at baseline was similar at 9.1 mmol/L in both treatment groups. From baseline to Week 26, FPG decreased by 2.60 mmol/L to 6.5 mmol/L for subjects treated with IDegLira and by 0.31 mmol/L to 8.8 mmol/L for subjects treated with placebo (treatment difference: -2.30 mmol/L [-2.72-1.89] p < 0.001).

Body weight

Body weight at baseline (Week 0) was 87.2 kg for IDegLira and 89.3 kg for placebo. In both treatment groups the body weight remained relatively stable throughout the trial and ended on 87.7 kg and 88.3 kg after 26 weeks of treatment, for the IDegLira and placebo groups, respectively. The estimated mean treatment difference between IDegLira and placebo was 1.48 kg, p <0.001; however this was less than the baseline differences between the groups.

Ancillary analyses

Comparison of results in sub-populations

The efficacy of IDegLira in sub-populations was assessed through statistical analysis by testing the null-hypothesis of equal treatment effect on HbA1c reduction at week 26 across the different sub-groups when comparing IDegLira vs. IDeg and IDegLira vs. liraglutide. The analyses were based on individual data from each of the two therapeutic confirmatory trials.

The subgroup analysis did not identify any clinically relevant effects related to age group, sex BMI, race, disease factors or concomitant treatments.

Analysis of clinical information relevant to dosing recommendations

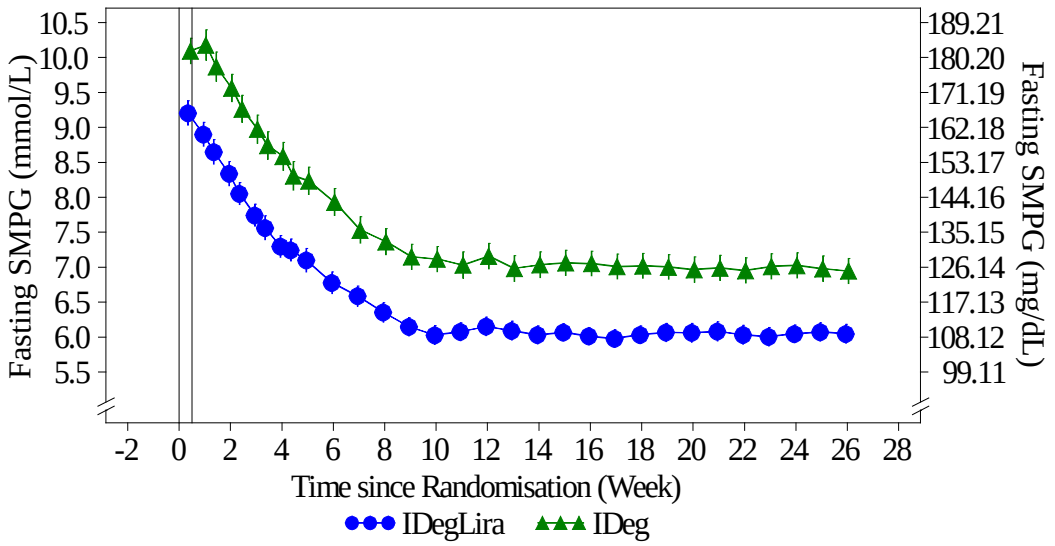
In clinical practice, determination of insulin dosing is based upon individual needs, considering the balance between glycaemic control and risk of hypoglycaemia. A 'treat-to-target' concept was applied in both therapeutic confirmatory trials, adjusting the dose for each individual subject with the aim of achieving pre-defined glycaemic targets for subjects receiving IDeg or IDegLira.

Analysis of dose results

Insulin-naïve subjects with type 2 diabetes (Trial 3697) were to start IDegLira treatment at a dose of 10 dose steps once daily. Subjects previously treated with basal insulin (20-40 units) (Trial 3912) were to start IDegLira treatment at a dose of 16 dose steps once daily.

Mean fasting SMPG levels in Trial 3912 (Figure 14) did not indicate any transient deterioration of glycaemic control in subjects transferring from 20-40 units of basal insulin to 16 dose steps of IDegLira. The fasting SMPG values and change from baseline during the initial 4 weeks of treatment show an immediate reduction in fasting SMPG values providing further support for sufficient coverage during initiation of IDegLira treatment.

Figure 14 Mean fasting SMPG for dose adjustment by treatment week – Trial 3912 - FAS

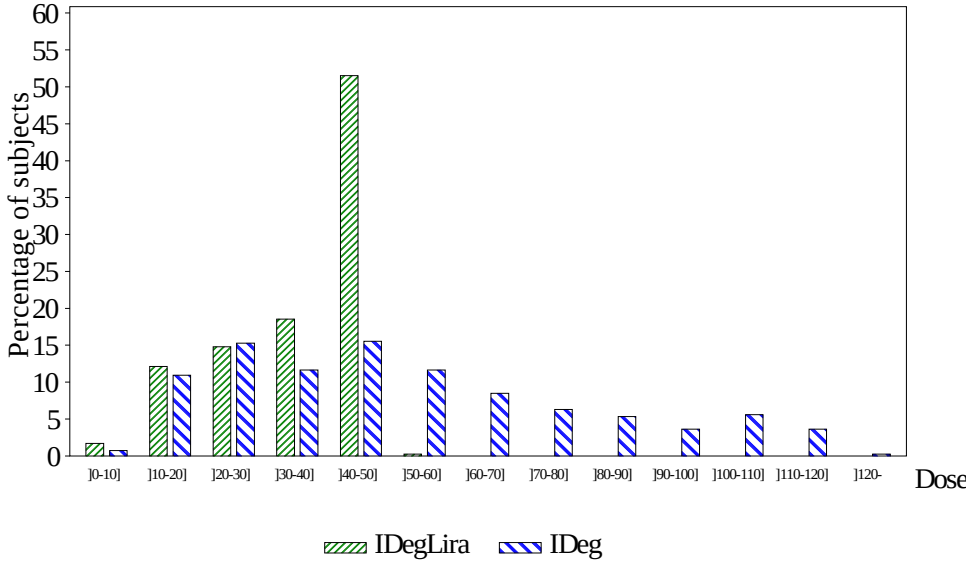


FAS: LOCF imputed data
SMPG = Self Measured Plasma Glucose
Endpoint is calculated as the mean of the available SMPG values used for titration
All values are only available post baseline at week 0.5
Error bars: +- Standard Error (Mean)

The distributions of end-of-trial doses of IDegLira and IDeg are shown for Trials 3697 and 3912 in Figure 15 and Figure 16, respectively. Doses of IDegLira after 26 weeks of treatment in Trial 3697 spanned the dose range of up to 50 dose steps of IDegLira, with approximately 55% of subjects receiving from 40 to 50 dose steps per day (Figure 15). At the end of the main trial period (Week 26) the mean daily IDegLira dose was 38 dose steps, and 39.7% of subjects reached a daily insulin dose of 50 dose steps. After 52 weeks of IDegLira treatment 43.0% of subjects had reached a daily insulin dose of 50 dose steps.

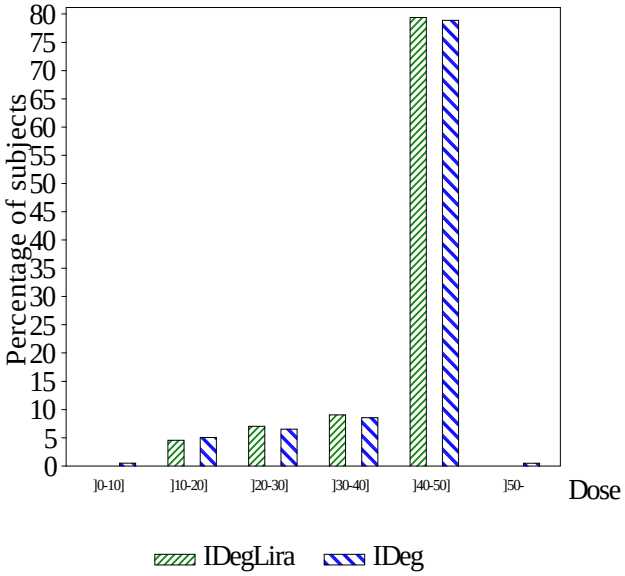
As expected, fewer subjects in Trial 3912 received doses in the lower range, (Figure 16) due to a trial population of previous insufficiently controlled basal insulin users with a presumed need of relatively high doses of trial medication. The mean daily IDegLira dose was 45 dose steps at end-of-trial, and 65.3% of IDegLira-treated subjects reached a daily insulin dose of 50 dose steps.

Figure 15 Actual daily dose of IDegLira (in dose steps) and IDeg (in units) after 26 weeks of treatment – Trial 3697 – SAS



Data is based on trial NN9068-3697
SAS: LOCF imputed data

Figure 16 Actual daily dose of IDegLira (in dose steps) and IDeg (in units) after 26 weeks of treatment – Trial 3912 – SAS



Data is based on trial NN9068-3912
SAS: LOCF imputed data

Glycaemic control was maintained in subjects who reached the maximum dose level of IDegLira, which supports the adequacy of the applied dose range of IDegLira. The HbA1c at end of trial (Week 26 and Week 52) in Trial 3697 was, however, slightly lower for subjects receiving a daily insulin dose < 50 dose steps/units versus those reaching 50 dose steps/units (after 26 weeks: 6.3% vs. 6.5%; after 52 weeks: 6.3% vs. 6.6%). The difference was relatively small, and the corresponding results for Trial 3912 did not show a similar difference. Results for HbA1c responders by actual daily insulin dose < 50 or ≥ 50 dose steps/units showed the same pattern, confirming that a substantial proportion of subjects reached glycaemic control, regardless of previous antidiabetic treatment.

Summary of main studies

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9 (overview) Key efficacy results of IDegLira treatment in the confirmatory trials

	Trial 3697 (insulin naïve)	Trial 3912 (insulin treated)	Trial 3951 (SU ± metformin)
HbA1c			
Baseline	8.3%	8.7%	7.9 %
Week 26	6.4%	6.9%	6.4 %
Change	-1.91 %-point	-1.90 %-point	-1.45 %
Responders, HbA1c <7%	80.6%	60.3%	79.2 %
Responders, HbA1c <6.5%	69.7%	45.2%	64.0 %
Mean daily insulin dose after 26 weeks	38 units	45 units	28 units
FPG			
Baseline	9.2 mmol/L	9.7 mmol/L	9.1 mmol/L
Week 26	5.6 mmol/L	6.2 mmol/L	6.5 mmol/L
Change	-3.62 mmol/L	-3.46 mmol/L	-2.60 mmol/L
Mean 9-point profile post prandial increment (across all meals)			
Baseline	2.3 mmol/L	2.5 mmol/L	2.6 mmol/L
Week 26	1.9 mmol/L	2.2 mmol/L	2.3 mmol/L
Change	-0.4 mmol/L	-0.3 mmol/L	-0.3 mmol/L
Body weight			
Baseline	87.2 kg	95.4 kg	87.2 kg
Week 26	86.7 kg	92.7 kg	87.7 kg
Change	-0.5 kg	-2.7 kg	0.5 kg

Table 9a Summary of efficacy for Trial 3697

Title: DUAL I - DUal Action of Liraglutide and insulin degludec in type 2 diabetes: A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in subjects with type 2 diabetes. A 26-week randomised, parallel three-arm, open-label, multi-centre, multinational treat-to-target trial comparing fixed ratio combination of insulin degludec and liraglutide versus insulin degludec or liraglutide alone, in subjects with type 2 diabetes treated with 1-2 oral anti-diabetic drugs (OADs) with a 26-week extension	
Study identifier	Protocol number: NN9068-3697; EudraCT number: 2010-021560-15; Study identifier: NCT01336023. See Trial 3697 report body (M 5.3.5.1).

Design	The trial was a 26-week randomised, controlled, parallel three-arm, open-label, multi centre, multinational, treat-to-target trial in subjects with type 2 diabetes inadequately controlled with 1−2 OADs (metformin or metformin + pioglitazone) with a 26-week extension comparing the efficacy and safety of insulin degludec/liraglutide (IDegLira) once daily with insulin degludec (IDeg) once daily and liraglutide once daily. Inadequately controlled type 2 diabetes was defined as an HbA1c level of 7.0−10.0% (both inclusive). Eligible subjects were randomised 2:1:1 to receive one of three parallel treatments consisting of once daily IDegLira, IDeg or liraglutide. Metformin or metformin + pioglitazone were continued at pre-trial doses and dosing frequency throughout the trial. The randomisation was stratified by previous treatment with metformin and metformin + pioglitazone and baseline HbA1c (≤ 8.3% and > 8.3%, respectively). Subjects in the liraglutide arm followed a dose escalation scheme with a starting dose of 0.6 mg and a dose increase of 0.6 mg weekly until the target dose of 1.8 mg was reached (in accordance with Victoza labelling). Starting dose for IDegLira was 10 dose steps (10 units IDeg and 0.36 mg liraglutide) and for IDeg 10 units, and both products were titrated twice weekly, according to the predefined titration algorithm based on fasting SMPG levels. Maximum dose for IDegLira was 50 dose steps (50 units IDeg and 1.8 mg liraglutide). There was no maximum dose for IDeg. At selected sites, a sub-study comprising continuous glucose measurement (CGM) and a meal test was performed. The main trial (26 weeks) and the full trial period (26 weeks + 26 weeks extension) were reported in separate trial reports. Below is a summary of the main trial.		
	Duration of main trial:		26 weeks + 1 week follow-up
Hypothesis	The main objective of the trial was to confirm efficacy of IDegLira in controlling glycaemia in subjects with type 2 diabetes, by investigating if non-inferiority of IDegLira vs. IDeg and superiority of IDegLira versus liraglutide was demonstrated: Non-inferiority of IDegLira vs. IDeg was confirmed when the 95% confidence interval (CI) for the treatment differences for change in HbA1c lies entirely below 0.3%; equivalent to a one-sided test with a significance level of 2.5%. Superiority of IDegLira over liraglutide was confirmed when the 95% CI for the treatment difference for change in HbA1c lies entirely below 0%; equivalent to a one-sided test with a significance level of 2.5%. Superiority was only investigated for the full analysis set (FAS). The trial also aimed at showing superiority of IDegLira vs IDeg for four confirmatory secondary endpoints using Holm-Bonferroni method to control for type-I error rate: 1) Daily insulin dose; 2) Change from baseline in body weight; 3) Number of hypoglycaemic episodes; 4) Meal test - post prandial glucose profile. The requirement for a successful result, in addition to the primary endpoint, was that at least one of the endpoints used for superiority of IDegLira vs. IDeg gave a statistically significant result after adjustment for multiple testing.		
Treatments groups	Insulin degludec/liraglutide (IDegLira)		A total of 834 subjects were randomised to the IDegLira treatment group (dosed OD + pre-trial OAD). The total treatment duration was 26 weeks.
	Insulin degludec (IDeg)		A total of 414 subjects were randomised to the IDeg treatment group (dosed OD + pre-trial OAD). The total treatment duration was 26 weeks.
	Liraglutide		A total of 415 subjects were randomised in the liraglutide treatment group (dosed OD + pre-trial OAD). The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA1c (%-point) after 26 weeks of treatment	See Hypothesis.

	1) Confirmatorysecondary endpoint	Daily insulin dose after 26 weeks of treatment	The daily insulin dose after 26 weeks of treatment was compared between the IDegLira and IDeg treatment groups and assessed by statistical analysis as part of the efficacy evaluation and adjusted for multiple testing.
	2) Confirmatory secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Change from baseline in body weight after 26 weeks of treatment was compared between the IDegLira and IDeg treatment groups and assessed by statistical analysis as part of the efficacy evaluation and adjusted for multiple testing.
	3) Confirmatorysecondary endpoint	Number of confirmed hypoglycaemic episodes after 26 weeks of treatment	The number of confirmed hypoglycaemic episodes after 26 weeks of treatment was compared between the IDegLira and IDeg treatment groups and assessed by statistical analysis as part of the efficacy evaluation and adjusted for multiple testing.
	4) Confirmatory secondary endpoint	Meal test - post prandial glucose increment ($iAUC_{0-4h}$) after 26 weeks of treatment	Change from baseline after 26 weeks of treatment in $iAUC_{0-4h}$ was compared between the IDegLira and IDeg treatment groups and assessed by statistical analysis as part of the efficacy evaluation and adjusted for multiple testing.
	Supportive secondary endpoint	Responders for HbA1c after 26 weeks of treatment	The numbers of subjects that met a pre-defined HbA1c target level after 26 weeks of treatment (HbA1c < 7.0% or HbA1c ≤ 6.5%) was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in FPG after 26 weeks of treatment	Change from baseline in FPG after 26 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in 9-point SMPG profile after 26 weeks of treatment	Mean of the 9-point profile was defined as the area under the profile (calculated using the trapezoidal method) divided by the actual measurement time after 26 weeks of treatment. This was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in 9-point post-prandial increments (all meals) after 26 weeks of treatment	Mean post prandial increment across all meals was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
Database lock	17 Jul 2012		
Results and Analysis			
Analysis description	**Key efficacy endpoints**		

Analysis population and time point description	The FAS included all randomised subjects, except for 3 subjects from Site 946 who were excluded due to unsigned case books (site closure). Analysis of the efficacy endpoints including confirmatory analysis on confirmed hypoglycaemia were based on the FAS (N = 833). The population consisted of male and female subjects with type 2 diabetes ≥ 18 years of age (78.4% in the age group 40-65 years), with a mean duration of diabetes of 6.84 years, mean HbA1c of 8.3%, and mean BMI of 31.3 kg/m^2. A total of 82.7% subjects reported metformin as their single OAD pre-trial whereas 17.3% reported metformin and pioglitazone as their pre-trial OAD. The percentage of completers in each group was 88.2%, 88.4% and 82.4% for IDegLira, IDeg and liraglutide, respectively. For the sub-study this was 94.7%, 96.9% and 93.8% of the subjects treated with IDegLira, IDeg and or liraglutide, respectively.			
Statistical methods	Change in HbA1c, insulin dose, body weight, post-prandial increment in glucose ($iAUC_{0-4h}$), FPG, mean of the 9-point profile (SMPG) and 9-point post-prandial increments at end of treatment were analysed using an analysis of variance (ANCOVA) model. The model included treatment, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation and region as fixed factors and the corresponding baseline value as a covariate. A mixed effect model using an unstructured residual covariance matrix for measurements within subject was fitted to the 9-point profile data. The model included treatment, time-point, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation, country and treatment by time-point interaction as fixed factors and baseline 9-point profile value as covariate. The number of confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation and country as fixed factors. Analysis of the responder endpoints was based on a logistic regression model with treatment, region, baseline HbA1c stratum, sub-study participation and previous OAD treatment as fixed factors and baseline HbA1c value as a covariate. The Holm-Bonferroni method was used to adjust for multiplicity.			
Descriptive statistics and estimate variability	**Treatment group**	**IDegLira**	**IDeg**	**Liraglutide**
	Number of subjects (FAS)	833	413	414
	Change from baseline in HbA1c after 26 weeks of treatment, mean %-point (SD)	-1.91 (1.07)	-1.44 (1.03)	-1.28 (1.13)
	HbA1c at baseline, mean % (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)
	HbA1c at Week 26, mean % (SD)	6.4 (1.0)	6.9 (1.1)	7.0 (1.2)
	Responder to HbA1c, 'yes'%: < 7.0%; ≤ 6.5%	80.6; 69.7	65.1; 47.5	60.4; 41.1
	Total daily insulin dose after 26 weeks of treatment, mean units (SD)	38 (13)	53 (28)	N/A
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	-0.5 (3.5)	1.6 (4.0)	-3.0 (3.5)
	Change from baseline in post-prandial glucose increments after 26 weeks of treatment, mean mmol/L (SD) – sub-population	-0.87 (1.65)	-0.17 (1.98)	-0.78 (1.62)
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	180.2	256.7	22.0

	FPG after 26 weeks of treatment, mean mmol/L (SD)	5.6 (1.8)	5.8 (2.3)	7.3 (2.5)	
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-3.62 (2.62)	-3.61 (2.97)	-1.75 (2.81)	
	Change from baseline in 9-point SMPG profile after 26 weeks of treatment, mean mmol/L (SD)	-3.2 (2.4)	-3.0 (2.4)	-2.1 (2.4)	
	Change from baseline in 9-point post-prandial increments (all meals) after 26 weeks of treatment, mean mmol/L (SD)	-0.4 (2.0)	-0.2 (2.1)	-0.6 (1.9)	
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA1c (%-point) after 26 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	**IDegLira – liraglutide**
		Treatment contrast		-0.47	-0.64
		95% CI		[-0.58;-0.36]*	[-0.75; -0.53]*
	1) Confirmatory secondary endpoint: Daily insulin dose after 26 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	
		Treatment contrast		-14.90	
		95% CI		[-17.14 ; -12.66]*	
	2) Confirmatory secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	
		Treatment contrast		-2.22	
		95% CI		[-2.64; -1.80]*	
	3) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	**Comparison groups**		**IDegLira – IDeg**	
		Treatment contrast		0.68	
		95% CI		[0.53 ; 0.87]*	
	4) Confirmatory secondary endpoint: Change in glucose $iAUC_{0-4h}$ after 26 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	
		Treatment contrast		-0.71	
		95% CI		[-1.17 ; -0.26]*	
	Secondary endpoint: Responders to HbA1c (<7.0%) after 26 weeks of treatment	**Comparison groups**		**IDegLira - IDeg**	**IDegLira – liraglutide**
		Rate ratio		2.38	3.26
		95% CI		[1.78 ; 3.18]*	[2.45 ; 4.33]*
	Secondary endpoint: Responders to HbA1c (≤6.5%) after 26 weeks of treatment	**Comparison groups**		**IDegLira - IDeg**	**IDegLira – liraglutide**
		Treatment contrast		2.82	3.98
		95% CI		[2.17 ; 3.67]*	[3.05 ; 5.18]*
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	**Comparison groups**		**IDegLira – IDeg**	**IDegLira – liraglutide**
		Treatment contrast		-0.17	-1.76
		95% CI		[-0.41 ; 0.07]	[-2.00 ;-1.53]*
	Change from baseline in 9-point SMPG profile after 26 weeks of treatment, mean mmol/L (SD)	**Comparison groups**		**IDegLira – IDeg**	**IDegLira – liraglutide**
		Treatment contrast		-0.30	-0.93
		95% CI		[-0.50; -0.09]	[-1.13; -0.73]*

	Change from baseline in 9-point post-prandial increments (all meals) after 26 weeks of treatment, mean mmol/L (SD)	**Comparison groups**	**IDegLira – IDeg**	**IDegLira – liraglutide**
		Treatment contrast	-0.45	0.06
		95% CI	[-0.63 ;-0.28]*	[-0.11 ; 0.23]
Notes	A total of 13.2% of the subjects withdrew during the trial. Lower proportions of withdrawals were observed with IDegLira and IDeg (11.8% and 11.6%, respectively) than compared to the liraglutide treatment group (17.6% withdrew). The differences in withdrawals between the treatment groups were driven by higher proportions of subjects treated with liraglutide withdrawing due to AEs. Most of the AEs leading to withdrawal in the liraglutide arm were related to gastrointestinal events (16 out of 24). The majority of all subjects, both in total and per treatment arm, withdrew due to fulfilment of withdrawal criteria: 69 (8.3%) subjects with IDegLira, 34 (8.2%) with IDeg and 40 (9.6%) with liraglutide. Number of subjects withdrawing due to fulfilling of the Withdrawal Criterion 2 (non-compliant and safety concern) was 32 out of 69 with IDegLira treatment, 11 out of 34 with IDeg and 16 out of 39 with liraglutide. Of the subjects withdrawing due to fulfilling of Withdrawal Criteria, 9 out of 39 subjects with liraglutide withdrew due to Withdrawal Criterion 5 (continuous high SMPG). For IDegLira and IDeg treatment groups this was 2 out of 69 or 2 out of 34, respectively. No trend for subject withdrawal could be determined based on the reasons specified in other. In total, there were 30 subjects withdrawn due to *other (*given as primary reason for withdrawal). All 30 subjects withdrew at or after randomisation. Of those, 17 subjects were randomised in error, 8 discontinued due to site closure, 2 were lost to follow up, 1 discontinued due to relocation, 1 due to hypoglycaemia and 1 due to unstable metformin dose.			

ANCOVA: analysis of variance; BMI: body mass index; CAS: completers analysis set, CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A1c; IDeg: insulin degludec; IDegLira: insulin degludec/liraglutide, OAD, oral anti-diabetic treatment, OD: once daily, PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose.*: statistically significant

Table 9b Summary of efficacy for Trial 3697-52w

Title: DUAL I - DUal Action of Liraglutide and insulin degludec in type 2 diabetes: A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in subjects with type 2 diabetes. A 26-week randomised, parallel three-arm, open-label, multi-centre, multinational treat-to-target trial comparing fixed ratio combination of insulin degludec and liraglutide versus insulin degludec or liraglutide alone, in subjects with type 2 diabetes treated with 1-2 oral anti-diabetic drugs (OADs) with a 26-week extension		
Study identifier	Protocol number: NN9068-3697; EudraCT number: 2010-021560-15; Study identifier: NCT01336023. See Trial 3697-52w report body (M 5.3.5.1).	
Design	The present trial was a 26-week randomised, controlled, parallel three-arm, open-label, multi centre, multinational, treat-to-target trial in subjects with type 2 diabetes inadequately controlled with 1-2 OADs (metformin or metformin + pioglitazone) with a 26-week extension comparing the efficacy and safety of insulin degludec/liraglutide (IDegLira) once daily with the single components insulin degludec (IDeg) once daily and liraglutide once daily. Inadequately controlled type 2 diabetes was defined as an HbA1c level of 7.0-10.0% (both inclusive). Eligible subjects were randomised 2:1:1 to receive one of three parallel treatments consisting of once daily IDegLira, IDeg or liraglutide. Metformin or metformin + pioglitazone were continued at pre-trial doses and dosing frequency throughout the trial. The randomisation was stratified by previous treatment with metformin and metformin + pioglitazone and baseline HbA1c (≤ 8.3% and > 8.3%, respectively). All treatments were open-label. Subjects in the liraglutide arm followed a fixed dose escalation scheme with a dose increase of 0.6 mg weekly until the target dose of 1.8 mg was reached. Initial dose for IDegLira and IDeg was 10 dose steps and 10 units, respectively, and titrated twice weekly, according to the predefined titration algorithm based on fasting SMPG levels. Maximum dose for IDegLira was 50 dose steps (50 units IDeg and 1.8 mg liraglutide). There was no maximum dose for IDeg. At selected sites, a sub-study comprising continuous glucose monitoring (CGM) and a meal test was performed. 26 weeks after randomisation, all subjects were invited to enter additional 26 weeks of treatment. The subjects were to continue the same treatment at unchanged dose (liraglutide arm) or dosing regimen (IDeg and IDegLira arms).	
	Duration of main phase: Duration of extension phase:	26 weeks (*+ 1 week follow-up for those subjects not entering the extension trial*) 26 weeks + 1 week follow-up (Trial 3697 ext)
Hypothesis	Sustained efficacy of IDegLira as compared to IDeg and liraglutide was investigated by evaluation of the mean HbA_{1c} value after 52 weeks and by estimating the 2-sided 95% CI for the treatment difference (IDegLira – IDeg) and (IDegLira – liraglutide) for the change in HbA_{1c} after 52 weeks of treatment.	
Treatments groups	Insulin degludec/liragltuide (IDegLira)	A total of 834 subjects were randomised to the IDegLira treatment group (dosed OD + pre-trial OAD). The total treatment duration was 52 weeks.
	Insulin degludec (IDeg)	A total of 414 subjects were randomised to the IDeg treatment group (dosed OD + pre-trial OAD). The total treatment duration was 52 weeks.
	Liraglutide	A total of 415 subjects were randomised to the liraglutide treatment group (dosed OD + pre-trial OAD). The total treatment duration was 52 weeks.

Endpoints and definitions	Primary endpoint	Change from baseline in HbA1c (%-point) after 26 weeks of treatment	The primary endpoint was analysed after 26-weeks of treatment and was not applicable for the 52-week trial
	Secondary endpoint	Change from baseline in HbA1c (%-point) after 52 weeks of treatment	Change from baseline in HbA1c after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation
	Secondary endpoint	Responders for HbA1c after 52 weeks of treatment	The numbers of subjects that met a pre-defined HbA1c target level after 52 weeks of treatment (HbA1c < 7.0% or HbA1c ≤ 6.5%) was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation
	Secondary endpoint	Daily insulin dose after 52 weeks of treatment	The daily insulin dose after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation
	Secondary endpoint	Change from baseline in FPG after 52 weeks of treatment	Change from baseline in FPG after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation
	Secondary endpoint	Change from baseline in 9-point SMPG profile after 52 weeks of treatment	Mean of the 9-point profile was defined as the area under the profile (calculated using the trapezoidal method) divided by the actual measurement time after 52 weeks of treatment. This was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Change from baseline in 9-point post-prandial increments (all meals) after 52 weeks of treatment	Mean post prandial increment across all meals was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Meal test - post prandial glucose increment ($iAUC_{0-4h}$) after 52 weeks of treatment	Change from baseline after 52 weeks of treatment in $iAUC_{0-4h}$ was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation
	Secondary endpoint	Change from baseline in body weight after 52 weeks of treatment	Change from baseline in body weight after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Number of confirmed hypoglycaemic episodes after 52 weeks of treatment	The number of confirmed hypoglycaemic episodes after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the safety evaluation.
Database lock	15 Jan 2013		

Results and Analysis

Analysis description	**Key efficacy endpoints**
Analysis population and time point description	The full analysis set (FAS) included all randomised subjects except for 3 subjects from Site 946 who were excluded due to unsigned case books (site closure). Analysis of the efficacy endpoints were based on the FAS (N= 833). The population consisted of male and female subjects with type 2 diabetes ≥ 18 years of age (78.4% in the age group 40-65 years), with a mean duration of diabetes of 6.85 years, mean HbA1c of 8.3%, and mean BMI of 31.2 kg/m^2. A total of 83.0% subjects reported metformin as their single OAD pre-trial, whereas 17.0% reported metformin and pioglitazone as their pre-trial OAD. The percentage of completers in each treatment group was 74.52%, 73.7% and 68.7% for IDegLira, IDeg and liraglutide, respectively. In the sub-study, 76.3%, 75.0% and 72.3% of the subjects treated with IDegLira, IDeg and or liraglutide, respectively, completed the trial.
Statistical methods	Change in HbA1c, insulin dose, body weight, post-prandial increment in glucose ($iAUC_{0-4h}$), FPG, mean of the 9-point profile (SMPG) and 9-point post-prandial increments at end of treatment were analysed using an analysis of variance (ANCOVA) model. The model included treatment, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation and region as fixed factors and the corresponding baseline value as a covariate. A mixed effect model using an unstructured residual covariance matrix for measurements within subject was fitted to the 9-point profile data. The model included treatment, time-point, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation, country and treatment by time-point interaction as fixed factors and baseline 9-point profile value as covariate. The number of confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation and country as fixed factors. Analysis of the responder endpoints was based on a logistic regression model with treatment, region, baseline HbA1c stratum, sub-study participation and previous OAD treatment as fixed factors and baseline HbA1c value as a covariate.

Descriptive statistics and estimate variability	**Treatment group**	**IDegLira**	**IDeg**	**Liraglutide**
	Number of subjects (FAS)	833	413	414
	Change from baseline in HbA1c after 52 weeks of treatment, mean %-point (SD)	-1.84 (1.08)	-1.40 (1.06)	-1.21 (1.21)
	HbA1c at baseline, mean % (SD)	8.3 (0.9)	8.3 (0.9)	8.3 (0.8)
	HbA1c at Week 52, mean % (SD)	6.4 (1.0)	6.9 (1.1)	7.1 (1.2)
	Responder to HbA1c, 'yes'%: < 7.0%; ≤ 6.5%	78.2, 66.9	62.5, 49.2	56.5, 38.2
	Total daily insulin dose after 52 weeks of treatment, mean units (SD)	39 (13)	62 (42)	N/A
	Change from baseline in FPG after 52 weeks of treatment, mean mmol/L (SD)	-3.45 (2.57)	-3.40 (3.00)	-1.67 (2.88)
	FPG after 52 weeks of treatment, mean mmol/L (SD)	5.7 (2.0)	6.0 (2.5)	7.3 (2.5)

	Change from baseline in 9-point SMPG profile after 52 weeks of treatment, mean mmol/L (SD)	-3.2 (2.3)	-3.0 (2.4)	-2.1 (2.4)	
	Change from baseline in 9-point post-prandial increments (all meals) after 52 weeks of treatment, mean mmol/L (SD)	-0.4 (2.0)	-0.2 (2.1)	-0.6 (2.0)	
	Change from baseline in post-prandial glucose increments after 52 weeks of treatments, mean mmol/L (SD) – sub-population	-0.86 (1.78)	-0.23 (1.84)	-0.93 (1.71)	
	Change from baseline in body weight after 52 weeks of treatment, mean kg (SD)	-0.4 (4.2)	2.3 (5.7)	-3.0 (4.1)	
	Observed rate of confirmed hypoglycaemic episodes after 52 weeks of treatment, per 100 PYE	176.7	279.1	19.1	
Effect estimate per comparison	Secondary endpoint: Change from baseline in HbA1c (%) after 52 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	**IDegLira - liraglutide**
		Treatment contrast		-0.46	-0.65
		95% CI		[-0.57 ;-0.34]*	[-0.76 ;-0.53]*
	Secondary endpoint: Responders for HbA1c(<7%) after 52 weeks of treatment	**Comparison groups**		**IDegLira - IDeg**	**IDegLira - liraglutide**
		Treatment contrast		2.35	3.42
		95% CI		[1.77 ; 3.13]*	[2.58 ; 4.54]*
	Secondary endpoint: Responders for HbA1c(≤6.5%) after 52 weeks of treatment	**Comparison groups**		**IDegLira - IDeg**	**IDegLira - liraglutide**
		Treatment contrast		2.26	3.94
		95% CI		[1.74 ; 2.93]*	[3.02 ; 5.14]*
	Secondary endpoint: Daily insulin dose after 52 weeks of treatment	**Comparison groups**		**IDegLira - IDeg**	**IDegLira - liraglutide**
		Treatment contrast		-23.38	N/A
		95% CI		[-26.44;-20.31]*	N/A
	Secondary endpoint: Change from baseline in FPG after 52 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	**IDegLira - liraglutide**
		Rate ratio		-0.20	-1.67
		95% CI		[-0.45 ; 0.05]	[-1.92 ;-1.42]*
	Secondary endpoint: Change from baseline in 9-point SMPG profile after 52 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	**IDegLira – liraglutide**
		Rate ratio		-0.30	-0.99
		95% CI		[-0.50 ;-0.11]	[-1.19 ;-0.80]*
	Secondary endpoint: Change from baseline in 9-point post-prandial increments (all meals) after 52 weeks of treatment	**Comparison groups**		**IDegLira – IDeg**	**IDegLira – liraglutide**
		Treatment contrast		-0.39	0.10
		95% CI		[-0.57 ;-0.21]*	[-0.08 ; 0.27]

	Secondary endpoint: Meal test - post prandial glucose profile after 52 weeks of treatment	**Comparison groups**	**IDegLira – IDeg**	**IDegLira - liraglutide**
		Treatment contrast	-0.64	0.05
		95% CI	[-1.11 ; -0.17]*	[-0.43 ; 0.53]
	Secondary endpoint: Change from baseline in body weight after 52 weeks of treatment	**Comparison groups**	**IDegLira – IDeg**	**IDegLira - liraglutide**
		Treatment contrast	-2.80	2.66
		95% CI	[-3.34 ;-2.27]*	[2.13 ; 3.20]*
	Secondary endpoint: Number of confirmed hypoglycaemic episodes after 52 weeks of treatment	**Comparison groups**	**IDegLira – IDeg**	**IDegLira - liraglutide**
		Treatment contrast	0.63	8.52
		95% CI	[0.50; 0.79] *	[6.09; 11.93]*
Notes	A total of 13.3% of the subjects withdrew after randomisation but before the extension period. In the liraglutide treatment group 17.6% withdrew whereas lower proportions were observed with IDegLira and IDeg (12.0% and 11.6%, respectively). Withdrawal during the extension period was 5.3% with IDegLira, 6.8% with IDeg and 6.7% with liraglutide. As for the main period of the trial the majority of subjects withdrew during the extension period due to fulfilment of different withdrawal criteria: 19 (2.3%) subjects with IDegLira, 14 (3.4%) with IDeg and 16 (3.9%) with liraglutide. There was no treatment specific trend except for withdrawals due to Withdrawal Criterion 5 (continuous high SMPG) (1 subject with IDegLira, and 5 with liraglutide treatment). No trend for subject withdrawal could be determined based on the reasons specified in other. In total, there were 30 subjects withdrawn due to primary reason for withdrawal other during the main period of the trial and 40 during the extension. All these subjects withdrew at or after randomisation. Of those, 43 discontinued due to site closure, 17 subjects were randomised in error, 3 were lost to follow up, 3 discontinued due to relocation, 1 due to personal reasons, 1 due to unstable metformin dose, and 1 due to hypoglycaemia.			

ANCOVA: analysis of variance; BMI: body mass index; CAS: completers analysis set, CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; ETS: extension trial set, FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A1c; IDeg: insulin degludec; IDegLira: insulin degludec/liraglutide, OAD, oral anti-diabetic treatment, OD: once daily, PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose.*: statistically significant

Table 9c Summary of efficacy for Trial 3912

Title: DUAL™ II - A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in subjects with type 2 diabetes. A 26-week randomised, parallel, two-arm, double-blind, multi-centre, multinational, treat-to-target trial comparing fixed ratio combination of insulin degludec and liraglutide with insulin degludec in subjects with type 2 diabetes	
Study identifier	Protocol number: NN9068-3912; EudraCT number: 2011-002336-72; Study identifier: NCT01392573. See Trial 3912 report body (M 5.3.5.1).

Design	The trial was a 26-week randomised, parallel, two-arm, double-blind, multi-centre, multinational, treat-to-target trial in subjects with type 2 diabetes inadequately controlled with basal insulin and metformin with or without SU or glinides comparing the efficacy and safety of IDegLira once daily (OD) with IDeg OD both added on to metformin. Inadequately controlled type 2 diabetes was defined as HbA1c level of 7.5−10.0% (both inclusive). Eligible subjects were randomised 1:1 to either once daily insulin degludec/liraglutide (IDegLira) or once daily insulin degludec (IDeg), both in combination with metformin. Pre-trial treatment with basal insulin and SU or glinides (if applicable) was to be discontinued at Visit 2. Throughout the trial, metformin treatment should be maintained at the stable, pre-randomisation dose and frequency, although dose adjustments for safety reasons were allowed. The starting dose was 16 dose steps for IDegLira and 16 units for IDeg and was titrated twice weekly according to the predefined titration algorithm, based on FPG levels. Subjects were to measure fasting self-measured plasma glucose (SMPG) values during the trial. The IDegLira starting dose of 16 dose steps (16 units IDeg and 0.6 mg liraglutide) is in accordance with the recommended start dose of 0.6 mg/day with Victoza®. The maximum dose in the two arms was 50 dose steps and 50 units for IDegLira and IDeg, respectively, allowing dose-equivalence with regards to the maximum insulin dose. This was done in order to demonstrate the additional benefits of the liraglutide component to overall glycaemic control and related endpoints, compared to IDeg at insulin dose equivalence.		
	Duration of trial:		26 weeks + 1 week follow-up
Hypothesis	Superiority of IDegLira over IDeg was concluded if the 95% confidence interval (CI) for the treatment difference for change in HbA1c lies entirely below 0%. If superiority was concluded, the primary objective was considered fulfilled. Conclusion of superiority was only based on the full analysis set (FAS).		
Treatments groups	Insulin degludec/liraglutide (IDegLira)		A total of 207 subjects were randomised to IDegLira dosed OD + metformin. The total treatment duration was 26 weeks.
	Insulin degludec (IDeg)		A total of 206 subjects were randomised to IDeg dosed OD + metformin. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA1c (%-point) after 26 weeks of treatment.	See Hypothesis.
	Secondary endpoint	Responders for HbA1c after 26 weeks of treatment.	The numbers of subjects that met a specific HbA1c target level after 26 weeks of treatment (HbA1c < 7.0% or HbA1c ≤ 6.5%) was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Total daily insulin dose after 26 weeks of treatment.	The total daily insulin dose after 26 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Change from baseline in FPG after 26 weeks of treatment.	Change from baseline in FPG after 26 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.

	Secondary endpoint	SMPG 9-point profiles including mean of 9-point profile and mean of post-prandial increments.	Mean of the 9-point profile was defined as the area under the profile (calculated using the trapezoidal method) divided by the actual measurement time after 26 weeks of treatment. This was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation. Mean post-prandial increment across all meals was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Change from baseline in body weight after 26 weeks of treatment.	Change from baseline in body weight after 26 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
Database lock	28-Nov-2012		

Results and Analysis

Analysis description	**Key efficacy endpoints**		
Analysis population and time point description	The FAS included all randomised subjects except all 15 subjects from site 105 that were excluded from all analyses due to compromised data integrity. Analyses of efficacy endpoints were based on the FAS (N=398). The population consisted of male and female subjects with type 2 diabetes ≥ 18 years of age, pre-trial diabetes treatment: 20-40 U of basal insulin and metformin ±SU/glinides, mean age: 57.2 years, mean duration of diabetes: 10.6 years, mean HbA1c: 8.8%, and mean BMI: 33.7 kg/m^2. In total, 84.5% and 83.0% of the subjects completed the trial in the IDegLira and IDeg treatment group, respectively.		
Statistical methods	Change in HbA1c from baseline after 26 weeks of treatment was analysed using a standard analysis of variance (ANCOVA) model. The model included treatment, previous antidiabetic treatment, and country as fixed factors and the corresponding baseline value as a covariate. The primary objective was fulfilled only if superiority of IDegLira vs. IDeg was confirmed. The daily insulin dose after 26 weeks of treatment was analysed using a standard ANCOVA model using FAS. The model included treatment, previous antidiabetic treatment and country as fixed factors and baseline HbA1c value and baseline insulin dose as covariates. Analysis of each of the two responder endpoints was based on a logistic regression model with treatment, region and previous anti-diabetic treatment as fixed factors and baseline HbA1c value as a covariate. Change from baseline in FPG and body weight after 26 weeks of treatment were analysed using the standard ANCOVA model. Change from baseline in the mean of the 9-point profile (SMPG) and postprandial increments endpoints after 26 weeks of treatment were analysed separately using the standard ANCOVA model. The endpoint value obtained at baseline was used as covariate.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegLira**	**IDeg**
	Number of subjects (FAS).	199	199
	Change from baseline in HbA1c after 26 weeks of treatment, mean %-point (SD).	-1.9 (1.09)	-0.89 (1.18)
	HbA1c at baseline, mean % (SD).	8.7 (0.7)	8.8 (0.7)
	HbA1c at Week 26, mean % (SD).	6.9 (1.0)	8.0 (1.2)
	Responders to HbA1c < 7.0%, N (%).	120 (60.3)	46 (23.1)
	Responders to HbA1c ≤ 6.5%, N (%).	90 (45.2)	26 (13.1)
	Total daily insulin dose after 26 weeks of treatment, mean units (SD).	45 (9)	45 (10)

	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD).	-3.46 (2.92)	-2.58 (3.31)
	FPG after 26 weeks of treatment, mean mmol/L (SD).	6.2 (2.4)	7.0 (2.7)
	Change from baseline in 9-point SMPG profile after 26 weeks of treatment, mean mmol/L (SD).	-3.2 (2.6)	-2.0 (2.6)
	Change from baseline in 9-point post-prandial increments (all meals) after 26 weeks of treatment, mean mmol/L (SD).	-0.3 (2.1)	0.1 (2.0)
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD).	-2.7 (3.7)	0.0 (3.4)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA1c (%) after 26 weeks of treatment.	**Comparison groups**	**IDegLira – IDeg**
		Treatment contrast	-1.05%
		95% CI	[-1.25; -0.84]*
	Secondary endpoint: Daily insulin dose after 26 weeks of treatment.	**Comparison groups**	**IDegLira – IDeg**
		Treatment contrast	-0.02 unit
		95% CI	[-1.88; 1.84]
	Secondary endpoint: Change from baseline in FPG after 26 weeks of treatment.	**Comparison groups**	**IDegLira – IDeg**
		Treatment contrast	-0.73 mmol/L
		95% CI	[-1.19; -0.27]*
	Secondary endpoint: Mean 9-point SMPG after 26 weeks of treatment.	**Comparison groups**	**IDegLira – IDeg**
		Treatment contrast	-1.07 mmol/L
		95% CI	[-1.44; -0.70]*
	Secondary endpoint: Mean postprandial increments across all meals after 26 weeks of treatment.	**Comparison groups**	**IDegLira – IDeg**
		Treatment contrast	-0.37 mmol/L
		95% CI	[-0.69; -0.04]*
	Secondary endpoint: Change from baseline in body weight after 26 weeks of treatment.	**Comparison groups**	**IDegLira – IDeg**
		Treatment contrast	-2.51 kg
		95% CI	[-3.21; -1.82]*

Notes	A total of 16.2% of the subjects withdrew during the trial. The withdrawal rate was 15.5% in the IDegLira treatment group and 17.0% in the IDeg treatment group. Subjects in both treatment groups withdrew due to withdrawal criteria adverse events, ineffective therapy, non-compliance with protocol and for 'other' reasons. The 3 AEs leading to withdrawal in the IDeg arm were related to 'acute myocardial infarction', 'cholelithiasis' and 'ischaemic stroke', and the single AE withdrawal in the IDegLira arm was related to 'major depression'. The majority of all subjects, both in total and per treatment arm, withdrew due to fulfilment of withdrawal criteria: 13 subjects in IDegLira (6.3%) and 15 subjects in IDeg (7.3%). More subjects withdrew at own will without explanation in the IDegLira treatment group (9 out of 13) compared to the IDeg treatment group (6 out of 15). More subjects withdrew due to fulfilling of the withdrawal criteria non-compliant and safety concern in the IDeg treatment group (4 out of 15) compared to the IDegLira treatment group (2 out of 13). Of the subjects withdrawing due to fulfilling of withdrawal criteria more subjects in the IDeg treatment group (5 out of 15) withdrew due to continuous high SMPG compared to the IDegLira treatment group (1 out of 13). In total, there were 30 subjects withdrawn due to primary reason for withdrawal "other". 15 of these subjects were withdrawn due to closure of site 105 (the site was closed due to suspicion of misconduct). The remaining 15 subjects were randomised in error (11 subjects due to non-fulfilment of inclusion criteria 5, 1 subject due to exclusion criteria 14, 2 subjects due to non-fulfilment of exclusion criteria 17, and 1 subject due to violation of both inclusion number 5 and exclusion number 15).

BMI: body mass index; CI: confidence interval; FAS: full analysis set; CAS: completer analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A1c; IDegLira: insulin degludec/liraglutide; IDeg: insulin degludec; met: metformin; OD: once daily; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast). *statistically significant.

Analysis performed across trials (pooled analyses and meta-analysis)

n/a

Clinical studies in special populations

n/a

Supportive study

Study 3948

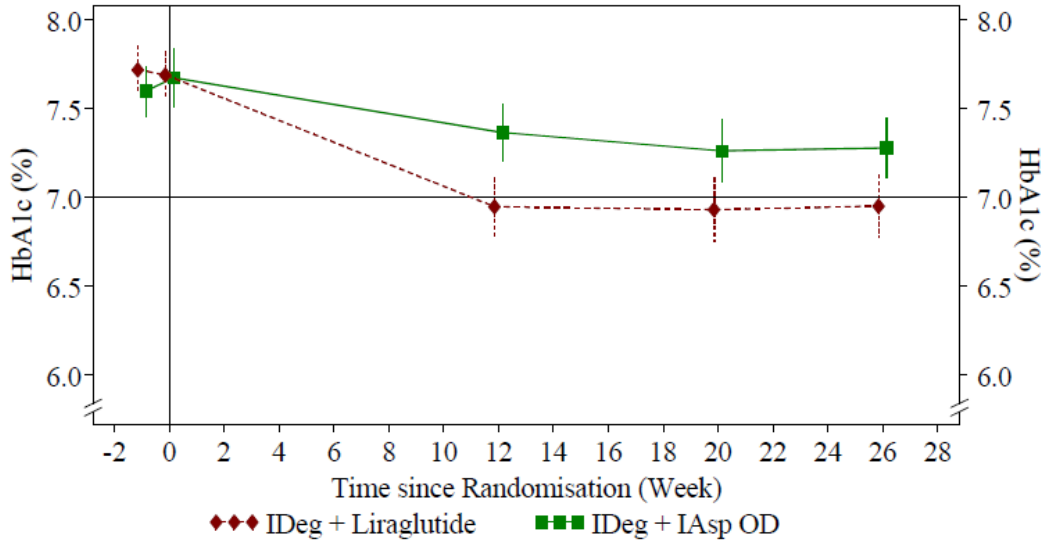
This trial was a 26-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing the efficacy and safety of adding liraglutide versus addition of IAsp with the largest meal to IDeg OD + metformin, in subjects with type 2 diabetes who had completed approximately 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643, with an end of treatment HbA1c ≥7.0% thus qualifying for treatment intensification.

A third treatment arm consisted of non-randomised subjects who completed NN1250-3643 and achieved the glycaemic target of HbA1c <7.0% at end of treatment. These subjects continued treatment with IDeg OD + metformin in order to further evaluate the long-term sustainability of glycaemic control. No comparisons were made between the non-randomised and the randomised treatment arms.

The primary objective of the study was to compare the efficacy of adding liraglutide versus adding IAsp to the largest meal on top of IDeg (OD) + metformin in controlling glycaemia.

The estimated mean reduction in HbA1c during the trial was −0.73 %-points with IDeg + Lira and −0.40 %- points with IDeg + IAsp, with a statistically significant estimated mean difference in favour of IDeg + Lira of −0.32 %−points [−0.53; −0.12]95%CI.

Figure 17 HbA1c (%) by treatment week – Mean plot – Full analysis set



FAS; LOCF imputed data
Error bars: +-Standard Error(Mean)
Screening (Visit 1) values are from end of treatment in NN1250-3643.
Baseline (Visit 2) values are from blood samples drawn at Visit 2.

The observed proportion of subjects achieving HbA1c <7% was 58.0% with IDeg + Lira and 44.9% with IDeg + IAsp. There was no statistically significant difference between treatment groups in terms of achieving HbA1c <7. The observed proportion of subjects achieving HbA1c <7% without confirmed hypoglycaemia during the last 12 weeks of treatment was 54.3% with IDeg + Lira and 19.3% with IDeg + IAsp. The odds of achieving HbA1c target <7% without confirmed hypoglycaemia was statistically significantly greater with IDeg + Lira than with IDeg + IAsp; estimated odds ratio (IDeg + Lira/IDeg + IAsp) 5.57 [2.67; 11.63]95% CI. There were no severe hypoglycaemic episodes in either of the randomised treatment arms. The observed proportion of subjects achieving HbA1c <7% without confirmed hypoglycaemia during the last 12 weeks of treatment and without weight gain was 49.4% with IDeg + Lira and 7.2% with IDeg + IAsp. The odds of achieving HbA1c target <7% without confirmed hypoglycaemia and without weight gain was statistically significantly greater with IDeg + Lira than with IDeg + IAsp, with an estimated odds ratio (IDeg + Lira/IDeg + IAsp): 13.79 [5.24; 36.28]95% CI.

Overall, there were minimal changes in FPG from baseline to end of treatment. There was no statistically significant difference between treatment groups. 9-point SMPG values improved for all time points in both treatment arms with no statistically significant difference between groups at the end of the trial at any time point.

There was a statistically significant difference in weight change between treatment groups in favour of IDeg + Lira after 26 weeks of treatment; the estimated mean weight change was −3.03 and 0.72 kg with IDeg + Lira and IDeg + IAsp, respectively, with an estimated treatment difference (IDeg + Lira−IDeg + IAsp) of −3.75 kg [−4.70; −2.79]95%CI.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application was supported by a limited study program in order to support the fixed combination. References are made to the data supporting the MAAs for the two mono-components. This is acceptable and in accordance with the EMA Guideline on fixed combination products (CHMP/EWP/240/95 Rev. 1).

The studies submitted appear well designed and conducted and follow in all essential part the advice given by the CHMP.

Studies 3697 and 3912 are considered the pivotal studies for this application. Some additional data in patients treated with the free combination has been provided with study 3948. One additional study, in patients receiving IDegLira as add-on to SU (3951), was submitted during the procedure.

No dose finding studies were performed. The doses for the fixed combination were chosen mainly based on clinical experience in order to allow the common dose-span for the insulin component while not exceeding the maximal recommended dose for the GLP-1 analogue. Although this argumentation is sound, this means that at the lowest recommended IDeg doses, the liraglutide dose is below the lowest dose shown to be efficient (0.36 mg compared to 0.6mg). From dose findings studies with liraglutide, it can be concluded that the effect decreases with doses below 0.6 mg but it is not totally absent. The analyses presented support that liraglutide contributes to the effect also at low doses of IDegLira. Whether this contribution is of clinical relevance or not remains uncertain.

However, judging from study data, it can be expected that in clinical practice most patients will be uptitrated to at least 16 dose steps of Xultophy, i.e. receiving at least 0.6 mg of liraglutide. In study 3912, < 2% were treated with a dose below 16 dose steps at any time point during the study, and in study 3697, the vast majority of patients had a dose above 20 dose steps after 26 weeks of treatment.

Thus it is considered acceptable to recommend a starting dose of 10 and 16 dose steps for patients on OADs and insulin, respectively.

Trial 3697 investigated the use of IDegLira therapy as add-on to metformin with or without pioglitazone, thus compared IDegLira to both the mono-components; IDeg and liraglutide. In Trial 3912 IDegLira was compared to IDeg (with a maximum dose of 50 units) as add-on to metformin, thereby investigating the contribution of the liraglutide component.

With regards to the inclusion criteria, in trial 3697 patients were to be insulin-naïve and treated with 1-2 OADs. Furthermore the lower HbA1c limit was set at 7.0 %. Thus the included population may not be totally representative of patients where insulin therapy is considered, since patients may not be considered for insulin therapy unless failing on at least two OADs. Intensifying treatment at HbA1c levels above 7.0 % is however in line with current practice guidelines and the inclusion criteria are therefore acceptable. For trial 3912, a population with more advanced diabetes was aimed at. Exclusion criteria were relevant and were in all essential parts in line with the given advice. No upper age limit was applied which is important in order to allow inclusion of sufficient numbers of elderly patients. Withdrawal criteria were adequate.

In both studies, background medication was restricted to metformin and in study 3697, pioglitazone was also allowed. Starting doses were lower (10 units of IDeg) in study 3697 where the patients were insulin naïve. This is in line with the dosing recommendation for IDeg. The corresponding liraglutide starting dose in the fixed combination, however, then is lower than recommended for use of liraglutide in its SmPC. A somewhat higher starting dose (16 dose steps) was used in study 3912, where patients were insulin treated at baseline resulting in a liraglutide dose of 0.6 mg as recommended in the current liraglutide SmPC.

In both studies, uptitration of IDegLira and IDeg and liraglutide was based on pre-breakfast (fasting) SMPG and the titration schedule is acceptable.

No rescue medication was allowed, instead withdrawal criteria related to self-monitored fasting plasma glucose (SMPG) were used. This is acceptable from a patient safety perspective but carries the risk of higher drop-out from the studies.

Considering that it should be shown that both components contribute to the combination, the objective of only showing non-inferiority for IDegLira vs. IDeg in trial 3697 is debatable unless secondary objectives would be met. It has to be shown that the combination provides other benefits to the patient than the mono-component, which was the case for some of the secondary outcome parameters. It should, however, be taken into account that in this study there was no upper limit for the IDeg dose whereas IDeg was to be titrated until target glucose levels were met.

Trial 3912 only compared IDegLira with IDeg and the maximum dose was 50 units in both arms, thus this study investigated the contribution of liraglutide in the combination.

The primary and secondary endpoints were adequate and in line with current guidelines.

Trial 3697 was conducted as an open-label study due to the differences in titration schedules between the treatment arms. This is acceptable. Trial 3912 was conducted as a double blind study which is acknowledged. However, due to the difference in safety profile, i.e. gastrointestinal side effects of the liraglutide component, the possibility to maintain the blind could be questioned.

The sample size calculations were appropriate. A non-inferiority margin of 0.3% is generally accepted. The randomisation procedure and the stratification in each study seem appropriate.

Trial 3951 investigated the use of IDegLira therapy as add-on to SU with or without metformin using placebo as control. The placebo-controlled design shows the absolute additional effect of IDegLira when added to SU+/- metformin, but does not compare to another treatment approach (for example, addition of a DPP-IV inhibitor) or the addition of insulin or liraglutide alone. The study was double-blind which is acknowledged. The dosing of IDegLira (starting dose, titration and maximum dose) is line with study 3697, apart from a higher upper FPG target limit. The study duration and the overall efficacy endpoints are also similar.

Statistical methods are generally acceptable.

Efficacy data and additional analyses

In trial 3697, withdrawal rates were generally low, although slightly higher in the liraglutide treated group. In this group more patients withdrew due to AEs. Since withdrawal rates were low and fairly balanced, the use of LOCF for the handling of missing values was acceptable. The vast majority of patients were included in the FAS and the proportion of patients excluded from the PP analysis set did not differ between the IDegLira and the IDeg treatment arms.

In trial 3912, withdrawal rates were balanced between groups as was the reasons for withdrawal. The number of patients excluded from the FAS was low and balanced between groups.

Both studies included an adequate proportion of European subjects (24 % in study 3697 and 44 % in study 3912), thus the data is considered representative for the European target population.

In trial 3697, baseline demographic characteristics were well balanced between groups as were the baseline diabetes characteristics. It is, however, noted that there were cases of HbA1c at inclusion outside the range in all three groups with the lowest values for IDegLira. Means and medians did not differ between groups. Mean diabetes duration was relatively short as could be expected in an insulin naïve group of patients with T2DM, but the range was very wide. All patients were on metformin treatment at inclusion and about 17 % were on concomitant pioglitazone treatment.

The primary endpoint was met showing superiority for IDegLira both when tested against IDeg and liraglutide. The absolute difference in HbA1c reduction was in the range of 0.5 % between IDegLira and

IDeg and about 0.6 % between IDegLira and liraglutide. This additional HbA1c reduction when combining the two mono-components is considered of moderate clinical significance.

Significantly higher proportions of patients achieved treatment targets with IDegLira than with the mono-components. In the study file, both unadjusted data and the above data where LOCF has been applied, is provided. The data show that the number of missing values was rather low and evenly distributed between groups. The data also show that in this context LOCF is a conservative method. When responder rates were calculated during the assessment of the dossier, assigning all missing data the status of non-responder, only marginal changes the outcome are observed, thus the results are considered robust and no further sensitivity analyses are warranted. The observed increase in responder rates with the combination is considered clinically relevant irrespective of the cut-off used (HbA1c <7 % or <6.5 %).

The proportion of patients achieving HbA1c targets without weight gain or hypoglycaemia was comparable for IDegLira and liraglutide. The data indicate that the liraglutide effect on body weight is maintained when given in combination with IDeg. Further to this, the risk of hypoglycaemia was attenuated by the co-administration of IDeg and liraglutide. The higher proportions of patients achieving the targets with IDegLira compared to IDeg are clinically relevant.

At 26 weeks, significantly lower insulin doses were used in the IDegLira group compared to the IDeg group while reaching similar mean fasting SMPG. Notably, in the IDegLira group, the mean IDeg dose was well below the maximum dose of 50 units. The reduced need for insulin with the combination is considered beneficial.

A significantly greater reduction in FPG was observed for IDegLira compared to liraglutide, whereas no difference was observed between IDegLira and IDeg. This finding is expected since both IDegLira and IDeg was to be titrated to target and IDeg has been shown to be efficient in reducing FPG.

The postprandial glucose levels following a standardised meal showed a smaller glucose increment for IDegLira compared to IDeg treatment alone and a comparable increment for IDegLira compared to liraglutide treatment alone. The data show that the pharmacodynamic characteristics of IDeg and liraglutide were preserved when administered as IDegLira.

The observation of lower post-prandial glucose increments with IDegLira compared to IDeg after a standardised meal was supported by the SMPG measurements in the entire study population. The postprandial increments (when corrected for fasting plasma glucose levels) were comparable for IDegLira treatment and liraglutide indicating that this effect is mainly attributable to the liraglutide component.

Significantly lower rates of confirmed hypoglycaemias (irrespective of the definition used) were observed with IDegLira compared to IDeg; however, the proportion of patients experiencing hypoglycaemia was comparable between groups. As expected, the lowest rates of hypoglycaemia were observed in the liraglutide treated group. An analysis of the rate of hypoglycaemia by HbA1c shows that hypoglycaemia rates were lower with IDegLira irrespective of the metabolic control.

IDegLira treatment was weight neutral as opposed to the weight gain seen with IDeg treatment and the weight reduction seen with liraglutide treatment.

Data from the 52 week extension have been included in the application. The proportion of patients included in the extension was slightly lower for the liraglutide arm compared to the IDegLira and IDeg arms; however drop-out rates were comparable between all three study arms in the extension period. The data show maintained efficacy over the study period. This is achieved with stable doses of IDegLira, whereas IDeg doses continued to increase over time.

In trial 3912, baseline demographic characteristics were well balanced between groups as were the baseline diabetes characteristics. Mean diabetes duration was rather long as could be expected in an

insulin treated group of patients with T2DM, but the range was very wide. About 50 % of patients were on dual OAD treatment at inclusion. Data to support the external validity of the inclusion limit of 20-40 units of basal insulin in Trial 3912 has been provided. The data show that relevant proportions of patients are treated with basal insulin doses in the range of 20-40 units in clinical practice.

When the maximum IDeg dose was fixed at 50 units, the treatment difference (attributable to liraglutide) between treatment arms was about 1 %. Thus liraglutide contributes significantly to the effect of IDegLira. Responder rates were higher in the IDegLira treated group. The rates were lower than in study 3697 which could be explained by the higher HbA1c at inclusion, however, the observed difference is clinically relevant.

In this study, FPG at week 26 was significantly lower with IDegLira than with IDeg. This is somewhat unexpected considering that treatment was to be titrated to target and 33 % of patients in the IDeg treated group did not reach the maximum IDeg dose. Indeed, the insulin doses were similar in both groups and the proportion of patients reaching the maximum dose was also similar between groups. In study 3697, the curves describing the daily insulin dose started to separate already at week 12. The issue is whether patients in the IDeg group treated with an optimal dose or if some could have been uptitrated to a higher dose. The analyses of FPG in subjects with an IDeg dose below 50 Units shows that the mean FPG in subjects completing study 3912 was close to 5 mmol/L and therefore, further uptitration was not indicated. The difference in FPG between the IDeg and IDegLira is therefore likely due to the liraglutide-component. As in study 3697, IDegLira resulted in an improved post-prandial control compared to IDeg alone although the difference appears small and mainly attributable to the difference in FPG.

No significant difference in hypoglycaemia rates was observed although the rates per 100 PYE were higher for IDeg.

Some weight decrease was observed with IDegLira whereas patients in the IDeg groups maintained their body weight.

In trial 3951, baseline demographic characteristics were well balanced between groups as were the baseline diabetes characteristics. Around 90% of patients at baseline were on a SU+ metformin, the rest on SU alone. Throughout the trial, OAD treatment was to be maintained at the stable, pre-trial dose and frequency, although dose adjustments for safety reasons were allowed. As expected, the addition of IDegLira in subjects on a SU +/- metformin with a baseline HbA1c of 7.0–9.0% (narrower range than study 3697) resulted in improved glycaemic control. The decrease from baseline in the IDegLira group was -1.45%, less than seen in study 3697, and probably reflecting the better baseline glycaemic control in study 3591 (mean HbA1c at baseline 7.9% compared to 8.3%).

HbA1c decreased from baseline by 0.46%-points to 7.4% in the placebo group, 28.8% of patients in the placebo group reached the target of <7.0% and 12.3% reached the target of HbA1c ≤ 6.5%. This is quite a large placebo effect but reflects the effect of study participation and the lack of a long run-in period.

Subgroup analyses were performed separately for studies 3697 and 3912 due to differences in study design and study populations. The analysis showed no influence on the effect by age group, sex or BMI. The small difference in treatment effect observed between non-Hispanic/Latino patients compared to Hispanic/Latino patients is based on a rather small number of patients in the Hispanic/Latino groups and findings were not consistent across the studies. Thus this finding is not considered clinically relevant. As expected, an association between treatment effect and baseline HbA1c was observed for all treatment arms with no obvious difference between groups. Diabetes duration, renal function or hepatic function showed no relevant treatment interaction. There were no clinically relevant differences in treatment effect by diabetes treatment or by concomitant drugs.

In the supportive study (3948), patients were treated with the free combination IDeg and liraglutide. The mean IDeg dose at 26 weeks was about 60 units and the majority of patients (65.5%) were taking liraglutide 1.8 mg/day. With this dosing a relevant HbA1c reduction of -0.73 % was achieved. This is less than observed in the pivotal studies in spite of the higher IDeg doses given, but it should be taken into account that the HbA1c was lower at baseline in this study. When compared to the combination IDeg + IAsp, more patients reached the target criteria and did so with less hypoglycaemias. A reduction in body weight was also observed. Thus the data from this study support the findings in the pivotal studies.

The Applicant has further analysed the data, focussing on issues related to the proposed dose recommendations. Transferring patients on basal insulin applying a starting dose of 16 dose steps IDegLira appears feasible and did not result in loss in metabolic control during the transition period.

In study 3697, only few patients remained on the lowest dose (10 dose steps) at 26 weeks, at what may be a suboptimal liraglutide dose (0.36 mg). Importantly, in both studies a large proportion of patients were on the maximum dose (39.7% and 65.3% in study 3697 and 3912, respectively) at week 26. Although data from the extension period in study 3697 indicate that efficacy is maintained over at least a year without the need for further dose increase the possibility to continue treatment over time will be limited, considering the progressive nature of the disease. However, a substantial proportion of patients will be satisfactorily controlled on ≤ 50 dose steps of IDegLira. Adequate information is included in the SmPC in order to prevent dosing of IDegLira above 50 dose steps per day. As a precautionary measure, the pen is constructed such that it can deliver a maximum of 50 dose steps of IDegLira with each injection.

No association was observed between the effect on HbA1c and dosing time, thus supporting the recommendation that IDegLira may be given at any time of the day.

2.5.4. Conclusions on the clinical efficacy

The fixed combination of liraglutide and insulin degludec combines two drugs with complementary mechanisms of action by a) substituting for the relative insulin deficiency in T2DM and b) stimulating endogenous insulin secretion. This rationale is adequate and carries the potential (although not yet established) of sparing beta-cell function over time.

The additive effect of the two components have been adequately shown and although the benefit in terms of additional reduction of HbA1c may be of moderate clinical relevance (about 0.5 %) compared to the mono-components, there are other benefits in terms of insulin dose requirements, weight control and hypoglycaemia risk

The target population for IDegLira includes patients not adequately controlled on metformin and insulin (study 3912) and those not controlled on OAD alone (study 3697).For the first group, IDegLira provided a superior glycaemic control compared to insulin alone combined with the benefit of weight stability. An alternative treatment strategy could have been to increase the insulin dose further, but this would very likely have been associated with increased risk of hypoglycaemia and weight increase.

For patients failing on OAD, in study 3697, adding IDegLira was beneficial compared to adding only insulin with respect to reduction of HbA1c and a lower risk of weight increase and hypoglycaemia. Conversely, adding IDegLira was associated with an increased risk of gastrointestinal adverse events.

Compared to adding only liraglutide, the benefits are less obvious considering that weight decrease was more pronounced with Lira compared to IDegLira. In addition, IDegLira was associated with more hypoglycaemic events than Lira. However, the glucose lowering effect was higher with IDegLira. For these patients IDegLira could represent one of several alternative treatments.

2.6. Clinical safety

Patient exposure

The safety evaluation primarily focuses on the data from the 2 therapeutic confirmatory trials (Trials 3697 and 3912, called the (pooled) safety analysis set). The safety analysis set includes data from the 26-week main and 26-week extension periods of Trial 3697 and from the 26-week Trial 3912. In the 2 therapeutic confirmatory trials combined, 1024 patients were exposed to IDegLira for a total of 797.5 PYE out of which 623 have been exposed for at least 52 weeks. The combined exposure to comparator treatments (insulin degludec; IDeg and liraglutide; Lira) was of a similar magnitude (n=1023). Safety data is also available from study 3948 examining the combination of the mono-components (88 patients randomised to the combination).
All patients in the 2 confirmatory therapeutic studies were exposed to IDegLira on a background therapy of metformin. In addition, in trial 3697, 17.0% were using a combination of metformin and pioglitazone.

Table 10 Exposure by trial – pooled safety analysis set

	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)
NN9068-3697-52w	825 (705.6)	412 (350.1)	412 (334.3)	1649 (1390.0)
NN9068-3912	199 (91.9)	199 (90.0)		398 (181.9)
Total	1024 (797.5)	611 (440.1)	412 (334.3)	2047 (1571.9)

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).

In Trial 3697, the mean average daily insulin dose during treatment was 31.0 units/day in the IDegLira group compared to36.9 units/day in the IDeg group. The mean average daily liraglutide dose in the IDegLira group was 1.1 mg/day compared to 1.7 mg/day in the Lira group.

In Trial 3912, the mean average daily insulin dose during treatment in the IDegLira group was 38.2 units/day compared to38.6 units/day in the IDeg group.

In addition, together with the responses to the day 120 LoQ, the results from trial 3951 has been submitted (IDegLira as add-on to SU+/- Met compared to placebo). In this study, 288 subjects were exposed to IDegLira and 146 subjects to placebo. The majority of the subjects (87.2% in the IDegLira group and 74.7% in the placebo group) were exposed to trial product for 25−28 weeks.

The mean insulin dose at Week 26 in the IDegLira group was 28 units/day.

Adverse events

In Trial 3697, the percentage of subjects reporting AEs during the first 26-week treatment period was 63.2%, 60.2% and 72.6%, for IDegLira, IDeg and Lira respectively with corresponding rates 482.8 and 430.0 and 640.5 events per 100 PYE. In Trial 3912, the percentages were 57.8% (rate; 398.1 events per 100 PYE) with IDegLira and 61.3% (355.5 events per 100 PYE) with IDeg.

The AE rates over the 52-week period in study 3697, were 407.9, 383.3 and 507.3 events per 100 PYE for IDegLira, IDeg and Lira, respectively.

Table 11 Adverse events possibly or probably related to investigational trial product in ≥ 1% of subjects by system organ class and preferred term – treatment-emergent - Trial 3697 (26 weeks) - safety analysis set

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	825				412				412			
Gastrointestinal disorders												
Nausea	54	(6.5)	60	15.5	5	(1.2)	6	3.1	73	(17.7)	92	49.4
Diarrhoea	36	(4.4)	45	11.6	7	(1.7)	7	3.6	37	(9.0)	52	27.9
Vomiting	14	(1.7)	16	4.1	3	(0.7)	3	1.6	25	(6.1)	34	18.3
Constipation	14	(1.7)	19	4.9					14	(3.4)	15	8.1
Dyspepsia	14	(1.7)	14	3.6	1	(0.2)	1	0.5	12	(2.9)	14	7.5
Abdominal distension	6	(0.7)	6	1.5					8	(1.9)	9	4.8
Gastritis	8	(1.0)	10	2.6					6	(1.5)	8	4.3
Abdominal discomfort	7	(0.8)	7	1.8	1	(0.2)	1	0.5	5	(1.2)	6	3.2
Abdominal pain upper	3	(0.4)	3	0.8	1	(0.2)	1	0.5	5	(1.2)	5	2.7
Hyperchlorhydria	3	(0.4)	3	0.8					6	(1.5)	6	3.2
Abdominal pain	3	(0.4)	3	0.8	1	(0.2)	1	0.5	4	(1.0)	4	2.1
Gastrooesophageal reflux disease	2	(0.2)	2	0.5					5	(1.2)	6	3.2
General disorders and administration site conditions												
Fatigue	9	(1.1)	11	2.8	4	(1.0)	6	3.1	9	(2.2)	11	5.9
Injection site haematoma	10	(1.2)	18	4.6	4	(1.0)	4	2.1	7	(1.7)	9	4.8
Investigations												
Lipase increased	23	(2.8)	24	6.2	3	(0.7)	3	1.6	10	(2.4)	10	5.5
Weight increased	5	(0.6)	6	1.5	9	(2.2)	10	5.2				
Amylase increased	8	(1.0)	8	2.1	2	(0.5)	2	1.0	1	(0.2)	1	0.5
Weight decreased	1	(0.1)	1	0.3					6	(1.5)	6	3.2
Nervous system disorders												
Headache	12	(1.5)	17	4.4	7	(1.7)	9	4.7	12	(2.9)	13	7.0
Dizziness	6	(0.7)	6	1.5	3	(0.7)	3	1.6	9	(2.2)	10	5.4
Metabolism and nutrition disorders												
Decreased appetite	17	(2.1)	18	4.6	1	(0.2)	1	0.5	25	(6.1)	26	14.0

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

Table 12 Adverse events possibly or probably related to investigational trial product in ≥ 1% of subjects 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			
Gastrointestinal disorders								
Nausea	11	(5.5)	17	18.5	4	(2.0)	4	4.4
Diarrhoea	7	(3.5)	11	12.0				
Abdominal distension	2	(1.0)	2	2.2	4	(2.0)	4	4.4
Abdominal pain	4	(2.0)	5	5.4				
Vomiting	2	(1.0)	2	2.2				
Investigations								
Blood fibrinogen increased	5	(2.5)	5	5.4	1	(0.5)	1	1.1
Lipase increased	5	(2.5)	5	5.4	1	(0.5)	1	1.1
Blood calcitonin increased					2	(1.0)	2	2.2
Weight decreased	2	(1.0)	2	2.2				
Metabolism and nutrition disorders								
Decreased appetite	5	(2.5)	5	5.4	1	(0.5)	1	1.1
Hypoglycaemia	2	(1.0)	2	2.2				
General disorders and administration site conditions								
Injection site pain					4	(2.0)	5	5.6
Injection site pruritus					2	(1.0)	2	2.2

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

In Trial 3951, the percentage of subjects reporting AEs during the 26-week treatment period was 64.2 and 58.2% in the IDegLira and placebo groups respectively (401.4 vs367.0 events per 100 PYE).

The most frequently reported AEs in the IDegLira group were 'lipase increased', 'nasopharyngitis',

‘dyslipidaemia’, ‘headache’ and ‘influenza’. At SOC level for AEs considered possibly or probably related to trial product, the rate was higher in the IDegLira group than in the placebo group for *gastrointestinal disorders* (24.1 vs. 11.3 events per 100 PYE), *investigations* (17.3 vs. 9.7 events per 100 PYE) and *metabolism and nutrition disorders* (9.8 vs. 1.6 events per 100 PYE).

Table 12b Adverse events by system organ class and preferred term – most frequent [≥5%]-treatment-emergent- Trial 3951 – summary safety analysis set

	IDegLira				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	288				146			
Events	83	(28.8)	104	78.3	38	(26.0)	50	80.5
Infections and infestations								
Nasopharyngitis	25	(8.7)	29	21.8	12	(8.2)	15	24.1
Influenza	8	(2.8)	8	6.0	8	(5.5)	9	14.5
Investigations								
Lipase increased	28	(9.7)	30	22.6	6	(4.1)	8	12.9
Metabolism and nutrition disorders								
Dyslipidaemia	19	(6.6)	19	14.3	6	(4.1)	7	11.3
Nervous system disorders								
Headache	15	(5.2)	18	13.6	8	(5.5)	11	17.7

N: Number of subjects, %: Percentage of subjects, E: Number of events,

An external independent event adjudication committee (EAC) was constituted for the therapeutic confirmatory trials to perform ongoing adjudication, standardisation and classification of selected events. The EAC was blinded to the trial treatment.

The following events were to be adjudicated by the external independent EAC:

1. Cardiovascular events
2. Pancreatitis or suspicion of pancreatitis
3. Neoplasms
4. Thyroid disease requiring thyroidectomy

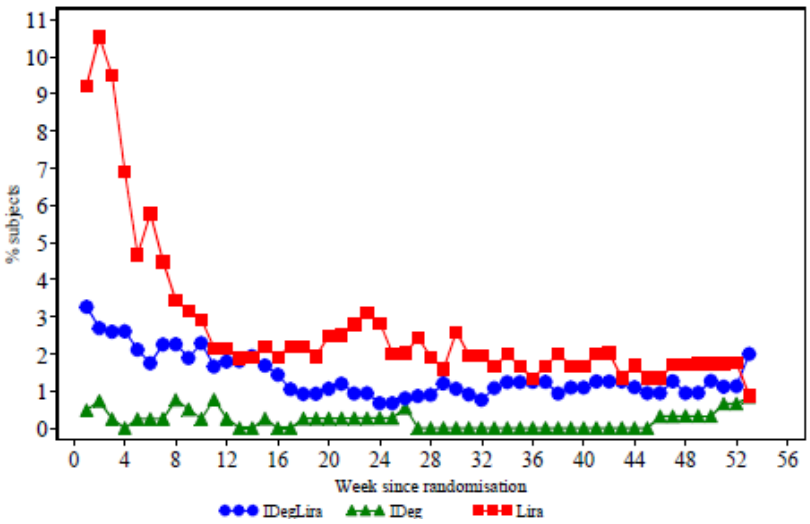
Gastrointestinal events

GI events were the most frequently reported AEs for IDegLira. In study 3697, the rate of gastrointestinal AEs in the IDegLira group was 98.7 events per 100 PYE compared to 51.1 events for IDeg and 157.9 events for Lira. Most gastrointestinal events were mild or moderate, and the rate of severe gastrointestinal AEs in the IDegLira, IDeg and Lira groups was 1.3, 0.7 and 5.1 events per 100 PYE, respectively. As seen for other GLP 1 agonists, the incidence decreased with time (figure 1).

Table 13 Nausea, diarrhoea and vomiting events – 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			
Nausea	85	(10.3)	102	14.5	65	(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

Figure 18 Percentage of subjects with nausea by week and treatment - Trial 3697 (52 weeks) – safety analysis set



In study 3912, the incidence of GI AEs was 21 % for IDegLira compared to 11.6% for IDeg.

In Trial 3951, there were no consistent treatment differences in the reporting of 'nausea', 'diarrhoea' or 'vomiting', except for a minor increase in rate of 'nausea' in the IDegLira group during treatment initiation.

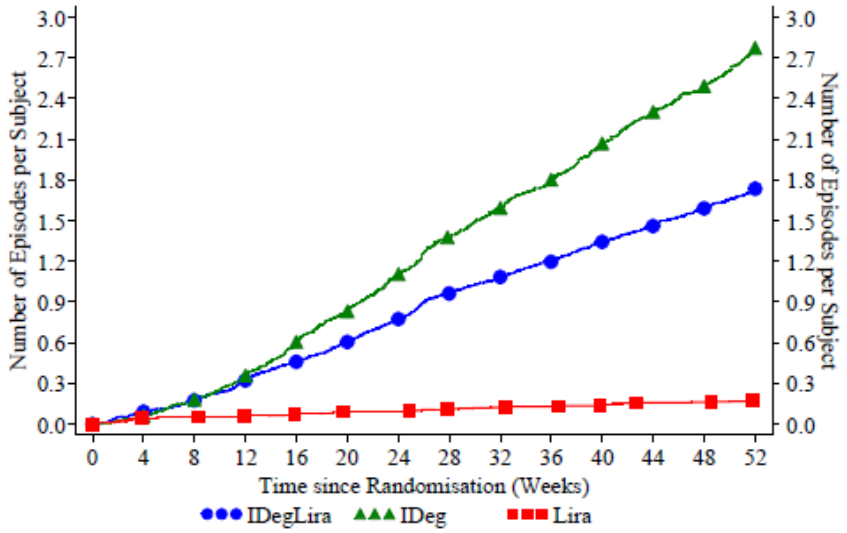
Hypo/hyperglycaemia

All statistical analyses were based on 'confirmed hypoglycaemic episodes', defined as severe hypoglycaemic episodes (patient not able to self-treat), or episodes of hypoglycaemia with plasma glucose < 3.1 mmol/L (56 mg/dL), regardless of symptoms.

In study 3697, the percentage of subjects who experienced confirmed hypoglycaemic episodes during the first 26-week treatment period was 31.9% in the IDegLira group compared to38.6% in the IDeg group and 6.8% for liraglutide.

In Trial 3912, the rate of confirmed hypoglycaemic episodes with IDegLira was 153.4 events per 100 PYE) and with IDeg 263.3 events per 100 PYE, although the proportion of subjects experiencing confirmed hypoglycaemic episodes were similar for IDegLira and IDeg (24.1% and 24.6%).

Figure 19 Confirmed hypoglycaemic episodes – treatment-emergent – Trial 3697 (52 weeks) - mean cumulative function - safety analysis set



In study 3951, the proportion of subjects who experienced confirmed hypoglycaemic episodes in the IDegLira and placebo groups was 41.7%, and 17.1% and the corresponding rates of confirmed hypoglycaemia were 351.7 and 135.2 episodes per 100 PYE, respectively.

The proportion of subjects who experienced nocturnal confirmed hypoglycaemic episodes during the treatment period in the IDegLira and placebo groups was 11.8% and 6.8% and the corresponding rates of confirmed hypoglycaemia were 49.0 and 32.2 episodes per 100 PYE, respectively. There were no severe nocturnal hypoglycaemic episodes.

In study 3697, during the first 26 weeks of treatment, 4 hyperglycaemic events for 4 (0.2%) subjects were identified. These were 2 events in subjects with IDegLira and 2 events with liraglutide. In study 3912, 1 event for 1 (0.5%) subject in the IDegLira group and 7 events for 7 (3.5%) subjects in the IDeg group were detected. When transferring a patient from basal insulin to Xultophy, the recommended starting dose is 16 units and thus, for patients treated with higher insulin doses, hyperglycaemia could be expected to occur during uptitration of Xultophy. However, mean fasting SMPG levels in Trial 3912 did not indicate any transient deterioration of glycaemic control in subjects transferring from 20-40 units of basal insulin to 16 dose steps of IDegLira.

Cardiovascular events

There was an increase in mean pulse rate (2-3 bpm) in the IDegLira group in both studies. This was also seen for Lira, but not for IDeg.

In study 3951, the pulse was statistically significantly higher after 26 weeks of treatment for subjects in the IDegLira group compared to the placebo group; estimated treatment difference was 3.8 beats/min [2.3; 5.4]95%CI, p <0.001.

Table 14 Mean pulse and change from baseline – Trial 3697– safety analysis set

	IDegLira		IDeg		Lira	
	N	Pulse (beats/min)	N	Pulse (beats/min)	N	Pulse (beats/min)
Week 0	825	75.6	412	75.6	412	76.3
Week 26	825	78.4	412	75.1	412	78.9
Week 52	825	77.4	412	75.4	412	77.7
Change to Week 26	825	2.8	412	-0.5	412	2.6
Change to Week 52	825	1.8	412	-0.2	412	1.4

Missing data are imputed using LOCF. LOCF = last observation carried forward, N = number of subjects.

Mean blood pressure was slightly reduced in the IDegLira group in all studies (study 3697; -1.8/-0.0 mmHg, Study 3912; -5.4/-1.4 mmHg).

Of the 216 cardiovascular events identified by search, 40 cardiovascular events qualified for adjudication and were sent to the EAC for adjudication. In addition, 8 events reported by the investigator, but not captured by the SMQ search, were also sent for adjudication. Based on the adjudication process, 26 adjudicated cardiovascular events for 17 subjects were confirmed by the EAC based on predefined criteria, and 25 of these events were treatment-emergent. Nine (9) of the 26 confirmed cardiovascular events were classified as MACEs based on the FDA criteria.

Table 15 Cardiovascular adverse events confirmed by adjudication – treatment-emergent - completed therapeutic confirmatory trials – safety analysis set

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Lira N	(%)	E	R
Number of subjects	1024				611				412			
EAC confirmed events	7	(0.7)	9	1.1	8	(1.3)	12	2.7	1	(0.2)	4	1.2
Acute coronary syndrome	3	(0.3)	3	0.4	4	(0.7)	4	0.9	1	(0.2)	2	0.6
Unstable angina pectoris					2	(0.3)	2	0.5	1	(0.2)	1	0.3
Myocardial infarction	3	(0.3)	3	0.4	2	(0.3)	2	0.5	1	(0.2)	1	0.3
STEMI	2	(0.2)	2	0.3								
NSTEMI	1	(0.1)	1	0.1	2	(0.3)	2	0.5	1	(0.2)	1	0.3
Cerebrovascular event					2	(0.3)	2	0.5				
Stroke					1	(0.2)	1	0.2				
Transient ischemic attack					1	(0.2)	1	0.2				
Heart failure					1	(0.2)	1	0.2				
Coronary revascularisation procedure	4	(0.4)	4	0.5	5	(0.8)	5	1.1	1	(0.2)	2	0.6
Cardiovascular death	2	(0.2)	2	0.3								

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

In study 3951, 4 events (all in the IDegLira group)were confirmed as cardiovascular events according the adjudication charter and 2 of these 4 events were identified as MACE.

Pancreatitis

In the pooled data from Trials 3697 and 3912, 5 events of pancreatitis for 5 subjects were identified. Of these, 2 events were treatment-emergent; 2 events were non-treatment-emergent (occurred after the defined treatment-emergent period) and 1 event was linked (as a symptom) to the event of 'pancreatic carcinoma stage IV. All 5 pancreatitis events were adjudicated by the external EAC and 2 of these were confirmed as events of acute pancreatitis (1 with IDeg and 1 with Lira). No confirmed episodes of pancreatitis were reported with IDegLira. No event of pancreatitis was reported in study 3951.

Neoplasms/Thyroid disease

In the pooled data from Trials 3697 and 3912, a total of 48 treatment-emergent neoplasm events reported for 43 (2.1%) subjects were identified by the SOC/SMQ search. The rate of neoplasm events in the IDegLira group was 3.3 events, for IDeg 2.5 events and for Lira 3.3 events per 100 PYE groups. 24

events of neoplasms were confirmed by the EAC. The event rate with IDegLira was mainly driven by skin events (4 events of 'basal cell carcinoma' and 1 event of 'malignant melanoma'). One subject treated with Lira in study 3697 was initially diagnosed with acute and chronic pancreatitis but was finally diagnosed metastatic pancreatic adenocarcinoma.

In study 3951, 3 treatment-emergent events were confirmed as neoplasms by the EAC; 1 in the IDegLira group and 2 in the placebo group.

Three (3) events of 'thyroid neoplasm' (2 with IDegLira and 1 with liraglutide) were sent for adjudication (as neoplasms); none of the events were confirmed according to predefined criteria for neoplasms. No medullary thyroid cancer (MTC) event was reported.

Serious adverse events and deaths

In total, 2 deaths (in the IDegLira group, classified as CV deaths) were reported in trial 3697, assessed as unlikely related to trial product by investigator and sponsor.

In Trial 3697, the percentages of subjects reporting SAEs during the first 26-week treatment period was 2.3%, 1.9% and 3.4%for IDegLira, IDeg and Lira, respectively. In Trial 3912, the percentage of subjects reporting SAEs was 3.5% in the IDegLira group and 5.5% in the IDeg group. There were 3 hypoglycaemia SAES reported in the IDegLira group but otherwise no clustering of events.

In study 3951, the overall rates of SAEs were 20.3 and 8.0 events per 100 PYE in the IDegLira and placebo groups, respectively. Two subjects in the IDegLira group reported 7 and 4 SAEs, respectively.
No SAEs occurred in ≥1% of subjects. 3 SAEs reported in 2 subjects (both in the IDegLira group) were possibly or probably related to trial product ('amylase increased'/'lipase increased' and 'hypoglycaemic unconsciousness). 1 death ('pleural mesothelioma malignant') occurred in the IDegLira group during the trial.

Laboratory findings

In trial 3697, based on the first 26 week treatment period, an increase in mean lipase was observed in the IDegLira group (mean change 11.4 U/L) and in the liraglutide group (mean change 15.3 U/L); whereas a decrease was seen in the IDeg group (mean change -6.8 U/L). A similar mean increase was observed for amylase for IDegLira with a mean change at Week 26 at 8.9 U/L, for IDeg it was 4.2 U/L, and for liraglutide it was 6.6 U/L.

In study 3951, an increase in mean lipase activity during the trial was observed in the IDegLira group (mean change at Week 26 was 11.6 units/L); a decrease was seen in the placebo group (mean change at Week 26 was -3.1 units/L).

In Trial 3697, a total of 28 subjects had calcitonin concentrations ≥ 20 ng/L at some time point over the 52-week treatment period of the trial (16 subjects with IDegLira, 9 subjects with IDeg and 3 subjects with Lira). In Trial 3912, a total of 14 subjects had calcitonin concentrations ≥ 20 ng/L at some time point during the trial (6 subjects with IDegLira and 8 subjects with IDeg)..

Blood creatinine increased 'was reported in 9 subjects with no difference among the treatment groups. 'Renal failure'/'renal failure acute' were reported for 6 subjects (2 with IDegLira, 3 with IDeg and 1 with liraglutide.

Safety in special populations

The extent of exposure to IDegLira in elderly subjects (≥ 65 years) was 154 subjects (121.7 PYE) and there were 14 (8.8 PYE) very elderly subjects (≥ 75 years) in studies 3912 and 3697. In study 3951, 58 patients 65-74 years and 20 patients(≥ 75 years were exposed to IDegLira. The exposure to IDegLira was similar for male (541 subjects and 415.5 PYE) and female subjects (483 subjects and 382.0 PYE). The majority of exposure to IDegLira was in subjects with BMI ≥ 25 kg/m^2 (926 subjects, 717.2 PYE) and 283 of the subjects had a BMI ≥ 35 kg/m2 (214.2 PYE).

The incidence of AEs were similar in patients below and above age 65 years.

Table 16 Adverse events by age - treatment-emergent – completed therapeutic confirmatory trials – safety analysis set (study 3912 and 3697)

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Safety analysis set [PYE]	1024	[797.5]			611	[440.1]			412	[334.3]		
Number of subjects [PYE]												
18-64 years	870	[675.9]			501	[364.1]			355	[287.2]		
65-74 years	140	[112.9]			95	[64.0]			48	[40.9]		
≥65 years	154	[121.7]			110	[76.0]			57	[47.1]		
≥75 years	14	[8.8]			15	[12.0]			9	[6.2]		
≥85 years					1	[0.5]						
Adverse events												
18-64 years	593	(68.2)	2791	413.0	336	(67.1)	1391	382.1	275	(77.5)	1438	500.6
65-74 years	98	(70.0)	419	371.2	66	(69.5)	236	368.5	36	(75.0)	228	557.4
≥65 years	109	(70.8)	453	372.4	77	(70.0)	271	356.5	43	(75.4)	258	547.7
≥75 years	11	(78.6)	34	387.7	11	(73.3)	35	292.5	7	(77.8)	30	483.8
Serious adverse events												
18-64 years	36	(4.1)	45	6.7	23	(4.6)	33	9.1	18	(5.1)	21	7.3
65-74 years	8	(5.7)	12	10.6	9	(9.5)	10	15.6	5	(10.4)	9	22.0
≥65 years	9	(5.8)	13	10.7	10	(9.1)	11	14.5	6	(10.5)	10	21.2
≥75 years	1	(7.1)	1	11.4	1	(6.7)	1	8.4	1	(11.1)	1	16.1

The overall rate of AEs was somewhat higher in females compared to males. This was seen in all treatment groups.

The overall incidences of adverse events were similar in patients with normal and mildly impaired renal function. The clinical experience of IDegLira in moderate renal impairment is very limited (n=11).

Table 17 Adverse events by renal function based on estimated creatinine clearance at baseline - treatment-emergent – completed therapeutic confirmatory trials – safety analysis set

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Safety analysis set [PYE]	1024	[797.5]			611	[440.1]			412	[334.3]		
Number of subjects [PYE]												
Normal	863	[667.0]			523	[374.3]			348	[287.7]		
Mild	150	[121.6]			82	[60.3]			55	[39.8]		
Moderate	11	[8.9]			6	[5.5]			9	[6.9]		
Adverse events	**702**	**(68.6)**	**3244**	**406.8**	**413**	**(67.6)**	**1662**	**377.6**	**318**	**(77.2)**	**1696**	**507.3**
Normal	588	(68.1)	2824	423.4	348	(66.5)	1415	378.0	271	(77.9)	1464	508.9
Mild	106	(70.7)	394	324.0	63	(76.8)	245	406.4	42	(76.4)	213	535.7
Moderate	8	(72.7)	26	290.7	2	(33.3)	2	36.5	5	(55.6)	19	275.0
Serious adverse events	**45**	**(4.4)**	**58**	**7.3**	**33**	**(5.4)**	**44**	**10.0**	**24**	**(5.8)**	**31**	**9.3**
Normal	37	(4.3)	48	7.2	26	(5.0)	34	9.1	18	(5.2)	23	8.0
Mild	7	(4.7)	9	7.4	7	(8.5)	10	16.6	6	(10.9)	8	20.1
Moderate	1	(9.1)	1	11.2								

MedDRA Version 15.0
Data is based on trials NN9068-3697-ext and NN9068-3912.
N = number of subjects with adverse events; % = proportion of subjects with adverse events; E = number of adverse events; R = rate (number of adverse events divided by patient years of exposure [1 PYE = 365.25 days] multiplied by 100).
Normal = estimated creatinine clearance > 80 mL/min; Mild = estimated creatinine clearance > 50 - <= 80 mL/min, Moderate = estimated creatinine clearance > 30 - <= 50 mL/min; Severe = estimated creatinine clearance <= 30 mL/min.

Immunological events

The rate of allergic reactions in the IDegLira, IDeg and Lira groups was 0.9, 1.8 and 1.8 events per 100 PYE, respectively. The most frequently reported allergic reactions were 'asthma' and 'urticaria' with no major difference among treatment groups.

In the pooled data from Trials 3697 and 3912, 117 injection site reactions reported for 67 (3.3%) subjects. The rate of injection site reactions in the IDegLira, IDeg and Lira groups was 8.3, 5.7 and 7.8 events per 100 PYE, respectively. The most frequently reported injection site reactions were 'injection site haematoma', 'injection site pain' and 'injection site reaction'.

In study 3951, the rate of injection site reactions was higher, but comparable between groups (21.1 vs. 20.9 events per 100 PYE).

Five percent of the patients from the IDegLira group developed antibodies towards insulin compared to 2% of the patients treated with IDeg in study 3697. In study 3912, the percentages were 5 and 3% for IDegLira and IDeg, respectively. None of these antibodies were shown to neutralize the activity of human insulin or insulin degludec.

Few subjects developed anti-liraglutide antibodies (0.5-3% at different time points). Of these 5 (4 with IDegLira and 1 with liraglutide) were demonstrated to have an *in vitro* neutralising effect at Week 53 in trial 3697.

Safety related to drug-drug interactions and other interactions

In general, IDegLira is not expected to be influenced by other drugs due to the fact that it is a combination of peptides subject to standard proteolytic processes and degraded to small peptides and amino acids.

A search was performed to identify events of congestive heart failure or events potentially related to congestive heart failure for subjects treated with IDegLira in combination with pioglitazone or without pioglitazone. The rates of these AEs for subjects using vs. not using pioglitazone in combination with IDegLira were 4.1 vs. 3.1 events per 100 PYE based on 5 events in 5 subjects and 18 events in 12 subjects, respectively).

Discontinuation due to AES

During the first 26-week treatment period of study 3697, a total of 43 (2.6%) subjects out of 1663 randomised subjects were withdrawn from the trial due to AEs: 11 (1.3%) in the IDegLira group, 8 (1.9%) in the IDeg group and 24 (5.8%) in the liraglutide group.

From 26−52 weeks, an additional 8 (0.5%) subjects were withdrawn from the trial due to AEs: 5 (0.6%) in the IDegLira group, 1 (0.2%) in the IDeg group and 2 (0.5%) in the liraglutide group. The majority of AEs leading to withdrawal were in the SOCs 'gastrointestinal disorders' (mainly in the liraglutide group) and 'investigations'.

In study 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. All AEs leading to withdrawal were considered unlikely to be related to trial product.

In study 3951, the proportion of the subjects with AEs leading to withdrawal during the 26-week treatment period was higher in the IDegLira group (9 subjects; 3.1%) than in the placebo group (2 subjects; 1.4%).

2.6.1. Discussion on clinical safety

In the pooled safety analysis set, 1,300 patients with type 2 diabetes have been exposed to IDegLira out of which 623 have been exposed for at least 52 weeks. All patients in the 2 confirmatory therapeutic studies were exposed to IDegLira on a background therapy of metformin. In addition, in trial 3697, 17.0% were using a combination of metformin and pioglitazone. Trial 3951, investigated IDegLira as add on to SU+/- metformin.
Previous safety data are also available for the mono-components, Tresiba and Victoza, respectively. For Victoza (liraglutide), the combination with insulin has recently been approved. However, the extent of the exposure to the combination in the current application is considered as sufficient to assess short term safety.
The most common adverse events associated with IDegLira are gastrointestinal side effects as expected due to the liraglutide component. In study 3697 the incidence for IDegLira, IDeg and Lira, respectively were; nausea (10.3, 3.9, 22.3 %), diarrhoea (10.2, 6.8, 16.3%), vomiting (5.0, 2.4, 9.2%). These adverse events have previously been shown to be related to the actual liraglutide dose and also to the rate of dose uptitration. Since the actual dose of liraglutide was lower and the dose uptitration slower in the IDegLira compared to the Lira group, this could be considered an expected finding. The GI AEs were transient and after 15 weeks treatment, there were no major differences between treatment groups.

The number of potential events of acute pancreatitis and pancreatic enzyme elevations was low and no confirmed episodes of pancreatitis were reported with IDegLira. However, there was an increase in serum lipase and amylase which was not seen in the IDeg groups. Acute pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class. Acute pancreatitis has been included in the RMP as important identified risk.

The incidence of allergic reactions seen in the IDegLira treated group in the pooled safety analysis set was low (0.9%) and numerically lower than for the other treatments. Injection site reactions related to IDegLira treatment was present in 2.9% of patients compared to 4.6% for liraglutide and 2.9% for IDeg. 4.8% of patients treated with IDegLira developed antibodies towards insulin compared to 1.9% of patients treated with IDeg. No neutralising insulin anti-bodies were detected. Few subjects developed anti-liraglutide antibodies (0.5-3% after 52 weeks treatment), 4 subjects treated with IDegLira had anti-bodies that were demonstrated to have an *in vitro* neutralising effect towards liraglutide. Overall, antibody development has previously been detected for both liraglutide (8.6%) and IDeg.
As expected, the incidence of hypoglycaemia was lowest in the liraglutide group in study 3697. The higher incidence for IDeg compared to IdegLira in that study is most likely due to the higher insulin dose. In study 3912 the incidences were similar in the two groups. In conclusion, there is no indication of an additive effect with respect to the risk of hypoglycaemia when IDeg is combined with Lira.

The rate of confirmed hypoglycaemia was higher in study 3951 when IDegLira was added to SU, both compared to placebo as well as compared to rates in other studies (351.7 and 135.2 episodes per 100 PYE, for IDegLira and placebo respectively). Information that a reduction of the SU may be needed has been included in sections 4.2 and 4.4 of the SmPC.

When transferring a patient from basal insulin to Xultophy, the recommended starting dose is 16 units and thus, for patients treated with higher insulin doses, hyperglycaemia could be expected to occur during uptitration of Xultophy. However, mean fasting SMPG levels in Trial 3912 did not indicate any transient deterioration of glycaemic control in subjects transferring from 20-40 units of basal insulin to 16 dose steps of IDegLira.

An increase in pulse was observed with IDegLira (mean change 2.8 beats/min) and liraglutide (mean change 2.6 beats/min). This has also been reported for other GLP 1 agonists. However, there were no signs of detrimental effects on blood pressure (rather a minor decrease in blood pressure). The clinical relevance of the increase in heart beats is currently not known. However, several CV outcome studies are ongoing for different products within the class.

In the current safety data base, there were numerically more CV events in the IDegLira and IDeg groups compared to Lira. The safety data base is too small to draw any conclusions with respect to cardiovascular safety. As mentioned above, a CV outcome study is ongoing for liraglutide. A CV outcome study is also ongoing for IDeg.

There is limited experience of use of Xultophy in patients with congestive heart failure NYHA class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.

GLP-1 receptor agonists have been associated with thyroid C-cells proliferative/hyperplasia in non-clinical carcinogenicity studies, but the relevance for humans is unsure. The current data base is too limited and the duration of the studies too short to provide any useful information about thyroid or other neoplasms. The potential tumour growth promoting effect of insulin analogues due to their anabolic properties is an ongoing discussion. However, no firm association has been established between any insulin analogues and increased cancer risk. Considering the findings of C-cell tumours in rats when given liraglutide, an additive effect on the risk of malignancies when combining Lira and Ideg could be hypothesised. However, this risk seems very remote and is not considered strong enough to justify a request for specific PAS studies. Long term PAS studies are ongoing for Lira which will provide more information about neoplasms. As a result of an Art 5(3) referral procedure in 2013, pancreatic neoplasms has been included in the RMP as a potential risk. In the current clinical development program, one subject treated with liraglutide was diagnosed with metastatic pancreatic adenocarcinoma. No medullary thyroid cancer event was reported in any of the treatment groups.
The incidence of AEs was similar in patients below and above age 65 years. The number of subjects ≥ 75 years is limited. The clinical experience of IDegLira in patients with moderate renal impairment is very limited (n=11) and use of IdegLira is not recommended in line with recommendations for Victoza.

In clinical practice it may be expected that some patients will transfer from basal insulin to Xultophy. These patients may also be treated with bolus insulin and may therefore have several pens at home. Efforts to mitigate the risk of mix-up have been implemented at the prescribing, dispensing and patient levels. In addition, in the usability test, no use errors were observed neither related to differentiation nor to handling of the device or cartons. The test included relevant comparators. It is considered that the Applicant has taken adequate measures to mitigate mix ups.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile for IDegLira is in general similar to the two included mono-components with no indications of additive toxicity. Since the actual liraglutide dose in the studies was lower and the up-titration of dose somewhat slower, the prevalence and severity of the well-known gastrointestinal side-effects were lower compared to liraglutide as monotherapy. No new safety issues have been identified for this combination. The incidence of confirmed hypoglycaemia was higher compared to liraglutide, but lower compared to IDeg in the actively controlled studies. The incidence of hypoglycaemia was highest when IDegLira was combined with SU. Relevant information has been included in the SmPC.

With regard to the long-term safety, the initial cardiovascular safety evaluation is acceptable with a potentially beneficial effect on systolic blood pressure in contrast to slight increase in heart rate in the

clinical studies. A CV outcome study is ongoing for liraglutide. Otherwise, the long-term safety concerns are the same as for the other GLP-1 agonist and insulin analogues, i.e. identified risk of pancreatitis and potential risks of malignancies e.g. pancreatic and thyroid tumours.

2.7. Additional expert consultations

A SAG expert meeting of the Scientific Advisory Group Diabetes/Endocrinology was held on the 5th June 2014 to obtain further input on the efficacy and safety of Xultophy in the treatment of type 2 diabetes mellitus.

ANSWERS FROM THE SAG ON XULTOPHY

1) **Xultophy is proposed to be used in the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products when these do not provide adequate glycaemic control.**

    a. **Is the available evidence base sufficient to draw conclusions on the risks and benefits of Xultophy as an add-on treatment in T2DM patients uncontrolled on oral agents alone? If not, in what regard is it considered deficient?**

    b. **Please discuss potential advantages and disadvantages of adding Xultophy compared to first adding either insulin or liraglutide in a sequential manner before using a combination of both products.**

As questions 1a and 1b are related, both parts of the question were discussed by the SAG together.

SAG Answer:

The experts had a split view: Some experts were in agreement to use the product as an option in patients uncontrolled on a therapy with oral antidiabetics alone. However, those experts also felt that not all such patients would be suitable to be switched to this therapy (see answer 1c and 2a).

Other experts would not use the product for switching from a therapy with oral antidiabetics, but only for patients who were already additionally either on insulin or on a GLP1-agonistic therapy and needed further treatment escalation. The reasons given for preferring a sequential add-on of therapies were that usually there was some rational to escalate therapy with either insulin or a GLP-1 agonist, that a certain percentage of patients would unnecessarily be exposed to 2 additional drugs at the same time, and that establishing a side effect profile relating to the individual components of Xultophy for the individual patient would be hampered. The SAG noted, that a study investigating the switch of therapy from an add-on therapy with a GLP-1 agonist to Xultophy (trial 3851) is currently ongoing and the results not yet available.

The main advantage of adding Xultophy, compared to first adding either insulin or liraglutide in a sequential manner, was seen in a more effective achievement of glycaemic control, i.e. achievement of a lower HbA1C, higher percentage of patients reaching certain target goals (e.g. 7% HbA1C), and reaching those goals more quickly, as well as convenience. However, the benefit of this “aggressive” glucose-lowering approach was questioned by some experts, in particular for prevention of macrovascular events, and particularly in older patients. It was mentioned that long-term ambitious glucose-lowering treatment goals have been shown to be associated with detrimental effects in some trials, e.g. ACCORD trial, but it was also pointed out by the applicant that this was in a very different population. In any case, treatment targets should be set for patients individually (in the studies treat to target principles applied), and may be less stringent in particular in older patients.

Main disadvantages were seen in the lesser opportunity to individualize the therapy (e.g. in terms of dosing), and to establish a link between side effects experienced by the individual patient and the 2 components of Xultophy, respectively.

One concern was raised regarding the use of Xultophy in diabetic patients with CKD; however the SmPC already recommends not to use the product in moderate to severe renal impairment, which is consistent with the same recommendation in the SmPC of Victoza (liraglutide).

Overall, the experts pointed out areas of missing knowledge and/or guidance in the PI, in particular: in case of intercurrent illness or GI affections such as norovirus affliction, it is not clear whether a switch to insulin only should occur, and under what circumstances, and how a restart of therapy with Xultophy should be managed; criteria when to stop therapy could be useful; it is also not clear, how change in therapy beyond >1 year should be handled in case of further progression of disease and higher insulin dose requirements, etc. More data regarding the latter question was advocated. A distinct lack of data in the elderly (> 75 years) was noted. Experts felt information in the PI should clearly inform patients and physicians which side effects of Xultophy are most likely related to insulin degludec or to liraglutide, respectively (as otherwise e.g. side effects of liraglutide might be related to insulin, etc.).

c. Is there a specific patient population with type 2 diabetes that could benefit from Xultophy compared to other available treatment alternatives?

SAG Answer: A scenario described by one expert where Xultophy might be particularly suitable could be patients in need of an add-on therapy with insulin, where Xultophy could have advantages such as weight neutrality and less propensity for hypoglycaemia compared to insulin. Other experts would prefer scenarios with patients already on a therapy with either one of the 2 components of Xultophy (i.e. insulin or a GLP-1 agonist). Most experts had concerns about a rather indiscriminate switch of patients on oral antidiabetic therapy only to add on Xultophy.

d. How does the proposed indication for Xultophy comply with current treatment algorithms (e.g. position statement of EASD and ADA, Diabetes Care, 35, June 2012)?

SAG Answer: The experts felt that the place in treatment algorithms would remain to be established once the product is used, but felt that a positioning as an equal alternative to other available options for the combination with metformin (once metformin only therapy fails) would be, with few exceptions, inappropriate.

2) There are some concerns with respect to dosing recommendations for Xultophy.

a. Xultophy is delivered at a fix dose ratio between the dose of liraglutide and degludec and thus the doses of the separate components cannot be titrated separately. Please comment on the usability of Xultophy in this respect compared to using the products separately, e.g. considering that the dose of liraglutide cannot be maximized at lower dosages of insulin. Is this considered as a problem in clinical practice?

SAG Answer: Some experts felt satisfied with the fixed dose-relationship, since they would titrate the product in their intended patients anyway. Others felt that this would not allow to adjust doses optimally, e.g. to prevent the use of the maximal liraglutide dose in some cases. One expert questioned the rational of the chosen dose-relationship and felt that there was a lack of data that this was the best dose-relationship for the vast majority of patients. Some experts saw difficulties when switching to Xultophy from either insulin or a GLP-1 agonist, as the SmPC recommends in that case to start with 16 dose steps and the related low liraglutide dose, whereas patients may already have been on a maximal

dose of GLP-1 agonists, or a higher dose than 16 units/day of insulin (30 units/day on average in the studies, according to the applicant), respectively.

b. The maximum daily dose of Xultophy is 50 dose steps (50 units insulin degludec and 1.8 mg liraglutide). Please comment on how the fact that the insulin dose cannot be increased above 50 units could impact the usability of the product.

SAG Answer: Experts considered that there will be situations with a need for a higher insulin dose than 50 units/day for patients on Xultophy, and noted a lack of guidance how to handle those situations (e.g. disease progression, severe illness).

c. The prefilled Xultophy pen will define and deliver the dose as 'dose steps' (1 to 50 dose steps) with one dose step containing 1 unit of insulin degludec and 0.036 mg of liraglutide. Thus, the actual liraglutide dose is not proposed to be visible in the pen window. Please comment on this strategy with respect to risk of medication errors. Please also comment on possible alternative ways to express the dose of insulin degludec and liraglutide in the product information for healthcare professionals and patients in order to minimise the possibility of medication error.

SAG Answer: Experts felt that to express only the insulin dose in the window was acceptable (given the lack of space, and being the more important dosing consideration with regard to the possibility of hypoglycaemia). Some experts felt it might be beneficial if the pen was more easily recognisable to contain insulin, and the same instruction and training principles as for insulin-only pens should apply. It was briefly discussed whether it would still be safer to use "Units" instead of "Dose Steps" but considered to be difficult. The mock-up pen distributed during the meeting was considered to be potentially mixed up with existing similarly-coloured pens (similar pink colour). The use of the term "IDegLira" (not currently used in the proposed materials) should be avoided as it may be then less clear that the product is composed of insulin degludec and liraglutide.

The experts emphasised the need for careful instruction of use for HCPs as well as patients, as this product would introduce a new treatment paradigm (see also responses to questions 1a and 1b).

2.8. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.9. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice relating to the implementation of additional risk minimisation measures in the form of educational material. The PRAC advice is attached.

The CHMP endorsed this advice with the following changes:

For the key elements to be addressed in the educational materials,

- the key element “the licensed indications and circumstances for use” has been removed because the final indication wording agreed in section 4.1 of the SmPC was simplified;
- the key element “this product contains a fixed combination of insulin degludec plus liraglutide (a GLP1-based product)” has been changed to “this product contains a fixed combination of insulin degludec plus liraglutide (a GLP1-based product) which constitutes a new treatment paradigm in the treatment of patients with type 2 diabetes. In this context, relevant precautions as reflected in the SmPC should be emphasised” to reflect the fact that although it is a fixed combination, the dose is not fixed and to emphasise the fact the licensed indication reflects a change in the treatment paradigm for type II diabetes.
- the key element “a reminder of the need to report all medication errors irrespective of whether or not they resulted in an adverse event” has been added to reflect the level of concern regarding the potential for medication errors with this fixed combination and the need to monitor this carefully.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP and the Annex II text of the SmPC has been amended accordingly.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 1: Summary of safety concerns

Important identified risks	– Gastrointestinal disorders – Hypoglycaemia – Immunogenicity (Allergic reactions) – Pancreatitis
Important potential risks	– Altered renal function – Cardiovascular disorders – Lack of efficacy due to anti-IDeg or anti-liraglutide antibody formation – Medication errors, including errors with transfer from injectable diabetes therapy – Medullary thyroid cancer – Neoplasms – Pancreatic cancer
Missing information	– Children and adolescents – Congestive heart failure NYHA III-IV – Drug–drug interaction with warfarin – Off-label use in patients with T1DM – Patients with hepatic impairment – Patients with moderate and severe renal impairment – Pregnant and lactating women – Transfer from injectable diabetes therapy – Use of Xultophy in the very elderly (≥75 years)

The PRAC agreed

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures. The PRAC highlighted the need however, for ***all*** medication errors to be reported during the routine pharmacovigilance; reporting should not be restricted to the medication errors resulting in an adverse event.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Gastrointestinal disorders	(Proposed) text in SmPC 4.4 Special warnings and precautions for use Dehydration 4.8 Undesirable effects Gastrointestinal adverse reactions	None
Hypoglycaemia	(Proposed) text in SmPC 4.4 Special warnings and precautions for use Hypoglycaemia 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects Hypoglycaemia 4.9 Overdose	None
Immunogenicity (allergic reactions)	(Proposed) text in SmPC 4.3 Contraindications 4.8 Undesirable effects Allergic reactions	None
Pancreatitis	(Proposed) text in SmPC 4.4 Special warnings and precaution for use	None
Altered renal function	(Proposed) text in SmPC 4.4 Special warnings and precautions for use Dehydration	None
Cardiovascular disorders	(Proposed) text in SmPC 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Lack of efficacy due to anti-IDeg or anti-liraglutide antibody formation	(Proposed) text in SmPC 4.4 Special warnings and precautions for use Antibody formation	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medication errors, including errors with transfer from injectable diabetes therapy	(Proposed SmPC) 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 5.1 Pharmacodynamic properties	Educational material for healthcare professionals in the EU, in the form of a brochure (See Annex 11 of the RMP)
Medullary thyroid cancer	(Proposed) text in SmPC 5.3 Preclinical safety	None
Neoplasms	None	None
Pancreatic cancer	None	None
Children and adolescents	(Proposed) text in SmPC 4.1 Therapeutic indication 4.2 Posology and method of administration Paediatric population .	None
Congestive heart failure NYHA III–IV	(Proposed) text in SmPC 4.4 Special warnings and precautions for use Populations not studied	None
Drug–drug interactions with warfarin	(Proposed) SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction	None
Off-label use in patients with T1DM	(Proposed) SmPC Section 4.4 Special warnings and precautions for use	None
Patients with hepatic impairment	(Proposed) text in SmPC 4.2 Posology and method of administration Special populations Hepatic impairment	None
Patients with moderate and severe renal impairment	(Proposed) text in SmPC 4.2 Posology and method of administration Special populations Renal impairment	None
Pregnant and lactating women	(Proposed) text in SmPC 4.6 Fertility, pregnancy and lactation Pregnancy Breast-feeding Fertility	None
Transfer from injectable	(Proposed) text in SmPC 4.1 Therapeutic indication	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
diabetes therapy	4.2 Posology and method of administration Transfer from basal insulin 4.4 Special warning and precautions for use Populations not studied	
Use of Xultophy® in the very elderly (≥ 75 years)	(Proposed) SmPC Section 4.2 Posology and method of administration	None

Abbreviations: NYHA = New York Heart Association; SmPC = summary of product characteristics; T1DM = type 1 diabetes mellitus.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

IDegLira (Xultophy) is a fixed combination of the basal insulin *insulin degludec* (IDeg, active substance of Tresiba), and the GLP-1 analogue *liraglutide* (active substance of Victoza). The concomitant use of basal insulin and some GLP-1 analogues is accepted in free combination but no fixed combinations have been previously assessed or approved.

The efficacy of IDegLira has been evaluated in three studies of which studies 3697 and 3912 were considered pivotal. The studies involved a total of 2481 subjects, of whom 1322 have received IDegLira. Study 3697 was a three-armed study including insulin-naïve patients with inadequate metabolic control on metformin+/-pioglitazone. In this study IDegLira, given at a maximum dose of 50 dose steps (50 units of IDeg and 1.8 mg liraglutide), was compared with IDeg which was titrated to target and liraglutide administered according to label. In the smaller study 3912, IDegLira treatment was compared with IDeg given at a maximum dose of 50 units, thereby evaluating the contribution of the liraglutide component. Study 3951 was a placebo-controlled study in patients who had failed on SU ± metformin.

The studies were generally well designed and conducted.

The outcome of study 3697 showed that the effect of IDegLira on HbA1c reduction was superior to both the mono-components (HbA1c decreased by 1.91%with IDegLira, by 1.44% with IDeg and by 1.28% with liraglutide). The differences were statistically significant. Data from the extension study showed that this effect was maintained up to 52 weeks with only marginally increased doses of IDegLira. The reduction in

HbA1c was also reflected in significantly higher responder rates with IDegLira, both when applying the HbA1c cut-off of 7 % (80.6 %) and the stricter cut-off of 6.5 % (69.7 %) compared to both mono-components (IDeg 65.1 % and 47.5 %; liraglutide 60.4 % and 41.1 %). Higher proportions of patients reached the responder target without experiencing hypoglycaemia or weight gain in the IDegLira group compared to IDeg treated subjects whereas no difference was observed compared to liraglutide.

Insulin doses were significantly lower in the IDegLira treated group compared to the IDeg treated group. At week 26 the mean insulin dose in the IDegLira group was 38 dose steps and 39.7% of subjects reached a daily insulin dose of 50 dose steps. In the IDeg groups the mean insulin dose was 53 units and 53.9 % of patients were on doses > 50 units.

Other secondary endpoints supported the primary outcome. A comparable effect on FPG was observed with IDegLira and IDeg (-3.62 mmol/L vs. -3.61 mmol/L, liraglutide -1.75 mmol/L), whereas the effect on post-prandial glucose increment was comparable for IDegLira and liraglutide ($iAUC_{0-4h}$: -0.87 mmol/L vs. -0.78 mmol/L, IDeg -0.16 mmol/L). Body weight was reduced by 0.5 kg in the IDegLira group as compared to an increase by 1.6 kg in the IDeg group and a decrease by 3.0 kg in the liraglutide group.

In study 3912, where the IDeg dose in both arms was maximised to 50 units, HbA1c decreased by 1.90 % with IDegLira and by 0.89 % with IDeg. The reduction in HbA1c was statistically significantly greater with IDegLira compared with IDeg. The HbA1c targets of 7% and 6.5% were reached by 60.3% and 45.2% of IDegLira-treated subjects as compared to 23.1% and 13.1% of IDeg-treated subjects. No difference in insulin dose was observed between treatment arms with a mean insulin dose of 45 units for both arms at week 26.

The primary endpoint was supported by significant reductions in FPG with IDegLira compared to IDeg (-3.46 mmol/L vs. -2.58 mmol/L). The SMPG profile which includes both the effect on FPG and post-prandial glucose increment was also lower with IDegLira compared to IDeg. After 26 weeks of treatment, a change in body weight from of -2.7 kg and 0.0 kg was observed for IDegLira and IDeg, respectively.

Transferring patients on basal insulin applying a starting dose of 16 dose steps IDegLira appears feasible and did not result in loss in metabolic control during the transition period.

In study 3912, which included patients with longer and more heavily treated T2DM, 65.3% of IDegLira-treated subjects reached a daily insulin dose of 50 dose steps after 26 weeks of treatment. As shown above, a substantial proportion of patients will be satisfactorily controlled on ≤ 50 dose steps of IDegLira. As diabetes is a progressive disease, the need for intensified treatment could be anticipated. Adequate information is included in the SmPC in order to prevent dosing of IDegLira above 50 dose steps per day. As a precautionary measure, the pen is constructed such that it can deliver a maximum of 50 dose steps of IDegLira with each injection.

In study 3951, IDegLira was given as add-on to patients who had failed to reach target on previous treatment with SU ± metformin. The addition of IDegLira, with a starting dose of 10 dose steps, resulted in a placebo-corrected decrease in HbA1c of -1.02 (95 % CI; -1.18-0.87). The target of HbA1c <7.0% was reached by 79.2% of patients in the IDegLira group and 28.8% of patients in the placebo group.

Uncertainty in the knowledge about the beneficial effects.

Patients on previous GLP-1 therapy have not been studied and there is consequently no data on whether transition from GLP-1 therapy to IDegLira is feasible. A study in this patient group is ongoing; until study results become available the SmPC has been amended to reflect the lack of experience to that regard.

Risks

Unfavourable effects

The most common adverse events associated with IDegLira are gastrointestinal side effects. In study 3697 the incidence for IDegLira, IDeg and Lira, respectively were; nausea (10.3, 3.9, 22.3 %), diarrhoea (10.2, 6.8, 16.3%), vomiting (5.0, 2.4, 9.2%). The GI AEs were transient and after 15 weeks treatment, there were no major differences between treatment groups.

In study 3697, the percentage of subjects who experienced confirmed hypoglycaemic episodes during the first 26-week treatment period was 31.9% in the IDegLira group compared to 38.6% in the IDeg group and 6.8% for liraglutide. In Trial 3912, the proportions of subjects experiencing confirmed hypoglycaemic episodes were 24.1% and 24.6% for IDegLira and IDeg, respectively (rate; IDegLira 153.4 events, IDeg 263.3 events per 100 PYE). The rate of confirmed hypoglycaemia was higher in study 3951 when IDegLira was added to SU, both compared to placebo as well as compared to rates in other studies (351.7 and 135.2 episodes per 100 PYE, for IDegLira and placebo respectively).

An increase in pulse was observed with IDegLira after (mean change 2.8 beats/min) and liraglutide (mean change 2.6 beats/min) 26 and 52 weeks treatment but not with IDeg. There were no signs of detrimental effects on blood pressure but rather a minor decrease in blood pressure.

The incidence of allergic reactions seen in the IDegLira treated group in the pooled safety analysis set was 0.9%. Injection site reactions related to IDegLira treatment was present in 2.9% of patients compared to 4.6% for Lira and 2.9% for IDeg.
Five (5)% of the patients from the IDegLira group developed antibodies towards insulin compared to 2% of patients in the IDeg group in study 3697. In study 3912, the percentages were 5 and 3% for IDegLira and IDeg, respectively. No neutralising insulin anti-bodies were detected. Few subjects developed anti-liraglutide antibodies (0.5-3% at different time points in the IDegLira group).

No confirmed episodes of pancreatitis were reported with IDegLira. However, a mean increase of serum lipase and amylase was seen the IDegLira and Lira groups compared to patients treated with IDeg. Acute pancreatitis has been previously identified as a potential safety issues for the GLP-1 receptor agonist class. Pancreatitis has been included in the RMP as important identified risk.

Uncertainty in the knowledge about the unfavourable effects

The rate of neoplasm events in the IDegLira group was 3.3 events, for IDeg 2.5 events and for Lira 3.3 events per 100 PYE groups. The event rate with IDegLira was mainly driven by skin events (4 events of ‘basal cell carcinoma’ and 1 event of ‘malignant melanoma’). In the current clinical development program, one subject treated with liraglutide was diagnosed with metastatic pancreatic adenocarcinoma. No medullary thyroid cancer event was reported in any of the treatment groups. As a result of the recent art 5(3) procedure, pancreatic neoplasms has been included in the RMP as a potential risk.

There were numerically more CV events in the IDegLira and IDeg groups compared to Lira, but no difference with respect to oedema. The safety data base is too small to draw any conclusions with respect to cardiovascular safety. A CV outcome study is ongoing for both Lira and IDeg.

There is limited experience of use of Xultophy in patients with congestive heart failure NYHA class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV. This is reflected in the product information.

The incidences of AEs were similar in patients below and above age 65 years, but the number of subjects ≥ 75 years is very low. This is reflected in the product information.

The clinical experience of IDegLira in patients with moderate renal impairment is very limited (n=11) and use is not recommended in line with recommendations for Victoza.

Benefit-risk balance

Importance of favourable and unfavourable effects

The pivotal studies show that the combination of IDeg and liraglutide results in a clinically relevant effect in terms of HbA1c lowering and that both components contribute to this effect. The glucose lowering effect was superior to the effect of the separate compounds titrated to target. IDegLira combines the IDeg effect on FPG and the liraglutide effect on post-prandial glucose increment. The data further show that the effect is achieved at lower insulin doses than with insulin mono-therapy. The effect on body weight was not entirely consistent across the studies, but IDegLira is at least weight neutral, compared to weight increase with IDeg, which is important in the T2DM population where overweight is often a problem. On the other hand, the effect on body weight was less beneficial compared to liraglutide monotherapy. The possibility to take one injection instead of two (if the components would be used separately) is an important benefit for the patient.

The safety profile for IDegLira is in general similar to the two included mono-components with no indications of additive toxicity. The incidence of GI adverse events is lower compared to liraglutide given as monotherapy since a lower dose of liraglutide was needed in the combination with IDeg in the pivotal study. This can be an advantage even though GI adverse events diminish over time. Risk of hypoglycaemia is driven by the insulin dose and since (in study 3697) the necessary dose to achieve glycaemic control was somewhat lower for IDegLira compared to IDeg, consequently the risk is be lower. However, in combination with SU, the risk of hypoglycaemia is higher compared to placebo and a dose reduction of SU may be needed. This is reflected in the product information. Further, the risk of hypoglycaemia is higher compared to liraglutide monotherapy.

No confirmed episodes of pancreatitis were reported with IDegLira, but have been reported for other GLP 1 agonists. Acute pancreatitis has previously been identified as a potential safety issues for the GLP-1 receptor agonist class and the risk, albeit small, should be taken into account when prescribing these products.

Other issues discussed for the GLP 1 agonists include risk of thyroid and pancreatic neoplasm. The current data base is too limited and the duration of the studies too short to provide any useful information. Long term PAS studies are ongoing for Lira which will provide more information, but there are currently no indications of an increased risk. As a result of the recent art 5(3) procedure, pancreatic neoplasm is included in the RMP as a potential risk.

As for some of the other GLP 1 agonists, a mean increase in heart rate was seen for patients exposed to IDegLira. There was no negative effect on blood pressure. The clinical relevance of the increase in heart rate is currently not known. However, as has previously been discussed for other products, since several CV outcome studies are ongoing, no further action is needed at the moment.

For Xultophy, both compounds are titrated simultaneously in a fixed ratio. Thus, for patients requiring low insulin doses, the liraglutide dose may be below the lowest dose considered to be effective. From the analyses presented by the Applicant, there is support that liraglutide contributes to the effect also at low doses of Xultophy. Whether this contribution is of clinical relevance or not can be discussed. However, judging from study data, it can be expected that in clinical practice most patients will be uptitrated to least 16 dose steps of Xultophy, i.e. receiving at least 0.6 mg of liraglutide.

On the other hand, the fact that the maximum dose is 50U/1.8 mg may imply a risk of too high liraglutide doses in the case of off label use to reach higher insulin doses. However, adequate information is included in the product information and it is foreseen that prescribers will inform the patients accordingly.

Benefit-risk balance

Discussion on the benefit-risk balance

The combination of basal insulin and a GLP-1 analogue in the treatment of T2DM has been previously evaluated and accepted for other products, however, the concept of a fixed combination is new. The main difference compared to the free combination is that the GLP-1 component will be titrated in smaller dose steps than currently recommended.

The fixed combination combines two drugs with complementary mechanisms of action by a) substituting for the relative insulin deficiency in T2DM and b) stimulating endogenous insulin secretion. This rationale is adequate and carries the potential (although not yet established) of sparing beta-cell function over time.

The target population for IDegLira includes patients not adequately controlled on metformin and insulin (study 3912) and those not controlled on OAD alone (study 3697). For the first group, IDegLira provided a superior glycaemic control compared to insulin alone combined with the benefit of weight stability. An alternative treatment strategy could have been to increase the insulin dose further, but this would very likely have been associated with increased risk of hypoglycaemia and weight increase. The incidence of GI adverse events was higher compared to insulin alone, but these events were transient and the incidence decreased over time.

For patients failing on OAD, in study 3697, adding IDegLira was beneficial compared to adding only insulin with respect to reduction of HbA1c and a lower risk of weight increase and hypoglycaemia, whilstassociated with an increased risk of gastrointestinal adverse events.

Compared to adding only liraglutide, the benefits are less obvious considering that GI AEs tend to diminish over time and weight decrease was more pronounced with Lira compared to IDegLira. In addition, IDegLira was associated with more hypoglycaemic events than Lira. However, the glucose lowering effect was higher with IDegLira. For these patients IDegLira could represent one of several alternative treatments. It can be argued that adding two active components simultaneously instead of a sequential addition of glucose lowering agents is not in line with current EU treatment guidelines. However, in a recently published ADA/EASD position statement it is emphasised that individualisation of treatment is essential for successful diabetes management. Metformin is still considered as first line treatment, but second line treatments should be based on the needs, preference and tolerance of each patient. Thus, to have several alternative treatment options can be considered to be in line with such recommendations. As with any treatment decision, the advantages and disadvantages of the available options for treatment intensification should be considered in the context of the characteristics and treatment goals of the individual patient.

In some patients it might be preferred to titrate the 2 components separately to understand the initial patient response and tolerability to each of these. The use of the 2 components separately may also simplify the management of treatment interruption. In some insulin-naïve patients on oral therapies, the addition of a single agent will be adequate.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Xultophy in the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these

alone or combined with basal insulin do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, 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 agreeed 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 dates for 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 educational materials 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 Xultophy.

The educational materials are aimed at increasing awareness about the introduction of a new fixed combination of insulin degludec and liraglutide (a GLP1-based product) in the European market and describing key aspects of the product to minimise the risk of medication errors with Xultophy.

The educational materials should contain:

- Summary of product characteristics and package leaflet;
- Health care professional brochure that should contain the following key elements:
  - this product contains a fixed dose combination of insulin degludec plus liraglutide (a GLP1-based product) which constitutes a new treatment paradigm in the treatment of patients with type 2 diabetes. In this context, relevant precautions as reflected in the SmPC should be emphasised.
  - a clear explanation of the posology of the product and the meaning of ‘dose steps’ - with reference to dose of each component for each dose step
  - a reminder of the need to report all medication errors irrespective of whether or not they resulted in an adverse event.

The MAH shall agree the final content and modality of distribution for the educational materials together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational materials in the Member State.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent position to the majority recommendation is appended to this report.

APPENDIX
DIVERGENT POSITION

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion to recommend the granting of a Marketing Authorisation for Xultophy.

The reasons for divergent opinion were as follows:

An indication that includes all patients who do not obtain adequate glycaemic control on oral glucose-lowering medicinal products alone is not supported. It is appreciated that individualisation of treatment is important, and it is agreed that for certain patients uncontrolled on oral agents alone in whom the addition of insulin is the next step, Xultophy would be an alternative option. However, in some insulin-naïve patients who do not obtain adequate glycaemic control on oral therapies, the addition of a single agent will be adequate to achieve glycaemic control, which means that some patients receiving Xultophy are exposed to a combination therapy unnecessarily. In particular, Xultophy might lead to an unnecessarily early introduction of insulin in the treatment course of patients with type 2 diabetes, which may be undesirable considering the associated risks of weight gain and hypoglycaemia, and absence of long-term outcome data for cardiovascular events. However, the clinical programme for Xultophy showed no weight gain and less hypoglycaemic events compared to insulin. Xultophy, with its fixed ratio dosing, offers less flexibility to titrate the individual components and manage interruption of treatment, and at the initiation of treatment does not allow the prescriber to understand how the patient responds to or tolerates each component.

London, 24 July 2014

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Alar Irs (ET)	Bruno Sepodes (PT)
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Daniel Brasseur (BE)	Daniela Melchiorri (IT)
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Greg Markey (UK)	Hubert Leufkens (Co-opted Member)
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Ingunn Hagen Westgaard (NO)	Ivana Mikacic (HR)
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Jacqueline Genoux-Hames (LUX)	Jan Mazag (SK)
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Jens Heisterberg (DK)	Natalja Karpova (LV)
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Pieter de Graeff (NL)	Robert Hemmings (Co-opted Member)