EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2012

EMA/700472/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Ryzodeg

International non-proprietary name: **insulin degludec/insulin aspart**

Procedure No. **EMEA/H/C/002499**

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail ☐nfo@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

List of abbreviations

3TW	3 times weekly
α-GI	alpha-glucosidase inhibitor
AE	adverse event
AUC	area under the curve
BB	basal–bolus
BID	twice daily
BMI	body mass index
C_{max}	maximum plasma concentration
CGM	continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSII	continuous subcutaneous insulin infusion
CV	coefficient of variation
CYP	cytochrome P450
DPP-4 inhib	dipeptidyl peptidase-4 inhibitor
ECG	electrocardiogram
ELISA	enzyme-linked immuno sorbent assay
ESRD	end-stage renal disease
FAS	full analysis set
FF	fixed flexible
FPG	fasting plasma glucose
GCP	good clinical practice
glin	glinide
HbA1c	glycosylated haemoglobin A1c
i.m.	intramuscular
i.v.	intravenous
IAsp	insulin aspart
IDeg	Insulin degludeg
IDegAsp	insulin degludec/insulin aspart
IDegLira	Ideg co-formulated with Liraglutide
IDet	insulin detemir
IG	interstitial glucose
IGF-1	insulin-like growth factor 1
IGlar	insulin glargine
IU	International Unit
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MTD	maximum tolerated dose
NN1250:	the name previously used for insulin degludec (IDeg)
NOEL	no observed effect level
NOAEL	no observed adverse effect level
NPH	neutral protamine Hagedorn
OAD	oral antidiabetic drug
OD	once daily
PD	phamacodinamics
PDCO	Paediatric Committee
PIP	paediatric investigational paln
PK	phamacokinetics
PP	per protocol
PRO	patient reported outcome
PSUR	Periodic Safety Update Report
PV	process validation
PYE	patient years of exposure
RIA	radio immuno assay
RMP:	risk management plan
s.c.	subcutaneous
SAE	serious adverse event
SAG	scientific advisory group
SAS	safety analysis set

SD	standard deviation
SMPG	self-measured plasma glucose
$T_{1/2}$	half life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TID	three times daily
TZD	thiazolidinedione
U	units
Vd	volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 26 September 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ryzodeg, 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: Treatment of diabetes mellitus.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/96/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/96/2011 was not yet completed as some measures were deferred.

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.

New active Substance status

The applicant requested the active substances insulin degludec and insulin aspart contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP in 2007, 2008 and 2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects during the development of insulin degludec/insulin aspart (IdegAsp) (EMEA/CHMP/SAWP/257964/2007, EMEA/CHMP/SAWP/311991/2008 and EMEA/CHMP/SAWP/80644/2009). The questions on the clinical development related mainly to the adequacy of the clinical pharmacology programme, to the choice of comparators in the clinical trials, number of subjects exposed, the in-and exclusion and withdrawal criteria, concomitant OADs, strategy for statistical analysis, the definition of responders and hypoglycaemia, the evaluation of antibody development and of cardiovascular events. Further to the CHMP advice, the applicant also received advice from the Netherlands, Germany, Denmark, Sweden, France and Portugal on the non-clinical

development with specific focus on the carcinogenicity assessment. The agencies confirmed that no further non-clinical or carcinogenicity testing is necessary.

Licensing status

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Jens Heisterberg**

CHMP Peer reviewer: Pieter Neels

- The application was received by the EMA on 26 September 2011.
- The procedure started on 19 October 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 January 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 06 January 2012.
- During the meeting on 16 February 2012, 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 20 February 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 5 June 2012.
- During the CHMP meeting on 21 June 2012, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the CHMP List of Outstanding Issues to all CHMP members on 03 September 2012.
- During the CHMP meeting on 20 September 2012, the CHMP agreed on a second List of Outstanding Issues to be addressed in writing and/or an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 26 September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the second CHMP List of Outstanding Issues to all CHMP members on 04 October 2012.
- During the CHMP meeting in October 2012, 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 Ryzodeg on 18 October 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Despite advances in insulin engineering and diabetes management, the majority of subjects with diabetes fail to meet the recommended levels of glycaemic control required to reduce long-term microvascular and macrovascular complications. Hypoglycaemia and the fear of hypoglycaemia are major limiting factors for achieving target levels of glucose control in insulin-treated subjects with diabetes and are also barriers for timely initiation of insulin once glycaemic control can no longer be sustained with oral antidiabetic drugs (OADs). Furthermore, inflexible and cumbersome treatment regimens adversely impact treatment compliance and quality of life.

Insulin analogues have been developed to more closely mimic endogenous insulin secretion and are now an established part of diabetes management. Insulin degludec/insulin aspart (IDegAsp) contains both a long-acting and a rapid-acting insulin. Development of IDegAsp has been pursued in parallel to the development of the long-acting basal insulin degludec (IDeg), for which a separate application was filed.

About the product

Insulin degludec/insulin aspart (IDegAsp) is a co-formulation of the long-acting basal insulin degludec (IDeg) and the rapid-acting prandial insulin analogue, insulin aspart (IAsp).

Insulin degludec is a long-acting basal insulin modified such that the amino acid residue threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a spacer of glutamic acid. The structural formula is LysB29(N(ε)-hexadecandioyl-γ-L-Glu)desB30 human insulin and the molecular formula $C_{274}H_{411}N_{65}O_{81}S_6$ giving a molecular mass of 6104.1 dalton. This structure allows insulin degludec to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of insulin degludec monomers from the multi-hexamers results in a slow and continuous delivery of insulin degludec from the subcutaneous injection site into the circulation, leading to long pharmacokinetic and pharmacodynamic profiles.

Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28. The molecular formula of insulin aspart is $C_{256}H_{381}N_{65}O_{79}S_6$ and it has a molecular mass of 5825.8 dalton. Insulin aspart is the active component of the marketed products NovoRapid/NovoLog (NDA 20-986) and NovoMix/NovoLog Mix. Insulin aspart has been on the market for more than 10 years, and safety and efficacy of the product is well established.

The formulation of IDegAsp has been optimized such that the individual components do not interact, with insulin aspart present as soluble and stable hexamers and insulin degludec as soluble and stable di-hexamers. Once injected into the subcutaneous tissue, the insulin aspart hexamers immediately form monomers which are rapidly absorbed into the capillaries while the insulin degludec di-hexamers form multi-hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which insulin degludec monomers are slowly and continuously absorbed into the circulation. In this manner, it has been possible to obtain a clear distinction between the effects of the bolus (insulin aspart) and basal (insulin degludec) components of IDegAsp. At the target tissues, insulin degludec and insulin aspart monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake. During development insulin

degludec has been named: insulin 454, SIBA, NN1250 and insulin degludec, whereas the co-formulation has been named: insulin 454/insulin aspart, SIAC and NN5401.

IDegAsp is intended for once-daily or twice-daily subcutaneous (s.c.) administration in patients with diabetes mellitus. IDegAsp is administered with the main meal(s). When needed, the patient can change the time of administration as long as IDegAsp is dosed with a main meal. IDegAsp is injected subcutaneously in the abdominal wall, the upper arm or the thigh.

IDegAsp is developed to cover basal insulin needs in patients with diabetes mellitus from early to late stages of the disease, either alone or in combination with bolus insulin as well as oral antidiabetic drugs.

For patients with type 2 diabetes mellitus, the recommended total daily starting dose of IDegAsp is 10 units with meal(s) followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, IDegAsp is to be used once-daily at meal-time and with short-/rapid-acting insulin at the remaining meals followed by individual dosage adjustments. The recommended starting dose of IDegAsp is 60–70% of the total daily insulin requirements.

IDegAsp has a strength of 100 U/ml and is a clear and colourless solution containing the drug substance insulin degludec in a concentration of 420 nmol/ml (70%) and insulin apart in a concentration of 180 nmol/ml (30%), respectively.

IDegAsp 100 U/ml is intended to be marketed in two presentations, as a Penfill 3ml cartridge for use with durable pens and as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialled in 1 U increments.

Type of Application and aspects on development

This is a complete application in accordance with article 8(3) of Directive 2001/83/EC as amended for approval of a new active substance through the centralised procedure with Kristina Dunder (SE) acting as Rapporteur and Jens Heisterberg (DK) acting as CoRapporteur.

The applicant has not requested an accelerated procedure, conditional approval or approval under exceptional circumstances.

The claimed indication submitted by the Applicant was: Treatment of diabetes mellitus. The indication granted on 18 October 2012 was "Treatment of diabetes mellitus in adults" which is in line with the recommendations of the SmPC guideline as insulin degludec has not been approved in children.

A paediatric investigation plan (PIP) for insulin degludec/insulin aspart has been agreed with the EMA (EMA/247853/2011).The EMA has waived the obligation to submit the results of studies with IDegAsp NN in:

- neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset
- children from birth to less than 10 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset
- children from 10 to less than 18 years of age with type 2 diabetes mellitus on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

The EMA has deferred the obligation to submit the results of studies with IDegAsp NN in:

- children from one to less than 18 years with type 1 diabetes mellitus.

2.2. Quality aspects

2.2.1. Introduction

Ryzodeg having a strength of 100 U/ml is a clear and colourless solution containing the drug substance insulin degludec in a concentration of 420 nmol/ml (70%) and insulin apart in a concentration of 180 nmol/ml (30%), respectively.

Ryzodeg 100 U/ml is intended to be marketed in two presentations, as a Penfill 3ml cartridge for use with durable pens and as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialled in 1 U increment.

Ryzodeg is a soluble co-formulation of long-acting basal insulin, insulin degludec and the marketed rapid-acting insulin analogue, insulin aspart (B28Asp human insulin). Ryzodeg is the first fully soluble ready-to-use insulin product for subcutaneous (s.c.) injection that comprises both a basal insulin component (insulin degludec) and a bolus insulin component (insulin aspart). The formulation of Ryzodeg has been optimised such that the individual components do not interact with insulin aspart present as soluble and stable hexamers and insulin degludec as soluble and stable di-hexamers. Once injected into the subcutaneous tissue the insulin aspart hexamers immediately form monomers which are rapidly absorbed into the capillaries while the insulin degludec di-hexamers form soluble multi-hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which insulin degludec monomers are slowly and continuously absorbed into the circulation.

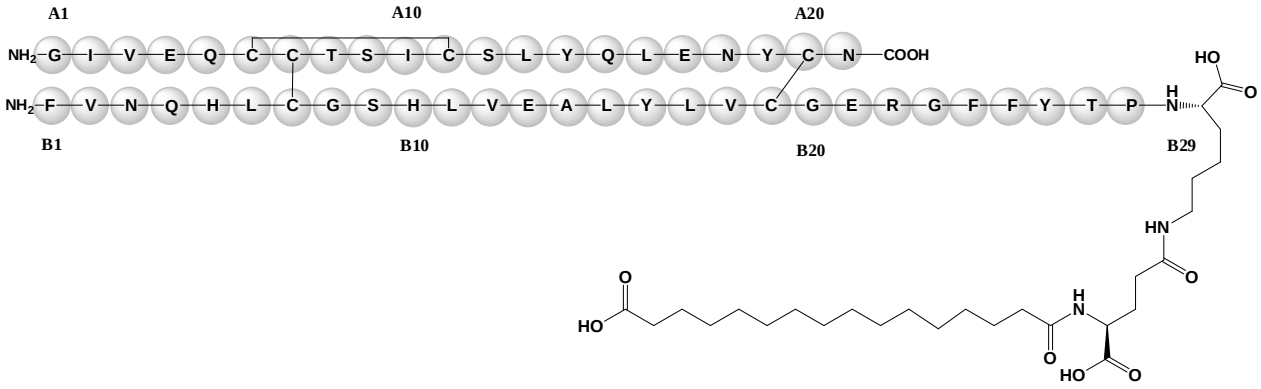
2.2.2. Active Substance

Drug substance – insulin degludec

Insulin degludec is an analogue of human insulin where threonine in position B30 has been omitted and where 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 chemical modification.

The theoretical average molecular weight of insulin degludec is 6103.97 Da.

The structural formula of insulin degludec is given in the figure below:



Origin, source and history of cells, characterisation and testing

Insulin degludec is an analogue of human insulin where threonine in position B30 has been omitted and where 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 chemical modification.

This structure allows insulin degludec to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of insulin degludec monomers from the multi-hexamers results in a slow and continuous delivery of insulin degludec from the subcutaneous injection site into the circulation, leading to long pharmacokinetic and pharmacodynamic profiles.

Source, history and generation of the cell substrate as well as the description of preparation and testing of the MCB, WCB and end of production cells are detailed and sufficient. No material of human or animal origin was used in the preparation of cell banks or in the fermentation process of insulin degludec.

Manufacture

The insulin degludec drug substance manufacturing process includes fermentation of yeast cells, recovery and purification. The fermentation produces a precursor-insulin, which is cleaved to desB30-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.

Filling, storage and transportation (shipping)

The handling of intermediates is carried out according to written procedures. The shipping of the drug substance is handled according to written procedures.

The storage times for intermediates and drug substance applied for are based on stability studies.

Manufacturing process development

The description of the in-process controls and tests are thorough.

Based on the results from the process validation, it can be concluded that the insulin degludec manufacturing process consistently produces insulin degludec drug substance of reproducible quality in accordance with the predetermined specifications. The process has a high removal capacity of process and product related impurities.

The process development history and the consequential comparability studies for insulin degludec drug substance were rather complex which is acceptable. Changes in relation to the insulin degludec manufacturing process are minor and well justified and supported by comparability data.

Characterisation and Impurities

The structural characterisation and elucidation of physico-chemical properties have confirmed the expected structure and properties of insulin degludec drug substance. Correlation of the bioassay with the content as measured by RP-HPLC has been evaluated with a substantial number of samples of drug substance and drug product both at release and during stability. The content by RP-HPLC offers a reliable indication of the biological activity of insulin degludec in drug substance and drug product.

Product and process related impurities formed during manufacture are acceptably described.

Specification

The specification for drug substance release contains parameters defining identity, content, potency and purity of insulin degludec. Methods used have been demonstrated to be suitable for their purpose.

References Standards of Materials

The Reference material is sufficiently described.

Container Closure System

Insulin degludec drug substance is stored in a container closure system.

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 were submitted. In addition, stability data for the supportive stability studies of insulin degludec drug substance pilot scale batches have been completed and were also included in the application.

All data are within specification, and no significant trends are seen in the studies. The same analytical method as in the drug substance specification was used in the stability studies of the primary and process validation batches.

Based on the available data, the proposed shelf-life for insulin degludec drug substance is supported.

Drug substance – insulin aspart

Origin, source and history of cells, characterisation and testing

Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28. Insulin aspart is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae).

Manufacture

The insulin aspart drug substance manufacturing process includes fermentation of yeast cells and recovery of insulin aspart precursor. The purification consists of the conversion of insulin aspart precursor followed by several purification steps to reach insulin aspart. Insulin aspart is stored at long term storage conditions.

Overall the control of source and starting materials is considered adequate. The construction of the expression plasmid, the source and history of *S. cerevisiae* strain and the generation of the *S. cerevisiae* strain producing insulin aspart precursor is described in sufficient detail. Description of preparation and testing of Master Cell Bank, Working Cell Bank and end of production cells are provided.

In general the fermentation, recovery, purification and storage have been described in sufficient details and are controlled by appropriate in-process controls and acceptance criteria of intermediate products.

Manufacturing process development

The description of Manufacturing Process Development focuses on the differences between insulin aspart manufacturing process.

Characterisation and Impurities

Extensive structural characterisation studies have been performed on the drug substance and the physicochemical properties have been shown. Careful discussion of product related substances/impurities and process related impurities are provided together with the results from the impurity testing of drug substance. All results are below the specification limits and comparable to historical ranges.

Specifications

The insulin aspart drug substance is tested by a range of physicochemical tests (identity, purity, assay and microbial content) to assure consistency in the production of drug substance.

All tests listed in the specification are specified in the Ph.Eur monograph for insulin aspart except for one method, that has been sufficiently described and validated.

Results from production scale batches of insulin aspart drug substance batches used in IDegAsp drug product used for non-clinical studies and clinical trials, stability studies and process validation are provided. All results are comparable and within the drug substance specification.

References Standards of Materials and Container Closure System

Primary and secondary reference materials and container closure system have been described in sufficient details.

Stability

Stability data of production scale insulin aspart drug substance batches are provided. All the stability results of insulin aspart were within the specification limits. Supplementary stability data (long term and accelerated) are also provided. The proposed shelf life is acceptable.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The drug product is a clear solution of 420 nmol insulin degludec,180 nmol insulin aspart, preservatives, glycerol as isotonic agent, and sodium chloride and zinc as a stabilising agents. The strength is 100 U/mL.

The drug product is filled in 3 mL glass cartridges assembled into pre-filled disposable pens. The pen is identical to the one used for the centrally approved product Levemir. The product is also provided in the glass cartridges, which are fitted by the patient into a Novo Nordisk delivery system.

Adventitious agents

Insulin degludec is considered to be safe with regards to adventitious agents.

Manufacture of the product

Overall, the manufacturing process for insulin degludec/insulin aspart has been sufficiently described and validated. Critical process parameters have been identified and are covered by appropriate in-process controls.

In general, appropriate drug product specifications have been set and justified. The release specification for insulin degludec/insulin aspart contains parameters defining identity, content, potency and purity of the product.

In general, the analytical methods have been adequately described and are validated.

Reference Standards or Materials

The same reference standard is used for insulin degludec drug substance and drug product.

Container Closure System

The container closure system for insulin degludec/insulin aspart 100 U/ml comprises a 3 ml cartridge (primary packaging). The 3 ml cartridge is assembled into a pre-filled disposable device, a PDS290 pen-injector (secondary packaging). The pen (FlexTouch) is already approved for other Novo Nordisk insulin products.

Stability of the product

A shelf life of 30 months at 5°C±3°C, and an in-use period of 28 days at up to 30°C, is proposed for insulin degludec/insulin aspart 100 U/ml.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the review of the data and the Applicant's response to the CHMP LoQ, the CHMP considered that the active substance insulin degludec – insulin aspart contained in the medicinal product Ryzodeg is to be qualified as a new active substance in itself.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Ryzodeg is considered satisfactory. All quality outstanding issues raised during the procedure have been resolved.

2.2.6. Recommendation for future quality development

Not Applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Insulin degludec is a modification of human insulin, where the amino residue threonine in position B30 has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a spacer of glutamic acid. This structure allows insulin degludec to form soluble and stable muti-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of insulin degludec monomers from the multi-hexamers results in a slow and continuous delivery of insulin degludec from the subcutaneous injection site into the circulation, leading to the observed long pharmacokinetic and pharmacodynamic profiles. Furthermore, binding of the fatty acid moiety of insulin degludec to albumin contributes to some extent to the protraction mechanism.

Insulin aspart is a modified recombinant insulin analogue, in which the native amino acid sequence of human insulin has been altered by replacing proline present at the B29 position with aspartic acid. Insulin aspart is relatively rapidly released from a s.c. injection site. In other respects it is considered identical to soluble human insulin.

Insulin degludec /insulin aspart (IDegAsp) is a co-formulation intended to achieve the effects of the bolus (insulin aspart) and the basal (insulin degludec) components within a single injection.

2.3.2. Pharmacology

Primary and secondary pharmacodynamic studies

The focus of the pharmacology program has been on *in vitro* studies comparing the biological activity of insulin degludec to human insulin. Binding studies showed that insulin degludec has a lower affinity of binding to the insulin receptor (relative affinity ~5%), with a similar relative difference when studying binding to the insulin receptor from different species (rat, dog, pig, human). The involvement of albumin binding was confirmed by the fact that results were influenced by the albumin concentration in the assay. The kinetics of binding (on- and off rates) was similar to that of human insulin.

Binding to the structurally similar IGF-1 receptor has been implicated to have importance for a mitogenic potential and possibly tumourogenicity. A number of binding studies showed that insulin degludec binds to IGF-1R with a lower affinity than human insulin, when normalising for the difference in binding to the insulin receptor.

In vitro studies on insulin receptor signal transduction showed similar dose response curve with insulin degludec and human insulin, with the same maximum response. The dose response curve was right-shifted reflecting the lower in vitro potency. The same maximum response shows that insulin degludec acts as a full agonist of the insulin receptor.

Insulin degludec showed the same rate of activation signal decline following insulin receptor stimulation as human insulin. This is in contrast to the mitogenic insulin B10Asp where prolonged signalling has been implicated as an important factor for mitogenicity and possibly tumorogenicity.

Metabolic effects of insulin receptor signalling were studied in cell lines and primary liver cells. In all systems, insulin degludec showed the same maximal response as human insulin with similar but right-shifted dose-response curve.

The mitogenic response was studied in a number of cell lines, in two cases with cell lines which were also studied for a metabolic response. The mitogenic response to insulin degludec in the various cells was the same as for human insulin, but with a right shift of the dose response curve. The balance between the metabolic and mitogenic effects of insulin degludec was similar to that of human insulin.

To establish the metabolic effects of insulin degludec *in vivo*, euglycaemic clamp studies were performed in rats and pigs. Studies in pigs were performed to select the appropriate formulation to be tested in early clinical trials.

Insulin degludec gave no significant effects in 67 different assays of standard receptors and transporters, including the hERG potassium channel. *In vivo* safety pharmacology studies were performed in rats and dogs addressing CNS, cardiovascular and respiratory effects. There were no findings except respiratory effects at the highest dose as a consequence of hypoglycaemia.

Insulin aspart was approved in 1999. The applicant performed a comprehensive literature search to cover non-clinical pharmacology, pharmacokinetic and toxicology information available on insulin aspart since the approval of NovoRapid. The new pharmacological data on insulin aspart published since the MAA approval establish that insulin aspart has the same pharmacology profile as human insulin, and the new data have not changed the conclusion in the originally submitted documentation. No new safety pharmacology studies were identified in the post-approval literature search. For this application it was therefore agreed that no further assessment of the pharmacology of insulin aspart was warranted.

In vitro studies with the combination were performed. It was shown that the effects of insulin degludec and insulin aspart were additive and that there were no synergistic or inhibitory interactions between the two.

Safety pharmacology programme

In vivo safety pharmacology studies were performed with insulin degludec in rats and dogs addressing CNS, cardiovascular and respiratory effects. The top dose 300 nmol/kg in rat and 24 nmol/kg in dog was approximately 66-fold (rat) and 5.3-fold (dog) the mean clinical dose of 1.08 U/kg (~ 4.54 nmol/kg) in the most insulin requiring therapeutic confirmatory clinical trial. The maximal concentration (1000 nmol/ml) tested *in vitro* was approximately 100-fold the human C_{max}. There were no findings except respiratory effects at the highest dose as a consequence of hypoglycaemia.

Pharmacodynamic drug interactions

Pharmacodynamic interactions are generally not observed for insulin products. In consistence with this, such studies have not been conducted. This was accepted by the CHMP.

2.3.3. Pharmacokinetics

The pharmacokinetic studies confirmed that insulin degludec has the desired prolonged pharmacokinetic profile after s.c. injection. This was based on a protracted absorption process such

that the elimination of the drug becomes dependent on the absorption rate. This phenomenon, which is evident in all species, is seen as a longer terminal plasma half-life (t½) after s.c. than after i.v. administration. However, in the animal species used in nonclinical studies, the half-life is much shorter than in humans (rat 3.1 h, dog 5.6 h, humans 25 h). Thus, once daily dosing which in humans results in a flat exposure profile, in the animals results in much more fluctuating exposure curve.

Insulin degludec is highly protein bound in plasma and thus has a relatively low apparent volume of distribution. The initial peptide cleavage of insulin degludec is the same as seen for human insulin and extensive metabolism of insulin degludec occurs before excretion.

The effect of insulin degludec antibodies on the insulin degludec pharmacokinetics was evaluated by comparing antibody positive and negative animals. No difference in the pharmacokinetics was observed, indicating that the presence of insulin degludec antibodies did not affect the pharmacokinetics of insulin degludec.

Insulin degludec was shown to cross the placenta to a minimal extent (< 1%).

Common protein-bound drugs like ibuprofen, warfarin, acetylsalicylate, salicylate and frequently used antidiabetic agents glimepiride, metformin, sitagliptin and liraglutide as well as palmitate, oleate and linoleate did not affect insulin degludec binding to human serum albumin at therapeutically/physiologically relevant drug concentrations. The potential of insulin degludec to competitively displace albumin-bound drugs is considered to be very low.

The new pharmacokinetic data on insulin aspart published since the MAA approval has not changed the conclusion in the originally submitted documentation. No pharmacokinetic (PK) studies were therefore submitted for insulin aspart; this was considered acceptable by the CHMP.

The pharmacokinetics of insulin degludec co-formulated with insulin aspart has been studied in rats and pigs. In both species it was demonstrated that insulin degludec could be administered co-formulated with insulin aspart without changing the individual pharmacokinetic profiles of the two insulin molecules.

2.3.4. Toxicology

Overview of pivotal toxicity studies with insulin degludec

Study type and duration	Route of administration	Species
Single-dose toxicity	s.c.	Rat and dog[a]
Repeat-dose toxicity		
4 week	s.c.	Rat and dog
26 week	s.c	Rat and dog
52 week including carcinogenicity assessment	s.c.	Rat
Reproductive and developmental toxicity studies		
Fertility	s.c	Rat
Embryo-foetal development	s.c.	Rat and rabbit
Pre- and post-natal development	s.c.	Rat

Local tolerance		
Early development drug product and ”to be marketed” drug product	s.c.	Pig/Minipig
”To be marketed” drug product	i.m., i.v., i.a.	Rabbit

Overview of pivotal toxicity studies with insulin degludec / insulin aspart

Study type and duration	Route of administration	Species
Repeat-dose toxicity		
13 week	s.c	Rat
Reproductive and developmental toxicity studies		
Embryo-foetal development	s.c.	Rat
Local tolerance		
Early development drug product and ”to be marketed” drug product	s.c.	Pig/Minipig
”To be marketed” drug product	i.m., i.v., i.a.	Rabbit

The general toxicity of insulin degludec was assessed after s.c single-dose administration in rats and dogs and after s.c. repeat-dose administration in rats and dogs for up to 52 and 26 weeks, respectively. In studies of 26 weeks duration or longer, recombinant human Neutral Protamine Hagedorn insulin (NPH insulin) was included as comparator to differentiate between effects considered related to pharmacological action of insulin and possible toxic effects of insulin degludec.

No non-clinical toxicity studies conducted with insulin aspart after MAA approval were identified upon a thoroughly search of public peer-reviewed literature.

Single dose toxicity

Dosing of insulin degludec to healthy normo-glycaemic animals lowered blood glucose to levels below the normal physiological concentration and thereby induced clinical signs of hypoglycaemia and hypoglycaemia-related mortality. These effects were dose-limiting factors in both species tested. In addition, the effect on blood glucose resulted in compensatory adaptive changes such as increased body weight gain and food consumption, various changes in clinical pathology, decreased liver weight and depletion of liver glycogen. The changes seen were similar in nature and magnitude to those induced by NPH insulin and showed recovery. The changes were considered related to pharmacological effects of insulin and not unexpected toxic effects.

Repeat dose toxicity

The combination of insulin degludec and insulin aspart was studied in a 13 week repeat dose toxicity study in rats. There were no findings not observed in studies with insulin degludec or human insulin.

Genotoxicity

In accordance with the ICH S6 guideline, genotoxicity studies were not performed as insulin degludec is considered a biotechnology-derived product. Insulin degludec consists of desB30 human insulin, glutamate and 1,16-hexadecanedioic acid and none of the individual components are considered to possess a mutagenic potential. Glutamate is a commonly used food additive and mutagenicity has been investigated and found negative in Ames test and *in vitro* chromosomal aberration test. Hexadecanedioic acid being a long-chain dicarboxylic fatty acid, and in general, fatty acids are not considered to possess a mutagenic potential.

Carcinogenicity

Standard 2-year carcinogenicity bioassay is in general considered inappropriate for biotechnology-derived pharmaceuticals such as insulin degludec [ICH S6]. Rather, as insulin is a hormone with multiple well-known effects, including regulation of glucose and lipid metabolism and stimulation of cell growth, the carcinogenic potential of insulin degludec has been evaluated in a range of *in vitro* and *in vivo* studies. *In vitro*, a comprehensive set of studies has been conducted comparing the effect of insulin degludec to human insulin. Where considered appropriate, the related growth factor, IGF-1 or the insulin analogue insulin X10 also were included as suggested in the EMA "Points to consider document on the non-clinical assessment of the carcinogenic potential of insulin analogues". *In vivo*, the carcinogenic potential of insulin degludec was assessed by evaluating hyperplastic and neoplastic lesions in all pivotal repeat-dose toxicity studies in both rats and dogs. Furthermore, the carcinogenic potential was the focus of detailed investigations included in the 52-week toxicity study in Sprague Dawley rats.

In the *in vitro* pharmacodynamic studies comparing insulin degludec to human insulin, insulin showed a lower affinity to the insulin receptor, and thus a lower activity in all *in vitro* models. However, there were no important biological differences that would cause any concerns.

Insulin degludec showed no carcinogenic potential in a 52-week toxicity study in Sprague Dawley rats upon complete histopathological evaluation of all animals. The female mammary gland was the focus of special attention and no treatment-related increase in incidences of hyperplasia, benign or malignant tumours was recorded in females dosed with insulin degludec. No treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation.

Reproduction Toxicity

In reproduction toxicity studies, there was no effect on mating performance and fertility, gestation index and length and post implantation survival, on embryo-foetal survival or on growth, offspring development and reproductive capacity. 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. This was further supported by the fact that 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 (hypoglycaemia) observed following insulin degludec dosing compared to NPH insulin.

The combination of insulin degludec and insulin aspart was studied in an embryofoetal toxicity study in rats. There were no findings not observed in studies with insulin degludec or human insulin.

Local Tolerance

The local tissue reaction after single or repeated subcutaneous administration was studied using a pig/minipig model or as an integrated part of the pivotal repeated-dose toxicity studies. Likewise, the local tissue reaction after single intramuscular, intravenous and intra-arterial administration was studied in rabbits. The local tissue reaction was mild and comparable to that of vehicle or NPH insulin.

Other toxicity studies

Antigenicity

Immunogenicity was evaluated by measurement of insulin degludec antibodies as an integrated part of the pivotal repeated dose toxicity studies. A few animals developed antibodies against insulin degludec:

Species	Rat			Dog	
Study duration in weeks (study identification)	4 (205239)	26 (206315)	52 (206539)	4 (205238)	26 (206314)
Insulin degludec antibody positive animals / total number of animals[a]	7 / 54	7 / 51	1 / 213	0 / 18	0 / 23
Insulin degludec antibody positive animals / total number of animals [a] - after 4 weeks recovery	-	2 / 16	-	-	0 / 4
NPH insulin antibody positive animals / total number of animals[a]	-	9 / 14	1 / 79	-	6 / 6

a - Only insulin degludec or NPH insulin dosed animals included

-: Not applicable

Only a few rats developed antibodies towards insulin degludec. The antibodies were not considered to possess a neutralizing effect as the insulin degludec exposure or the blood glucose lowering effect of insulin degludec were not affected.

In dogs, antibodies towards insulin degludec were not detected neither immediately after termination of dosing nor after a 4-week recovery period. In all samples drawn at termination of dosing, remaining concentrations of insulin degludec were detected which could potentially have masked a weak antibody response. Whereas no insulin degludec remained in the samples obtained from recovery animals. Based upon absence of antibodies in the recovery animals, where no interference from insulin degludec could have occurred, insulin degludec exposure confirmation in all dosed animals and effect on plasma glucose, it is unlikely that neutralising antibodies were formed.

The insulin degludec antibody response in rat and the potential weak antibody response in dog were not considered to possess a neutralizing effect and were therefore considered of no significance for the validity of the studies.

Immunotoxicity

No specific immunotoxicity studies have been performed. Standard immunotoxicity parameters such as evaluation of haematologic parameters, plasma globulins, weight and histopathology of immune

organs were included in the pivotal repeat-dose studies in rat and dog. No treatment-related signs of immunotoxicity were identified.

Dependence

Insulin degludec has not been evaluated in non-clinical tests for drug abuse (drug dependency) since it is not considered belonging to the classical drug abuse categories of opiates and narcotics, central nervous system stimulants/depressants, hallucinogens or cannabinoids. Furthermore, dependency (abuse) is not known for already marketed insulin products.

Metabolites

Insulin degludec is metabolised to protein, peptide, fatty acid degradation products and amino acids. Therefore, no toxicity studies of metabolites are warranted or were performed.

Studies on impurities

Product related impurities have been adequately qualified in the non-clinical program. The levels of leachables from the container closure system have been determined. The potential human exposure levels were evaluated and no safety concerns were identified.

2.3.5. Ecotoxicity/environmental risk assessment

Insulin degludec consists of a protein, and a fatty acid chain coupled via an amino acid spacer. Insulin aspart is a protein. No environmental risk assessment is required for this product.

2.3.6. Discussion on non-clinical aspects

The applicant has performed a comprehensive pharmacology programme, with the relevant focus on *in vitro* studies comparing the biological activity of insulin degludec to human insulin. While showing a lower affinity to the insulin receptor, and thus a lower activity in all *in vitro* models, there were no important biological differences that would cause any concerns.

The nonclinical evaluation of carcinogenicity is considered a particularly important issue in the development of novel insulin analogues. The program performed by the applicant is in line with the recommendations in the CHMP "Points to consider document on the non-clinical assessment of the carcinogenic potential of insulin analogues". In the Points to Consider document, it is stated that insulin X10 should be considered as a positive control in the studies. The applicant has not included X10 in the *in vivo* study and this is justified based on the substantial background data on spontaneous tumour incidence in the Sprague-Dawley rat and its known responsiveness to insulin X10. Furthermore, insulin X10 is a rapid-acting insulin analogue and since dose (tolerability) and pharmacokinetic profile is very different from insulin degludec, insulin X10 is not seen as an appropriate positive control. This justification is endorsed. In addition, the applicant has included data from a previous study with the insulin analogue insulin detemir where insulin X10 was included as a control. In this study, insulin X10 showed a significant proliferative effect only with one label (Ki-67) but not with two others (PCNA and BrdU), questioning the value of insulin X10 as a positive control.

For the *in vivo* study, it should be pointed out that the exposure profile in rats is different to the human situation. In humans, the long half-life (25 h) leads to a very flat PK profile while in rats with a shorter half-life (3h) the PK profile will be fluctuating. The rat study is therefore not fully relevant for the human situation. Considering that the human PK profile is likely to be similar to the physiological basal insulin levels in a healthy person, and the convincing pharmacodynamic similarity to human

insulin shown in the *in vitro* studies, it is agreed that the studies performed by the applicant indicate and support the conclusion that the carcinogenic potential of insulin degludec is not greater than that of human insulin.

The published data on insulin aspart did not change the overall non-clinical assessment of insulin aspart: Insulin aspart is rapidly released from the s.c. injection site. In respects to efficacy and safety insulin aspart is identical to soluble human insulin.

The pharmacokinetics of insulin degludec co-formulated with insulin aspart demonstrated that insulin degludec could be administered co-formulated with insulin aspart without changing the individual pharmacokinetic profiles of the two insulin molecules. No toxicological findings were found with the combination of the two insulins.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence insulin degludec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin.

From the pharmacokinetic point of view, it was confirmed that insulin degludec has a prolonged pharmacokinetic profile after subcutaneous injection. This is evident in all species; however, in the animal species used in nonclinical studies, the half-life is much shorter than in humans. Thus, once daily dosing which in humans results in a flat exposure profile in the animals results in much more fluctuating exposure curve.

Insulin degludec is highly protein bound in plasma and thus has a relatively low apparent volume of distribution. The initial peptide cleavage of insulin degludec is the same as seen for human insulin and extensive metabolism of insulin degludec occurs before excretion.

The effect of insulin degludec antibodies on the insulin degludec pharmacokinetics was evaluated and no difference in the pharmacokinetics was observed, indicating that the presence of insulin degludec antibodies did not affect the pharmacokinetics of insulin degludec.

The potential of insulin degludec to competitively displace albumin-bound drugs is considered to be very low.

Overall, the toxicology programme did not reveal any safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction. This information has been included in the SmPC.

Insulin aspart is rapidly released from the s.c. injection site. In respects to efficacy and safety insulin aspart is identical to soluble human insulin.

The pharmacokinetic data demonstrated that insulin degludec could be administered co-formulated with insulin aspart without changing the individual pharmacokinetic profiles of the two insulin molecules. No toxicological findings were found with the combination of the two insulins.

2.4. Clinical aspects

2.4.1. Introduction

The completed clinical development programme for IDegAsp comprises 13 clinical pharmacology trials, 3 therapeutic exploratory trials of 6-16 weeks duration, 5 therapeutic confirmatory trials of 26 weeks

duration and one completed therapeutic confirmatory, 26-week extension trial (see Figure "**Overview of Clinical Trials in the IDegAsp Development Programme**). In addition, evaluation of clinical pharmacology is supported by the IDeg clinical pharmacology programme.

The therapeutic confirmatory programme investigated the efficacy and safety of IDegAsp in subjects with type 1 diabetes mellitus (T1DM) in combination with bolus insulin, and in both insulin-naïve and previously insulin-treated subjects with T2DM in combination with OADs. IDegAsp was administered once daily (OD) in T1DM. In T2DM, both OD and twice-daily (BID) dosing was investigated. Throughout the completed confirmatory trial programme, 1360 subjects were exposed to IDegAsp and 1037 subjects were exposed to comparators.

As of the clinical cut-off date of 31 January 2011, ongoing clinical trials comprised a therapeutic confirmatory trial in Japanese subjects (Trial 3896), an extension trial to Trial 3590 (Trial 3726), and a trial comparing two different titration algorithms (Trial 3844). All three ongoing trials investigate OD dosing in insulin-naïve subjects with T2DM. Important blinded safety information from these trials is included with a cut-off date of 31 March 2011.

Apart from several advices given by national competent authorities, the applicant received CHMP Scientific Advice in June 2007 (EMEA/CHMP/SAWP/257964/2007) and follow-up Scientific Advice on the Paediatric development programme in June 2008 (EMEA/CHMP/SAWP/311991/2008). In February 2009 extensive Scientific Advice was later provided (EMEA/CHMP/SAWP/80643/2009) on questions concerning quality, pre-clinical and clinical development. The clinical questions related to the choice of comparators, the numbers of elderly and obese patients, the inclusion-, exclusion-and withdrawal criteria, the possibility for flexible dosing, the definitions of responders and hypoglycaemia, the strategy for statistical testing and the safety evaluation (meta-analysis for hypoglycaemia, antibodies, CV risk profile).

The Applicant applied for the following indication: "Treatment of diabetes mellitus". The indication "Treatment of diabetes mellitus in adults" was granted which is in line with the recommendations of the SmPC guideline as IDegAsp has not been approved in children.

The Applicant proposed that in patients with type 2 diabetes mellitus, insulin degludec be administered alone, in combination with oral anti-diabetic products as well as in combination with bolus insulin. In type 1 diabetes mellitus, insulin degludec/insulin aspart must be combined with short-/rapid-acting insulin at the remaining meals. This was accepted by the CHMP.

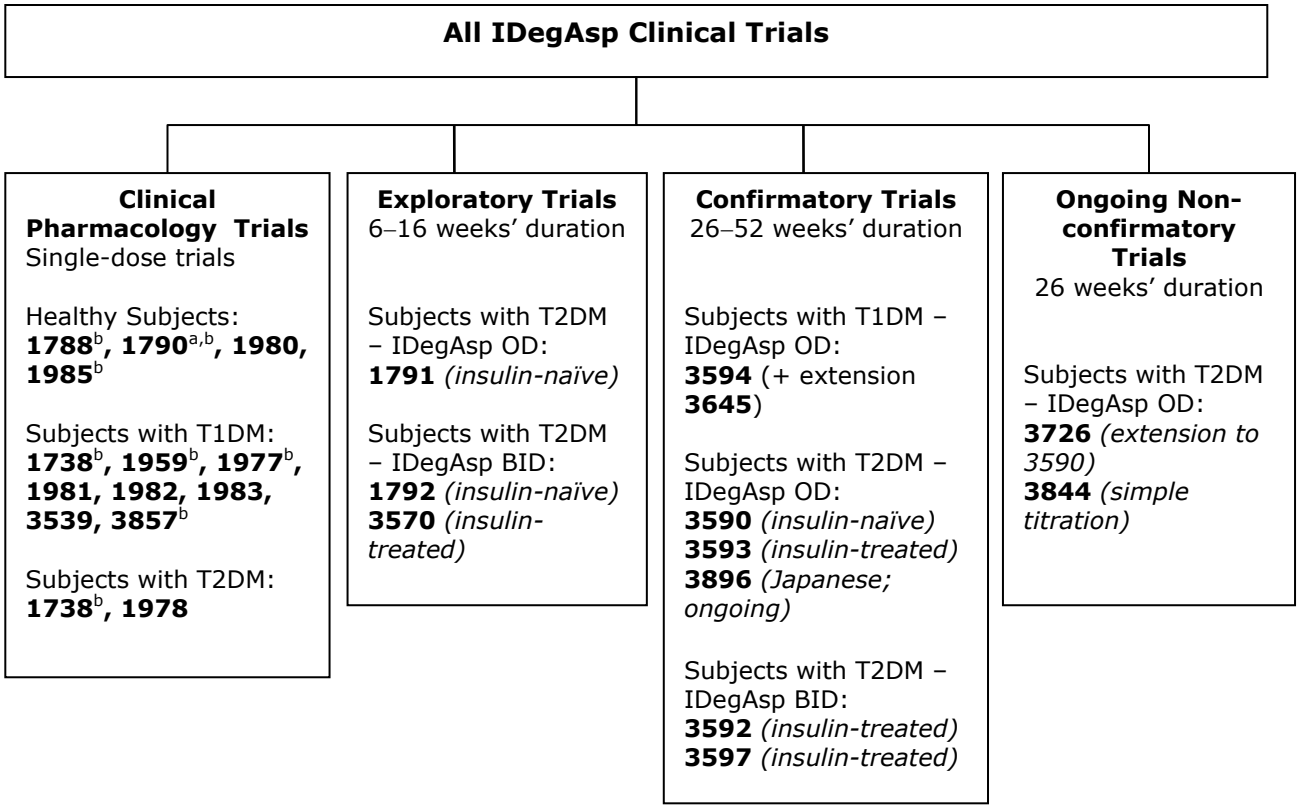
GCP

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.

Tabular overview of clinical studies

Figure: Overview of Clinical Trials in the IDegAsp Development Programme



OD = once daily; BID = twice daily
[a] Clinical Pharmacology Trial 1790 was multiple-dose
[b] Clinical Pharmacology Trials also including IDeg

The IDegAsp clinical development programme includes 5 therapeutic confirmatory trials designed to cover the spectrum of potential use in both T1DM and T2DM, from insulin initiation in newly diagnosed subjects to insulin intensification in high-risk patients with advanced diabetes. An overview of trial designs is provided below. All trials were randomised, controlled, multinational, treat-to-target trials of 26 weeks duration, the latter to ensure that stable glycaemic control was maintained for a sufficient time period. A 26-week extension trial to Trial 3594 in subjects with T1DM (Trial 3645) has been completed and provides additional evidence of long-term efficacy. The full trial of 52 weeks duration is denoted Trial 3594/3645. Differences across treatment arms in pen systems and dosing regimens necessitated open-labelled trial designs in all trials. A 'treat-to-target' concept was applied in all trials, aiming for a predefined fasting plasma glucose (FPG) of <5 mmol/L (90 mg/dL) in order to achieve an HbA1c < 7%, as recommended by current guidelines. As the glycaemic control target was the same for IDegAsp and comparator treatments, the primary endpoint of change in HbA1c from baseline to end-of-trial was tested using a non-inferiority criterion.

In subjects with T1DM (Trial 3594/3645), IDegAsp OD + IAsp at remaining meals was compared with IDet + IAsp at all meals, which is representative for the standard of care for subjects with T1DM. IDet was dosed OD at initiation with a possibility of adding a second IDet dose in the event of inadequate

glycaemic control. In the trials including subjects with T2DM, comparators for OD and twice-daily (BID) dosing with IDegAsp were IGlar OD and BIAsp 30 BID, respectively. IGlar is the preferred comparator for OD dosing, as it is widely used and approved for OD dosing and has a well-known efficacy and safety profile. BIAsp 30 BID is considered the preferred comparator for BID dosing since it is the most widely used pre-mixed insulin worldwide, and because it contains a basal component and the same rapid-acting component (IAsp) as IDegAsp.

Concomitant antidiabetic treatment in subjects with T1DM (Trial 3594/3645) consisted of mealtime IAsp. The efficacy and safety of treatment with IDegAsp in combination with OADs were studied in Trials 3590, 3593, 3592 and 3597. In subjects with T2DM, metformin is recommended as the drug of choice as first-line therapy and was mandatory in IDegAsp OD trials (Trials 3590 and 3593) and optional in IDegAsp BID trials (Trials 3592 and 3597). Subjects treated with metformin prior to enrolment were instructed to continue taking the same total dose throughout the trial. The same applied for treatment with DPP-4 inhibitor and pioglitazone, which were allowed in Trials 3593 and 3592. Use of insulin secretagogues, α-glucosidase inhibitors and GLP-1 agonists were not allowed as concomitant medication in any of the trials.

Table: Overview of IDegAsp Therapeutic Confirmatory Trials

Trial No.	Duration (Weeks)	Trial Description	OAD Combination	Population	Randomisation (IDegAsp: Comparator)	No. of Subjects Randomised	Antidiabetic Treatment at Screening	Stratification
T1DM								
3594	26 (+ 26-week extension, NN5401-3645)	IDegAsp OD + IAsp vs. IDet† + IAsp	None	Insulin-treated	2:1	IDegAsp: 366 IDet: 182	Basal–bolus insulin regimen or other mixed insulin regimen	Prior treatment: • basal–bolus insulin regimen • other insulin regimen
T2DM								
3590	26	IDegAsp OD vs. IGlar OD	Metformin	Insulin-naïve	1:1	IDegAsp: 266 IGlar: 263	Metformin and ≥1 other OAD except TZD	None
3593	26	IDegAsp OD vs. IGlar OD	Metformin ± pioglitazone ± DPP-4 inhibitor	Insulin-treated	1:1	IDegAsp : 230 IGlar: 233	Basal insulin OD and metformin ± other OADs	Prior treatment: • TZD Yes • TZD No
3592	26	IDegAsp BID vs. BIAsp 30 BID	± metformin ± pioglitazone ± DPP-4 inhibitor	Insulin-treated	1:1	IDegAsp: 224 BIAsp 30: 222	Premixed/self-mixed insulin OD or BID ± OADs	Prior treatment: • OD insulin regimen • BID insulin regimen
3597	26	IDegAsp BID vs. BIAsp 30 BID	± metformin	Insulin-treated	2:1	IDegAsp: 280 BIAsp 30: 142	Basal insulin OD or BID ± metformin or premixed/self-mixed insulin OD or BID ± metformin	Prior treatment: • basal without metformin • basal with metformin • premix without metformin • premix with metformin

†OD from start, but a second IDet dose could be added after 8 weeks in case of inadequate glycaemic control.

BIAsp: biphasic insulin aspart; BID: twice daily; DPP-4: di-peptidyl peptidase-4; IAsp: insulin aspart; IDet: insulin detemir; IGlar: insulin glargine; OAD: oral antidiabetic drug; OD: once daily; TZD: thiazolidinedione.

2.4.2. Pharmacokinetics

A total of 22 key trials were conducted with the commercial formulation of IDegAsp and/or IDeg. IDeg and IAsp have been quantified by validated sandwich enzyme-linked immunosorbent assays (ELISA) throughout the clinical trials.

Absorption

IDeg is administrated by subcutaneous injection. Absolute bioavailability was to be determined in study 1992 but in the end, no estimate could be obtained due to an error in the i.v. dosing arm. The longer IDeg t½ seen after s.c. administration (25 hours) compared to that after i.v. administration (approximately 5 hours) suggests that the rate at which IDeg is eliminated after administration is determined by the absorption rate (flip-flop PK).

Regarding site of injection, a greater AUC (5-10 %) and higher Cmax (20-30 %) was seen after s.c. administration of IDeg in the abdomen and deltoid region compared to s.c. administration in the thigh.

When comparing i.m. administration with s.c. administration, a greater extent of absorption (7 %) and higher maximum exposure (58 %) was seen following i.m. administration. Regarding IAsp, no studies on injection sites have been performed. This is acceptable as the use of various injection regions (abdominal wall, the thigh, the upper arm (the deltoid region) or the gluteal region) has previously been established.

Based on data from trials 1959, 3857 and 1977, the pharmacokinetic profile of IDeg was not affected by co-formulation with IAsp in the IDegAsp product. It may therefore be concluded that IDeg dosing alone is representative of the basal component in IDegAsp.

With respect to the IAsp component, both AUC and Cmax were 15-30% lower for IDegAsp compared to separate simultaneous injections of the IDeg and IAsp products.

Distribution

Based on *in vitro* studies using surface plasmon resonance (SPR) methodology, IDeg seems to have high plasma protein binding >99%. The Vd of IDeg is unknown. IAsp binding to plasma proteins has been reported as low (<10%) and similar to human insulin.

Elimination

Subcutaneously administered IDeg have an average t½ of approximately 25 hours in both T1DM and T2DM. This is longer than the t½ seen after i.v. administration (approximately 5 hours), which suggests that IDeg elimination rate is determined by the absorption rate of IDeg (flip-flop kinetics). Regarding IDeg, no indication of time dependency is seen. IAsp has not been studied in any multiple dose study and no conclusion regarding time dependency can be drawn based on the applicant´s documentation.

According to the applicant, the dominating route of IDeg elimination is via degradation at the insulin receptor. IDeg is degraded by cathepsin D *in vitro* to the same metabolites as for human insulin. Studies in human, rat, rabbit and dog hepatocytes showed that IDeg was extensively degraded and that no IDeg metabolites were human specific. Renal excretion of intact IDeg is negligible.

The metabolism and excretion of IAsp is assumed to be similar to human insulin.

Variability

IDeg exhibit a more flat PK profile than insulin glargine and insulin detemir where the t½ of IDeg was more than twice and three times as long compared to IGlar and IDet (25 vs. 12 and 7 hours). Intra-individual variability in AUC was lower with IDeg (13 %) than with IGlar (24 %) in subjects with T1DM.

Target population

No major differences in IDeg or IAsp PK is observed between T1DM or T2DM populations but there is a trend towards lower IDeg and IAsp Cmax in the T2DM population compared to the T1DM population. Dose proportionality for IDeg and IAsp between doses of 0.4, 0.6 and 0.8 U/kg in T1DM and T2DM populations, respectively, was demonstrated. In both populations, IDeg steady state was reached after 2–3 days (48–72 hours) of once-daily s.c. dosing with IDeg with no further increase in exposure thereafter.

Special populations

A dedicated renal impairment study was performed and there were only minor differences in the pharmacokinetic properties of IDeg between subjects with renal impairment (mild, moderate, severe and ESRD) and healthy subjects. The data suggest very limited clearance of IDeg during haemodialysis. Hepatic impairment was also studied separately and there is no indication of differences in the pharmacokinetic properties of IDeg between subjects with hepatic impairment (Child-Pugh A, B and C) as compared to healthy subjects. The pharmacokinetic properties of IAsp have previously been shown not to be affected by renal impairment or hepatic impairment. The lack of new data is acceptable.

There were only minor differences in the pharmacokinetic properties (AUC and Cmax differed < 15 % in all comparisons) of IDeg and IAsp between sexes, subjects of different race and ethnicity.

When comparing younger adults and elderly, there is no indication of any difference in the pharmacokinetic properties of IDeg. Regarding IAsp, the AUC and Cmax was higher (27 % and 38% in average, respectively) for geriatric than younger adult subjects.

When comparing children with adults, IDeg AUC and Cmax was ≈ 20-50 % higher and IAsp AUC and Cmax was ≈ 70 % higher in children compared to adult subjects. When comparing adolescents with adults, IDeg AUC and Cmax was ≈ 15-35 % higher and IAsp AUC and Cmax was ≈ 15 % higher in adolescents compared to adult subjects.

Regarding IDeg, there seems to be a slight trend towards increased total exposure and maximum concentration with increased BMI in subjects with either T1DM or T2DM. The inter-individual variability seems also to increase with increased BMI. There seems to be no correlation between BMI and total exposure or maximum concentration of IAsp in subjects with either T1DM or T2DM.

In general, any observed differences in the pharmacokinetic exposure between different special populations are not believed to have any clinical implications considering that the product should be dosed according to individual needs.

Pharmacokinetic interaction studies

The major elimination pathway of IDeg is through degradation at the insulin receptor. Furthermore, insulins are not described as inhibitors or inducers of human CYP and it is considered unlikely that insulin degludec will differ in that aspect. Therefore, CYP interaction studies have not been conducted *in vitro* or *in vivo*. This approach was endorsed by the CHMP. Protein binding interactions with common protein-bound drugs where studied *in vitro* and no effect on insulin degludec binding to human serum albumin was seen. These studies in addition to theoretical discussion regarding *in vivo* IDeg concentrations versus albumin levels indicate that no *in vivo* protein interactions are expected.

Regarding IAsp, no pharmacokinetic interactions are listed in the Novorapid (IAsp) SmPC and no new data is requested.

2.4.3. Pharmacodynamics

Mechanism of action

Insulin degludec is a long-acting basal insulin modified such that the amino acid residue threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a spacer of glutamic acid.

The gradual separation of insulin degludec monomers from the multi-hexamers results in a slow and continuous delivery of insulin degludec from the subcutaneous injection site into the circulation, leading to very long pharmacokinetic and pharmacodynamic profiles.

Insulin aspart is a short-acting analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28. Insulin aspart is the active component of the marketed products NovoRapid/NovoLog (NDA 20-986) and NovoMix/NovoLog Mix.

At the target tissues, IDeg and IAsp monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake as confirmed by the non-clinical data. The mechanism of action of IDeg is similar to that of other insulins, only with a slightly lower activity and prolonged duration of action.

Primary and Secondary pharmacology

The program investigating the pharmacodynamic properties of IDegAsp consisted of nine studies conducted with IDegAsp and nine studies conducted with the long-acting component IDeg (Table 1).

Table 1. Key Trials Investigating Pharmacodynamic Properties of IDegAsp and/or IDeg

Type of Trial	Single-Dose Trials	Multiple-Dose Trials[a]
Subjects with T1DM	1959, 1977, 1981, 1982, 1983, 3539, 3857	1991, 1993, 1994, 1996, 3538
Subjects with T2DM	1978	1987, 3762
Healthy subjects	1980	1992[b], 3769
Intrinsic factors:		
Age	1981	1994
BMI (across trials)	1977, 1981, 3539, 3857 (T1DM); 1978 (T2DM)	1991, 1993, 1994, 3678 (T1DM); 1987, 3762 (T2DM)
Sex (across trials)	1977, 1981, 3539, 3857	1991, 1993, 1994, 3678
Race/Ethnicity		3762
Japanese	1983	1996

[a] Trials conducted with the IDeg product.
[b] Trial 1992 was conducted using different s.c. injection regions (the abdomen, thigh and deltoid) as well as i.v. and i.m. injection.

The dose-response Trials 3539 and 1978 are considered pivotal for describing the single dose pharmacodynamic properties of IDegAsp in subjects with T1DM and T2DM, respectively. This includes the shape of the profiles and the separation between the effect of the prandial and basal components in IDegAsp. Results from IDeg Trials 1993 and 1987 are used to describe the pharmacodynamic properties of the basal component (IDeg) of IDegAsp in subjects with T1DM and T2DM, respectively, in terms of dose–response, steady-state profile and duration of action. Trial 1991 with IDeg is used to describe the pharmacodynamic variability of the basal component (IDeg) of IDegAsp, while IDeg Trial 3538 is used to describe the response to controlled hypoglycaemia induced by the basal component (IDeg) of IDegAsp. Finally, the steady state pharmacodynamic response of the basal component has been established in IDeg trials with geriatric subjects (Trial 1994), Japanese subjects (Trial 1996) and subjects of different race/ethnicity (Trial 3762).

All but one trial employed the euglycaemic clamp for the characterisation of the PD profile of IDegAsp and IDeg. The euglycaemic clamp procedure used across the IDegAsp and IDeg clinical pharmacology trials was standardised in a systematic way. A meal test was used to assess the pharmacodynamic properties of IDegAsp in children, adolescents and adults in Trial 1982.

The counter-regulatory response to controlled hypoglycaemia induced by IDeg or IGlar after multiple doses in subjects with T1DM was investigated using a stepwise manual, hypoglycaemic, glucose clamp in Trial 3538.

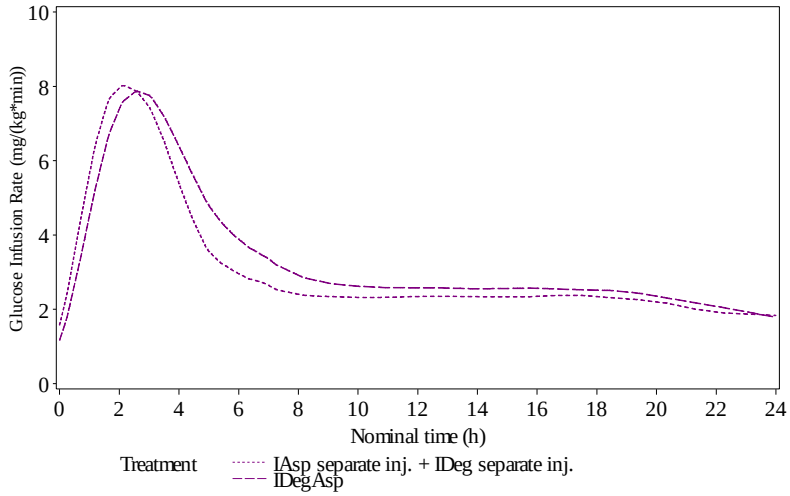
Single-Dose Pharmacodynamic Properties of IDegAsp

IDegAsp vs. Corresponding Simultaneous Separate Injections of IAsp and IDeg

The single-dose pharmacodynamic properties of IDegAsp were compared with corresponding separate simultaneous injections of the IDeg and IAsp products in a single-centre, randomised, double-blind, incomplete block cross-over design in Trial 1959 (T1DM). The dose levels of the separate simultaneous injections of the IDeg and IAsp products were chosen to mimic the fraction of each component in IDegAsp (0.92 U/kg). This design enabled a direct comparison between the pharmacodynamic profile of IDeg and IAsp when co-formulated in IDegAsp and the corresponding pharmacodynamic profile from separate simultaneous injections of the IDeg and IAsp products.

The pharmacodynamic profiles following a single s.c. injection of IDegAsp and corresponding separate, simultaneous injections of the IAsp and IDeg products are presented in Figure 1. Despite the observed differences in the pharmacokinetic profile of IAsp administered in co-formulation with IDeg as compared to the IAsp product, there were no statistically or clinically significant effects on pharmacodynamics based on $GIR_{max,SD,}$ $AUC_{GIR,0\text{-}6h,SD}$ (both reflecting the effect of the rapid-acting IAsp) and $AUC_{GIR,0\text{-}24h,SD.}$ Furthermore, a comparable time to GIR_{max} ($tGIR_{max}$) was observed for IDegAsp (2.6 hours) and separate simultaneous IAsp and IDeg administration (2.2 hours) based on summary statistics.

Figure 1. 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp vs. IDeg+IAsp in Subjects with T1DM



Trial 1959: 0.92 U/kg IDegAsp or 0.28 U/kg IAsp + 0.64 U/kg IDeg.

IDegAsp Dose Response After Single dose

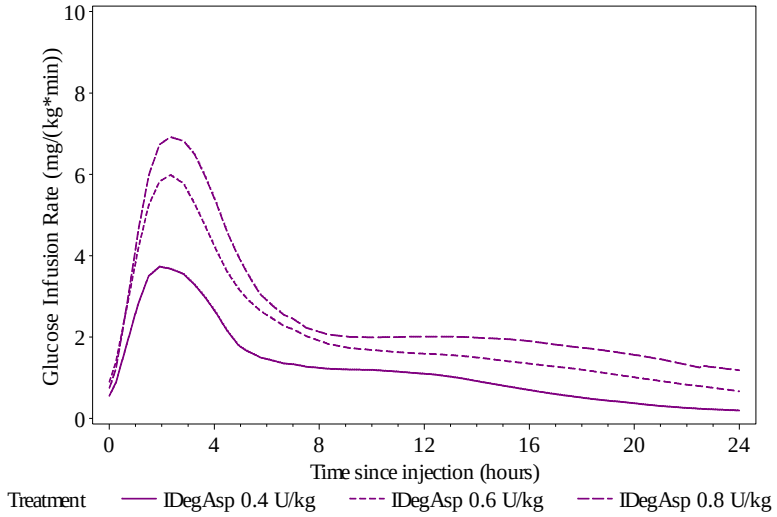
Subjects with Type 1 Diabetes

The pharmacodynamic properties of IDegAsp were investigated in a randomised, single centre, double-blind, four period, incomplete block cross over trial with single-dose administration of IDegAsp and BIAsp 30 at doses of 0.4, 0.6 and 0.8 U/kg in subjects with T1DM (Trial 3539). The pharmacodynamic properties were investigated during a 26-hour euglycaemic clamp after a single dose.

The glucose-lowering effects of the prandial and basal components of IDegAsp were separated (Figure 2). It should be noted that, in the clinical setting, IDegAsp will have a generally higher glucose-lowering effect than seen in Figure 2, as the basal component builds up to reach a steady state exposure level of approximately twice the magnitude within 2-3 days.

The total ($AUC_{GIR,0\text{-}24h,SD}$) and maximum ($GIR_{max,SD}$) glucose-lowering effect of IDegAsp increased with increasing dose (Table 2). The estimated log-dose slope and 95% CI was 1.19 $[0.99; 1.40]_{95\%CI}$ for $AUC_{GIR,0\text{-}24h,SD}$ and 0.89 $[0.66; 1.13]_{95\%CI}$ for $GIR_{max,SD}$, thus supporting dose proportionality.

Figure 2. 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp in Subjects withT1DM



Trial 3539: 0.4, 0.6 and 0.8 U/kg IDegAsp

Table 2. Glucose Infusion Rate Endpoints after Single Dose IDegAsp in Subjects with T1DM

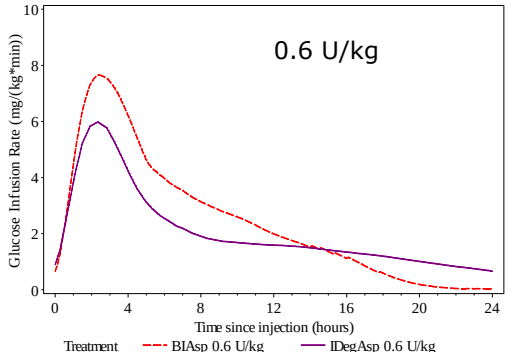
Dose (U/kg)	N	$AUC_{GIR,\ 0\text{-}24h,SD}$ (mg/kg) Geom. mean (CV%)	$GIR_{max,SD}$ (mg/kg*min) Geom. mean (CV%)
0.4	21	1681 (34)	3.8 (32)
0.6	20	2700 (42)	6.0 (38)
0.8	20	3603 (25)	6.9 (32)

Trial 3539: 0.4, 0.6 and 0.8 U/kg IDegAsp

N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

As compared with BIAsp 30, IDegAsp had a similar onset of glucose-lowering effect, similar time to maximum effect ($tGIR_{max,SD}$) and a similar shape of the mean GIR profiles during the first 4 hours after injection (Figure 3). However, the prandial and basal effects were more clearly separated with IDegAsp than BIAsp 30. For IDegAsp, the glucose-lowering effect declined from its maximum until end of the prandial coverage, after which the glucose-lowering effect remained at a nearly constant and stable rate until 24 hours after injection.

Figure 3 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp and BIAsp 30 in Subjects with T1DM



Trial 3539: 0.4, 0.6 and 0.8 U/kg IDegAsp

The mean duration of action was longer for IDegAsp than for BIAsp 30 as determined from the blood glucose concentration. Based on the compiled individual glucose infusion rate profiles, a lower between-subject variability in the pharmacodynamic response was observed with IDegAsp than with BIAsp 30 for all three dose levels.

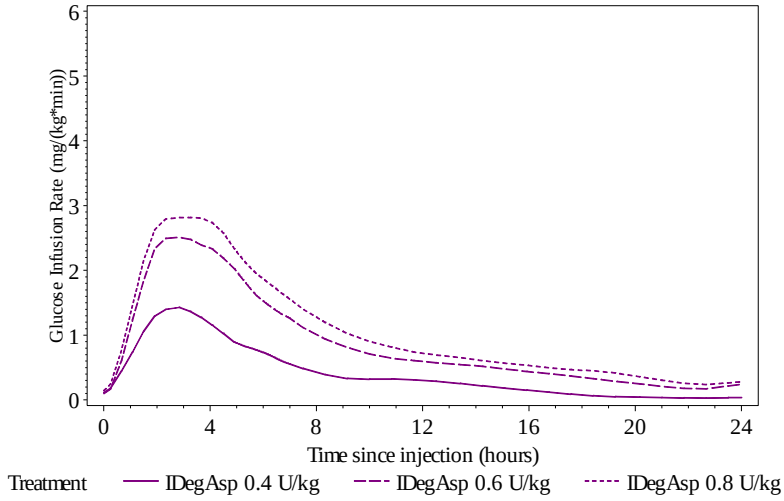
In addition to Trial 3539, the single dose pharmacodynamic properties of IDegAsp in subjects with T1DM were also investigated in Trials 1959, 1977, 1981 and 3857. When presented as dose-normalised values (geometric mean with 95% confidence intervals) across trials it was seen that $AUC_{GIR,0\text{-}24h,SD}$ and $GIR_{max,SD}$ were in the same range across trials.

Subjects with Type 2 Diabetes

The pharmacodynamic properties of IDegAsp were investigated in Trial 1978 in subjects with T2DM. This trial was a randomised, single-centre, double-blind, four period, incomplete block cross-over trial with single dose administration of IDegAsp and BIAsp 30 at doses of 0.4, 0.6 and 0.8 U/kg. The pharmacodynamic properties were investigated during a 26-hour euglycaemic clamp (target glucose level of 5.0 mmol/L [90 mg/dL]) after a single dose. One subject was excluded from the analyses due to a markedly higher GIR response compared with the mean response.

The glucose-lowering effects of the prandial and basal components of IDegAsp were separated (Figure 4).

Figure 4 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp in Subjects with T2DM



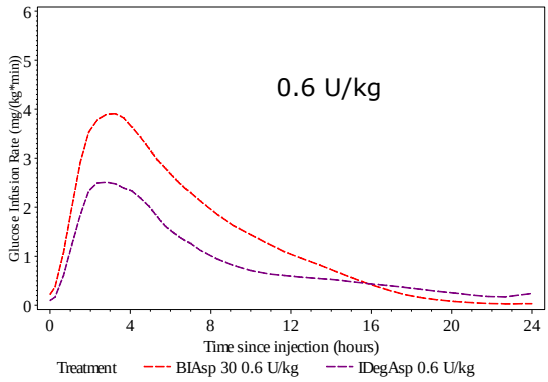
Trial 1978: 0.4, 0.6 and 0.8 U/kg IDegAsp.

The 24-hour glucose infusion rate profiles as well as descriptive statistics showed that the glucose-lowering effect increased with increasing dose. The total and maximum glucose-lowering effect of IDegAsp ($AUC_{GIR,0\text{-}24h,SD}$ and $GIR_{max,SD}$) increased with increasing dose, and linearity was demonstrated (p=0.78 and p=0.67, respectively).

As compared with BIAsp 30, IDegAsp had a similar time to maximum effect ($tGIR_{max,SD}$) and a similar shape of the mean GIR profiles during the first 5 hours after injection (Figure 5). For IDegAsp, the glucose-lowering effect declined from its maximum until end of the prandial coverage, after which the glucose-lowering effect remained at a nearly constant and stable rate until 24 hours after injection.

A reliable estimate of time to onset of action could not be calculated in subjects with T2DM (Trial 1978) as some of the subjects with impaired insulin sensitivity received a dose that was lower than their normal insulin requirement. It is however notable that the onset of appearance of IAsp was within the same range for T2DM (14 to 17 minutes) and T1DM (16 to 21 minutes).

Figure 5 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp and BIAsp 30 in Subjects with T2DM



Trial 1978: 0.4, 0.6 and 0.8 U/kg IDegAsp.

The mean duration of action was longer for IDegAsp than for BIAsp 30 as determined from the blood glucose concentration. Based on the compiled individual glucose infusion rate profiles, a lower

between-subject variability in the pharmacodynamic response was observed with IDegAsp than with BIAsp 30 for all three dose levels.

Steady State Pharmacodynamic Properties of the IDeg Component

Since the pharmacokinetic profile of IDeg is not affected by co-formulation with IAsp, IDeg dosing alone can be used to characterise the pharmacodynamic profile of the basal component in IDegAsp. Therefore, the current section is based on trials with IDeg only.

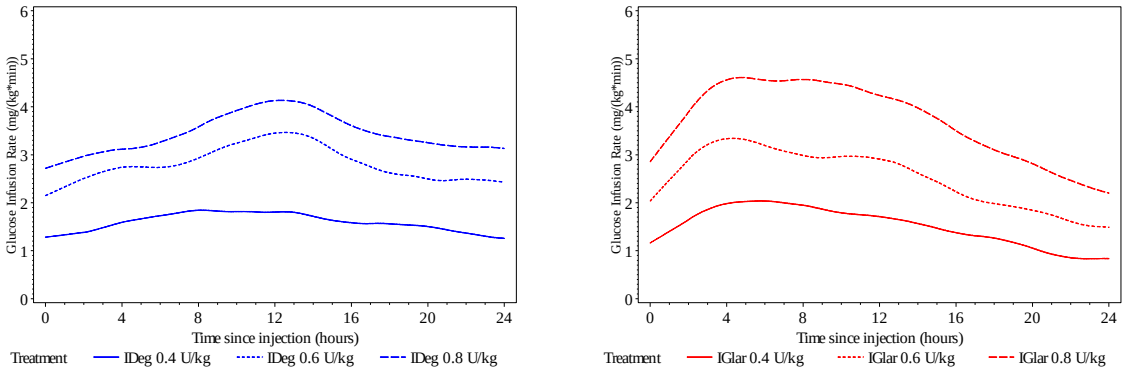
Subjects with Type 1 Diabetes

The steady-state pharmacodynamic properties of IDeg in subjects with T1DM were investigated in Trial 1993. This trial was a randomised, single-centre, double-blind, incomplete block cross-over, multiple-dose trial with 8 days of once-daily administration of IDeg or IGlar at doses of 0.4, 0.6 and 0.8 U/kg. Pharmacodynamic properties were investigated during a 42-hour euglycaemic clamp (target glucose level of 5.5 mmol/L [100 mg/dL]) conducted at steady state.

The mean 24-hour glucose infusion rate profiles obtained at steady state show that the glucose-lowering effect increased with increasing dose for both IDeg and IGlar. The glucose-lowering effect of IDeg was flatter and more stable compared to IGlar, and IDeg had a less pronounced peak effect and a smaller decline in effect between 12 and 24 hours after dosing compared to IGlar (Figure 6).

Descriptive statistics and statistical analyses confirmed that the glucose-lowering effect of IDeg increased with increasing dose (Table 3). The estimated log-dose slope and 95%CI for $AUC_{GIR,T,SS}$ was 1.35 $[0.94; 1.75]_{95\%CI}$ thus supporting dose proportionality within the investigated dose range. The time to maximum glucose infusion rate was observed approximately 12 hours after dosing at all three dose levels for IDeg.

Figure 6. 24-hour Mean Glucose Infusion Rate Profiles for IDeg (Left) and IGlar (Right) at Steady State in Subjects with T1DM



Trial 1993

Table 3. Glucose Infusion Rate Endpoints for IDeg at Steady State in Subjects with T1DM

Dose (U/kg)	N	$AUC_{GIR,\tau,SS}$ (mg/kg) Geom. mean (CV%)	$GIR_{max,SS}$ (mg/kg·min) Geom. mean (CV%)	$tGIR_{max,SS}$ (h) Median (CV%)
0.4	21	1948 (54)	2.0 (49)	11.6 (60)
0.6	21	3854 (31)	3.6 (30)	12.4 (36)
0.8	22	4766 (27)	4.2 (29)	12.3 (40)

Trial 1993. N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV: coefficient of variation.

Very similar results were observed for AUC_{GIR} and GIR_{max} at the three dose levels for both IDeg and IGlar (data not shown), whereas t GIR_{max} was longer for IDeg. When AUCs for six hour periods were analysed, there is a more even distribution with IDeg compared to IGlar, where a higher proportion of the effects is observed during the first 12-18 hours.

In addition to Trial 1993, the steady-state pharmacodynamic properties of IDeg in subjects with T1DM were investigated in Trials 1991, 1994 and 3678. Glucose-lowering effect ($AUCGIR_{\tau,SS}$ and $GIR_{max,SS}$) was in the same range across trials. The variation in $AUC_{GIR\tau,SS}$ and $GIR_{max,SS}$ between dose levels as well as across trials was comparable for IGlar and IDeg.

- *Molar Dose Ratio*

The molar dose ratio between IDeg and IGlar was estimated based on an analysis of $AUC_{GIR,\tau,SS}$ across the three dose levels of 0.4, 0.6 and 0.8 U/kg in Trial 1993. The molar dose ratio was estimated to be $1.03\ [0.95;\ 1.12]_{95\%CI}$, thus similar glucose-lowering effect of IDeg and IGlar was obtained when the two products were administered at identical molar doses.

- *Distribution and Fluctuation of Effect*

The ratio between glucose-lowering effect during the first 12 hours ($AUC_{GIR,0\text{-}12h,SS}$) and glucose-lowering effect during the entire dosing interval ($AUC_{GIR,\tau,SS}$) was 45-50% for IDeg and 57-60% for IGlar. This is in accordance with the distribution estimated for pharmacokinetic exposure.

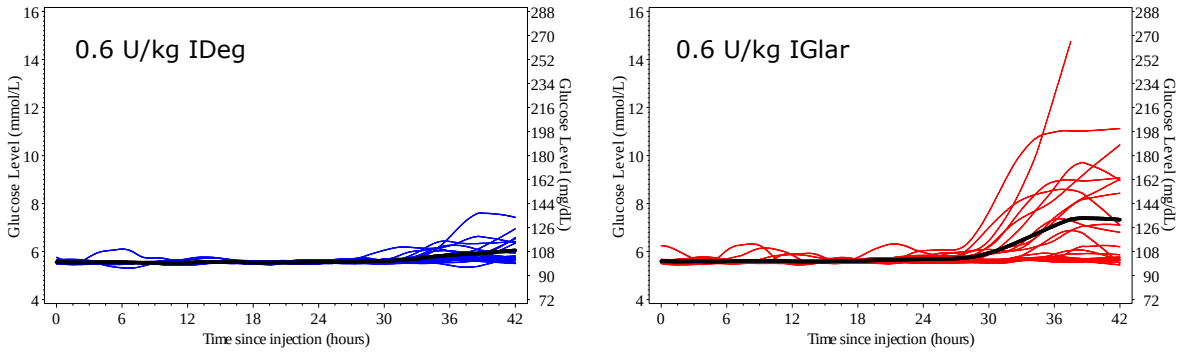
In addition, the fluctuation in glucose infusion rate ($AUCF_{GIR,\tau,SS}$) was calculated to illustrate how much the glucose infusion rate deviated from the individual mean. The estimated mean fluctuation values were lower for IDeg than for IGlar at all three dose levels, thus, the glucose infusion rate for IDeg was more consistent over the 24 hours compared to IGlar.

- *Duration of Action*

Duration of action of IDeg at steady state in subjects with T1DM was estimated during the 42-hour euglycaemic clamp. Duration of action was defined as the time from trial product administration until blood glucose concentration was consistently above 8.3 mmol/L (150 mg/dL) defined as end of action.

With IDeg, mean and compiled individual blood glucose profiles showed that blood glucose did not exceed 8.3 mmol/L (150 mg/dL) within the 42-hour clamp period for any subject at the 0.6 and 0.8 U/kg dose levels, and only for three subjects at the 0.4 U/kg dose level. Thus, end of action did not occur within the clamp period implying that duration of action extended beyond 42 hours for IDeg but could not be exactly estimated. For IGlar, blood glucose started to escape after 26 hours for several subjects at all three dose levels (Figure 7; data only shown for the 0.6 U/kg dose).

Figure 7 42-Hour Mean and Compiled Individual Blood Glucose Profiles for IDeg (Left) and IGlar (Right) at Steady State in Subjects with T1DM



Trial 1993. Black lines represent the mean.

Since an exact duration of action could not be estimated, it was decided to estimate the difference in duration of action at steady state between IDeg and IGlar in an analysis using a binomial test. The analysis demonstrated that at all three dose levels, duration of action was longer for IDeg compared to IGlar, and the difference was statistically significant when the three dose levels are combined (Table 4).

Table 4 Comparison of Duration of Action between IDeg and IGlar at Steady State in Subjects with T1DM

Dose (U/kg)	N	IDeg = IGlar	IDeg longest	IGlar longest	Unknown[a]	p-value[b]
0.4	21	0	8	0	13	0.0078
0.6	21	0	7	0	14	0.0156
0.8	22	0	5	0	17	0.0625
All combined	**64**	**0**	**20**	**0**	**44**	**< 0.0001**

Trial 1993. N: number of subjects contributing to the analysis.

[a] In these subjects, duration of action was beyond 42 hours for both IDeg and IGlar, i.e. it could not be determined for which trial product the duration of action was longest.

[b] The p-value is from a test for treatment symmetry i.e. testing within the unequal observations if the probability of IDeg being longest is equal to the probability of IGlar being longest.

Overall, the differences in duration of action between IDeg and IGlar were more apparent at the lower doses where more subjects reached end of action. At the dose levels investigated the effects well exceeds 24 hours, however, the duration of action appears to be dose dependent with some subjects experiencing an escape after approximately 30 hours at the lowest dose. The Applicant has provided both pharmacodynamic and clinical data to support the once daily use of doses lower than 0.2 U/kg in T1DM patients.

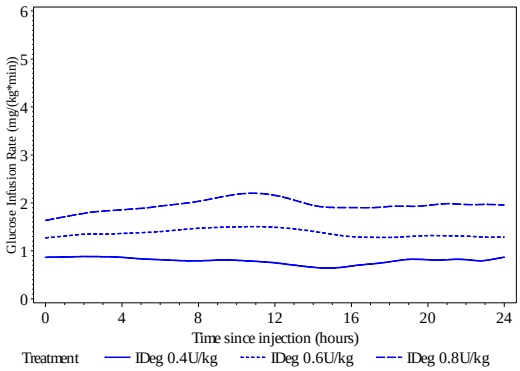
Subjects with Type 2 Diabetes

The steady-state pharmacodynamic properties of IDeg in subjects with T2DM were investigated in Trial 1987. This trial was a randomised, single-centre, double-blind, two-period, incomplete block cross-over, multiple-dose trial with 6 days of once-daily administration of 0.4, 0.6 and 0.8 U/kg IDeg 100 U/mL and 0.6 U/kg IDeg 200 U/mL. The pharmacodynamic properties of IDeg were investigated during

a 26-hour euglycaemic clamp (target glucose level of 5.0 mmol/L [90 mg/dL]) conducted at steady state. In the following, results are presented only for IDeg 100 U/mL as this is the IDeg product relevant to characterise the basal component of IDegAsp.

The mean 24-hour glucose infusion rate profiles obtained at steady state were flat and stable at all three dose levels, and the glucose-lowering effect increased with increasing dose (Figure 8). The glucose-lowering effect of IDeg increased with increasing dose (Table 5), and linearity was demonstrated (p = 0.83). The time to maximum glucose infusion rate was observed to be 10–13 hours after dosing, with a less pronounced peak compared to what was observed in T1DM subjects.

Figure 8 24-Hour Mean Glucose Infusion Rate Profiles for IDeg at Steady State in Subjects with T2DM



Left: Trial 1987; Right: Trial 3762 (only Caucasian subjects).

Table 5 Glucose Infusion Rate Endpoints for IDeg at Steady State in Subjects with T2DM

Dose (U/kg)	N	$AUC_{GIR,τ,SS}$ (mg/kg) Geom. mean (CV%)	$GIR_{max,SS}$ (mg/kg·min) Geom. mean (CV%)	$tGIR_{max,,SS}$ (h) Median (CV%)
0.4	22	828 (68)	1.1 (52)	12.6 (70)
0.6	37	1694 (56)	1.7 (49)	10.5 (81)
0.8	21	2482 (46)	2.4 (54)	10.5 (61)

Trial 1987. N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

- *Duration of Action*

The duration of action of IDegAsp is determined by the basal component (IDeg). The duration of action of IDeg at steady state in subjects with T2DM was estimated during the 26-hour euglycaemic clamp as the time from trial product administration until blood glucose concentration was consistently above 8.3 mmol/L (150 mg/dL), defined as end of action.

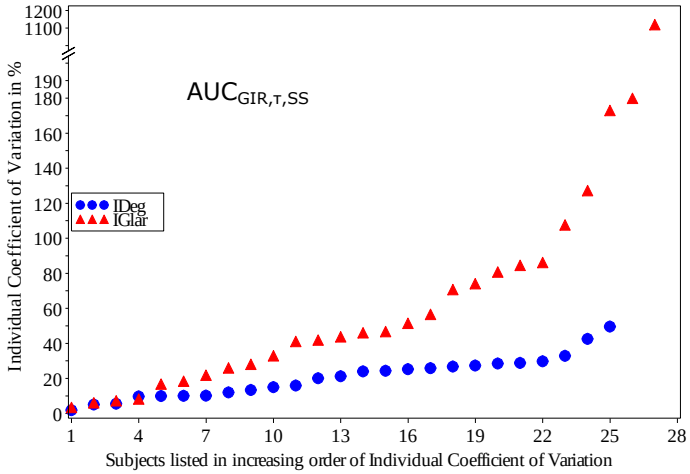
Mean and compiled individual blood glucose profiles showed that blood glucose did not exceed 8.3 mmol/L (150 mg/dL) within the 26-hour clamp period for any subject at any dose level. Thus, end of action did not occur within the clamp period implying that duration of action extended beyond 26 hours for IDeg, but could not be exactly estimated. Since insulin requirements are usually higher in T2DM than in T1DM, a 24-hour coverage with IDeg would be expected in clinical use.

Variability of Pharmacodynamic Properties

The pharmacodynamic within-subject day-to-day variability of IDeg at steady state was investigated in Trial 1991. This trial was a randomised, single-centre, double-blind, parallel-group trial with 12 days of once-daily administration of 0.4 U/kg IDeg or 0.4 U/kg IGlar in subjects with T1DM. The glucose-lowering effect was assessed on treatment days 6, 9 and 12, and the day-to-day variability was measured as the within-subject coefficient of variation (CV) corresponding to the difference in the glucose-lowering effect from one insulin injection to another under comparable conditions in the same subject.

In Figure 9, the individual CVs (%) for $AUC_{GIR,\tau,SS}$ are presented in increasing order for the two treatment groups (IDeg and IGlar). The estimated differences in day-to-day variability between IDeg and IGlar were driven by the majority of the subjects in the IGlar group. The individual day-to-day variability was consistently lower for IDeg compared to IGlar when presented in ranked order and CV was low (< 50%) for all subjects treated with IDeg (Figure 9).

Figure 9 Individual Day-to-Day Variability in Glucose-Lowering Effect for IDeg and IGlar at Steady State in Subjects with T1DM



Trial 1991: 0.4 U/kg IDeg or 0.4 U/kg IGlar.

Statistical analysis showed that the day-to-day variability in $AUC_{GIR,\tau,SS}$ measured as CV was 4 times lower for IDeg compared to IGlar (Table 6). The same difference between IDeg and IGlar was obtained for $AUC_{GIR,2\text{-}24h,SS}$, which is a more clinically relevant endpoint, since the measured glucose infusion rate from 2 hours onwards is not influenced by i.v. insulin infusion at the start of the euglycaemic clamp.

Table 6 Day-to-Day Variability in Glucose-Lowering Effect for IDeg and IGlar at Steady State in Subjects with T1DM

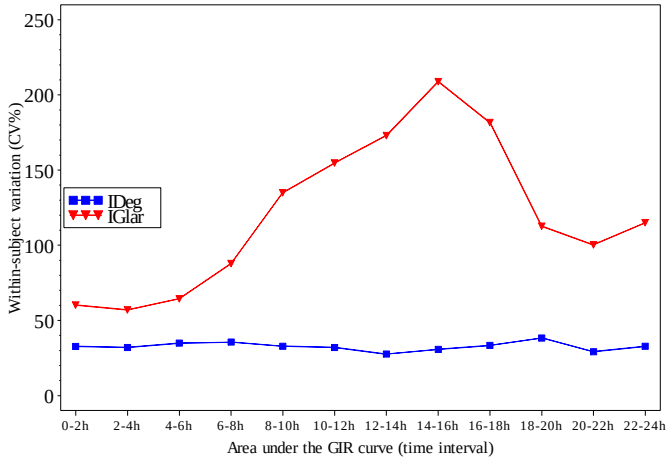
Endpoint	IDeg (CV%)	IGlar (CV%)	p-value
$AUC_{GIR,\tau,SS}$	20	82	<0.0001
$AUC_{GIR,2\text{-}24h,SS}$	22	92	<0.0001
$GIR_{max,SS}$	18	60	<0.0001

Trial 1991: 0.4 U/kg IDeg or 0.4 U/kg IGlar. CV%: coefficient of variation in %.

An analysis of the area under the glucose infusion rate curve in 2-hour intervals was also performed. The day-to-day variability of IDeg was consistently low over the entire 24-hour period, whereas the

variability of IGlar was significantly higher and increased substantially 6–8 hours after dosing reaching a maximum at 14-16 hours after dosing, where variability was 7 times greater compared to IDeg (Figure 10). Mean CVs for IDeg were 33% for $AUC_{GIR,0-2h}$, 33% for $AUC_{GIR,10-12h}$ and 33% for $AUC_{GIR,22-24h}$, and mean CVs for IGlar were 60% for $AUC_{GIR,0-2h}$, 135% for $AUC_{GIR,10-12h}$ and 115% for $AUC_{GIR,22-24h}$).

Figure 10. Day-to-day Variability in Glucose-Lowering Effect over Time for IDeg and IGlar at Steady State in Subjects with T1DM



Trial 1991: 0.4 U/kg IDeg or 0.4 U/kg IGlar.

The effects of the measured variability were modelled to predict the clinical impact of the lower pharmacodynamic day-to-day variability of IDeg versus IGlar. The width of the prediction interval reflects the day-to-day variability in the pharmacodynamic response. The predicted range was found to be narrower for IDeg compared to IGlar. Furthermore, it was predicted that the risk of experiencing less than half the usual average effect (i.e. an average glucose infusion rate < 1 mg/kg·min) on any given day (i.e., potential hyperglycaemia) was <0.1% for IDeg and 17% for IGlar.

Similarly, the risk of experiencing more than 1.5 times the usual average effect (i.e. an average glucose infusion rate > 3 mg/kg·min) on any given day (i.e. potential hypoglycaemia) was calculated to be 2% for IDeg and 29% for IGlar. Thus, the lower variability in glucose-lowering effect with IDeg compared to IGlar is hypothesised by the Applicant to result both in a lower risk of hyper- and hypoglycaemia for the IDeg component in IDegAsp.

Injection Regions

The use of various injection regions (abdominal wall, the thigh, the upper arm (the deltoid region) or the gluteal region) has been established and demonstrated through several years of market use of the prandial component (IAsp) of IDegAsp.

The pharmacodynamic response of IDeg between different injection regions and routes of administration was evaluated during a 24-hour euglycaemic clamp (target glucose level of 4.5 mmol/L [81 mg/dL]) in Trial 1992. This was a randomised, single-centre, open-label, five-period cross-over trial with single-dose administration of 0.4 U/kg IDeg s.c. in the thigh, the abdomen and the deltoid (upper arm), 0.4 U/kg IDeg i.m. in the thigh, and 0.04 U/kg IDeg i.v., respectively, on five different dosing visits in healthy subjects.

Mean glucose infusion rate profiles showed that the glucose-lowering effect was similar following 0.4 U/kg IDeg administered s.c. in the thigh, the abdomen and the deltoid, and extended beyond 24 hours, and descriptive statistics supported these findings (Table 7). Thus, the differences in

pharmacokinetic properties observed following s.c. administration in the abdomen or the deltoid compared to the thigh were not accompanied by differences in glucose-lowering effect. A slight numerical difference in AUC and GIR was, however, observed with the largest difference seen between "thigh" and "deltoid". With the responses to the Day120 LoQ the Applicant provided simulations showing that the observed differences decrease at steady state, indicating that the observed differences are not clinically relevant.

Table 7 Glucose Infusion Rate Endpoints for IDeg after Single Dose in the Thigh, Abdomen and Deltoid in Healthy Subjects

		$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	$GIR_{max,SD}$ (mg/kg·min)	$tGIR_{max,SD}$ (h)
Injection Region	N	Geom. mean (CV%)	Geom. mean (CV%)	Median (CV%)
Thigh	19	2572 (38)	2.7 (32)	13.2 (34)
Abdomen	20	2833 (42)	3.0 (37)	11.1 (43)
Deltoid	20	2960 (43)	3.0 (42)	12.4 (36)

Trial 1992: 0.4 U/kg. N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

Routes of Administration: Intramuscular vs. Subcutaneous Injection

The mean glucose infusion rate was higher following i.m. administration of IDeg compared to s.c. administration in the thigh and descriptive statistics supported these findings (Table 8). The significant change in maximum concentration and duration of appearance is, however, not reflected to the same extent in the pharmacodynamic profile as in the pharmacokinetic profile. However, due to the increased glucose lowering effect observed, i.m. injections should be avoided. Section 4.2 of the SmPC includes adequate wording to this respect.

Table 8 Glucose Infusion Rate Endpoints for IDeg after Single Dose i.m. and s.c. in Healthy Subjects

		$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	$GIR_{max,SD}$ (mg/kg·min)	$tGIR_{max,SD}$ (h)
Administration Route	N	Geom. mean (CV%)	Geom. mean (CV%)	Median (CV%)
i.m.	19	3269 (25)	3.4 (24)	12.4 (38)
s.c.	19	2572 (38)	2.7 (32)	13.2 (34)

Trial 1992: 0.4 U/kg. N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

Intrinsic Factors

Body Mass Index (BMI)

The effect of BMI on pharmacodynamic endpoints for IDeg was investigated in subjects with T1DM (across Trials 1991, 1993, 1994 and 3678), and in subjects with T2DM (across Trials 1987 and 3762). Similar analyses were made for IDegAsp in subjects with T1DM (across Trials 1977, 1981, 3539 and 3857), and in subjects with T2DM (Trial 1978). The endpoints ($AUC_{GIR,\tau,SS}$ and $GIR_{max,SS}$ for IDeg trials and $AUC_{GIR,0\text{-}24h,SD}$ and $GIR_{max,SD}$ for IDegAsp trials) were log-transformed and analysed in a linear mixed model with sex, dose and period within trial as fixed effects, and subject as a random effect.

For both IDegAsp after single dose and IDeg (the basal component alone) at steady state, scatter plots indicated that total and maximum glucose-lowering effect decreased with increasing BMI in subjects with either T1DM or T2DM, and statistical analyses showed that the correlation was significant. This is in line with the well-known association between obesity and insulin resistance.

Age

Children and Adolescents

The pharmacodynamic properties of IDegAsp in children and adolescents in comparison to adults were investigated in Trial 1982 by means of a meal test. Trial 1982 was a single-centre, open-label, parallel group trial with single-dose administration of 0.5 U/kg IDegAsp in children (6–11 years), adolescents (12–17 years) and adults (18–65 years) with T1DM.

The shape of the mean plasma glucose profiles obtained over a period of 6 hours following trial product administration and meal ingestion was similar in children, adolescents and adults.

The glucose-lowering effect of IDegAsp (as assessed from $AUC_{PG\ baseline,0\text{-}6h,std.meal,SD}$) was comparable for children, adolescents and adults although with a large between-subject variability. Maximum plasma glucose concentration after a standard meal ($PG_{max,meal,SD}$) and maximum plasma glucose excursion (Delta $PG_{max,meal,SD}$) were comparable for children, adolescents and adults based on descriptive statistics.

In addition to the reporting by age group described in the objectives of Trial 1982, the pharmacodynamic properties of IDegAsp were also reported by pubertal status according to Tanner stage scoring. Based on the Tanner stage scores, 6 subjects were categorised as pre-pubertal, and 19 subjects were categorised as pubertal. In accordance with the pharmacodynamic response analysed by age group, there were no apparent differences between the pharmacodynamic response for the pre-pubertal, pubertal and adult groups.

Geriatric Subjects

The pharmacodynamic properties of IDegAsp in geriatric subjects in comparison to younger adult subjects were investigated in Trial 1981. This was a randomised, single-centre, double-blind, cross-over trial with single-dose administration of 0.5 U/kg of IDegAsp and BIAsp 30 in younger adult (18−35 years) and geriatric (≥65 years) subjects with T1DM. The pharmacodynamic properties were investigated during a 26-hour euglycaemic clamp (target glucose level of 5.5 mmol/L [100 mg/dL]).

The mean 24-hour glucose infusion rate profile for IDegAsp after single dose were similar in geriatric and younger adult subjects with T1DM as was the pharmacodynamic response (based on $AUC_{GIR,0\text{-}24h,SD}$) with an estimated ratio and 95% CI of 1.01 $[0.69; 1.47]_{95\%CI}$ for geriatric/younger adults.

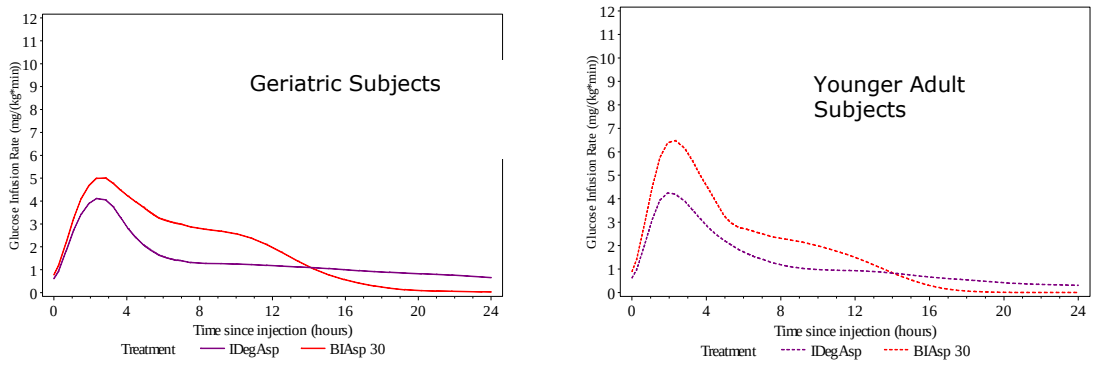
Furthermore, the tendency towards greater IAsp exposure in geriatric subjects than in younger adult subjects was not reflected in a similar tendency for the early glucose lowering effect, as also indicated by descriptive statistics of $AUC_{GIR,0\text{-}6h,SD}$ and $GIR_{max,SD}$. Altogether, these findings are in line with the fact that insulin sensitivity is known to decrease with ageing.

IDegAsp Compared With BIAsp 30 in Geriatric and Younger Adult Subjects

Mean glucose infusion rate profiles and descriptive statistics showed that the similarities and differences between IDegAsp and BIAsp 30 were preserved in geriatric subjects: In particular, the prandial and basal components were more clearly separated with IDegAsp than BIAsp 30, while maintaining a similar rapid onset of action and time to maximum glucose-lowering effect (Figure 11).

In addition, there was no difference between IDegAsp and BIAsp 30 with respect to the effect of age group on $AUC_{GIR,0\text{-}24h,SD}$ and $GIR_{max,SD}$ (p=0.75 and p=0.25, respectively).

Figure 11 24-Hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp and BIAsp 30 in Geriatric Subjects (Left) and Younger Adult Subjects (Right) with T1DM



Trial 1981: 0.5 U/kg IDegAsp and 0.5 U/kg BIAsp 30.

Sex

Single Dose

The glucose-lowering effect after a single dose of IDegAsp was compared between women and men in a statistical analysis across Trials 1977, 1981 (only younger adult subjects), 3539 and 3857 including 13 women and 85 men. The endpoints $AUC_{GIR,0\text{-}24h,SD}$ and $GIR_{max,SD}$ were dose-adjusted to 0.4 U/kg, log-transformed and analysed in a linear mixed model with sex, dose and period within trial as fixed effects and subject as a random effect. The estimated mean total ($AUC_{GIR,0\text{-}24,SD}$) and maximum ($GIR_{max,SD}$) glucose lowering effects after a single dose of IDegAsp were comparable for women and men when dosed per kg body weight.

Steady State

The results from an across trial analysis with IDeg trials are used to describe the pharmacodynamic properties at steady-state of the basal component of IDegAsp in women and men.

The glucose-lowering effect of IDeg at steady state following 6 to 8 days of once-daily administration of IDeg was compared between women and men in a statistical analysis across Trials 1991, 1993, 1994 and 3678 including 22 women and 113 men with T1DM. To ensure comparable conditions across the four trials, results obtained in geriatric subjects (Trial 1994) and with IDeg 200 U/mL (Trial 3678) were not included. The endpoint, $AUC_{GIR,\tau,SS}$, was dose-adjusted to 0.4 U/kg, log-transformed and analysed in a similar model as the sex analysis for IDegAsp.

The total and maximum glucose-lowering effect of IDeg was greater in women than in men, and this was confirmed by statistical analysis, as 1 was not included in the 95% CI.

Previous studies have shown that women have comparable or a higher insulin sensitivity than men, thus the findings are as expected.

<u>Response to hypoglycaemia</u>

The response to controlled hypoglycaemia induced by IDeg or IGlar after multiple doses was investigated in subjects with T1DM (Trial 3538) applying a hypoglycaemic clamp technique. Relevant glucose-lowering was achieved for both IDeg and IGlar.

The difference in counter-regulatory hormone response during development of hypoglycaemia was estimated as the treatment ratio between the slopes of the hormone profiles for IDeg and IGlar. There was a greater increase in the counter-regulatory hormone response with IDeg compared to IGlar for adrenaline (epinephrine) (1.07 $[1.01; 1.14]_{95\%CI}$). In addition, there was a greater increase for growth hormone (1.35 $[1.19; 1.54]_{95\%CI}$), and a trend towards a slightly greater increase for cortisol (1.03 $[1.00; 1.06]_{95\%CI}$). The effect on noradrenaline (norepinephrine) and glucagon was similar for IDeg and IGlar. This was supported by a statistical analysis of the estimated area under the hormone profile (Table 9). There was no difference in the hormone levels between IDeg and IGlar at baseline.

There was no statistically significant difference between IDeg and IGlar with regards to pulse or blood pressure at the different glucose levels.

Table 9 Ratios between Hormone Profiles for IDeg and IGlar during Development of Hypoglycaemia in Subjects with T1DM

	$AUC_{Hormone,IDeg}$ / $AUC_{Hormone,IGlar}$	
Hormone	**Estimate [95% CI]**	**P-value**
Adrenaline (epinephrine)	1.40 [0.96; 2.04]	0.07
Growth hormone	2.44 [1.30; 4.60]	0.01
Cortisol	1.23 [1.01; 1.50]	0.04
Noradrenaline (norepinephrine)	1.17 [0.85; 1.60]	0.32
Glucagon	1.16 [0.91; 1.48]	0.21

Trial 3538: individual doses; N=26. CI: confidence interval.

Recovery from hypoglycaemia and the time to re-establishment of euglycaemia was not different between IDeg and IGlar; however, after blood glucose had been raised to 3.9 mmol/L (70 mg/dL), less glucose was needed to alleviate hypoglycaemia for IDeg compared with IGlar as shown by glucose infusion rate profiles and statistical analysis of $AUC_{GIR,0\text{-}2h,recovery}$ (0.68 $[0.49; 0.95]_{95\%CI}$) and $AUC_{GIR,PG\ nadir\ end\ -\ 2h}$ (0.71 $[0.53; 0.93]_{95\%CI}$). The clinical relevance of this finding remains to be shown. During recovery from hypoglycaemia, all hypoglycaemic response assessments returned to baseline in a similar manner for IDeg and IGlar. Thus the hypoglycaemic clamp did not reveal any attenuation of the counter-regulation in response to hypoglycaemia with IDeg as compared to IGlar.

Relationship between plasma concentration and effect

As IDegAsp is a co-formulation of the long acting IDeg and the rapid-acting IAsp, it follows that the pharmacokinetic properties of IDegAsp should be described by both of these two pharmacokinetic profiles. The pharmacokinetic profiles of IAsp and IDeg are consistent with the action profile of IDegAsp showing distinct and separate prandial and basal components. As is also seen with other subcutaneously administered insulin products, the pharmacodynamic action lagged slightly behind the pharmacokinetic profile, most likely as a result of tissue distribution from the plasma compartment and activation of insulin receptors in the target tissues.

For the prandial effect of IDegAsp, the pharmacokinetic and pharmacodynamic properties were characterised in the dose range (0.4 to 0.8 U/kg) of IDegAsp.

There was a correlation between early or maximum exposure and early or maximum glucose-lowering effect for the prandial component of IDegAsp in subjects with T1DM. This was supported by the

observation that both $C_{max,IAsp,SD}$ and $GIR_{max,SD}$ of IDegAsp increased proportionally with increasing dose.

For the basal component of IDegAsp, the pharmacokinetic and pharmacodynamic properties were characterised in a the dose range (0.4 to 0.8 U/kg) of IDeg. There was a correlation between total exposure ($AUC_{IDeg,\tau,SS}$) and total glucose-lowering effect ($AUC_{GIR,\tau,SS}$) within the investigated dose range of IDeg in subjects with T1DM. This was supported by the observation that both $AUC_{IDeg,\tau,SS}$ and $AUC_{GIR,\tau,SS}$ of IDeg at steady state increased proportionally with increasing dose.

Dosing Recommendations

The basal component of IDegAsp is present in the circulation for at least 120 hours and has an estimated $t_{½}$ of approximately 25 hours, supporting the duration of action beyond 42 hours. Given the long duration of action and the continuous absorption of the basal component in IDegAsp, the same total daily dose may be administered once daily or split in two administrations, with respect to basal coverage. Moreover, the long duration of action for the basal component in IDegAsp permits once-daily dosing with the ability to vary the daily injection time, if needed, as long as the dose is administered with the main meal(s) to accommodate the IAsp in the formulation.

For the IAsp component in IDegAsp, it is well-established that the molar dose ratio between IAsp and human insulin is 1, i.e. the glucose-lowering effect of IAsp is similar to human insulin when given in identical doses. The molar dose ratio between IDeg and IGlar was estimated based on a statistical analysis of $AUC_{GIR,\tau,SS}$ across the three dose levels of 0.4, 0.6 and 0.8 U/kg in Trial 1993. The molar dose ratio was estimated to be 1.03 $[0.95; 1.12]_{95\%CI}$, thus similar glucose-lowering effect of IDeg and IGlar was obtained when the two products were administered at identical molar doses. The data are deemed sufficient to conclude that 1 U of IDeg 100 U/mL corresponds to 1 U of all other insulin analogues and to 1 IU of human insulin.

Investigations of the pharmacokinetic and pharmacodynamic properties of IDegAsp and IDeg in special populations (children, adolescents, geriatric subjects, subjects with renal or hepatic impairment, and subjects of different race and ethnicity) did not indicate a need for any special precautions. Thus, the dose adjustment of IDegAsp, as with all other insulin products, should be based on individual needs.

Pharmacodynamic interactions with other medicinal products or substances

No discussion on pharmacodynamic interactions has been provided by the applicant. This is acceptable considering the mechanism of action. Pharmacodynamic interactions known for other insulins are expected to occur also for IDeg and these interactions are sufficiently reflected in the SmPC.

Genetic differences in PD response

The pharmacodynamic properties of IDeg at steady state were investigated in African American, Hispanic and Caucasian Subjects. The mean glucose infusion rate profiles at steady state were similar for the three race/ethnic groups. No statistically significant or clinically relevant differences were observed in the pharmacodynamic profiles.

Furthermore, the pharmacodynamic properties of IDegAsp and IDeg alone have been compared between Japanese (Trials 1983 and 1996) and Caucasian (Trials 3857 and 1993) subjects. In addition, the pharmacodynamic properties of BIAsp 30 have been compared between Japanese subjects (Trial 1983) and Caucasian subjects (Trial 1981).

As in Caucasian subjects, the shape of the mean GIR profile for IDegAsp was similar to that of BIAsp 30 during the first 4 hours after injection in Japanese subjects, but the pharmacodynamic effects of the prandial and basal components of IDegAsp were more clearly separated with IDegAsp than BIAsp 30.

The shape of the pharmacodynamic profile of IDegAsp was similar in Japanese and Caucasian subjects. The pharmacodynamic response of IDegAsp was generally lower in Japanese than in Caucasian subjects. However, a lower pharmacodynamic response in Japanese than Caucasian subjects was also observed for BIAsp 30. Since the shape of the mean glucose infusion rate profiles was similar in Japanese and Caucasian subjects, the observed differences were not believed to have any important clinical implications, considering that IDegAsp, as any insulin, should be dosed according to individual needs. In addition, the differences should be interpreted with caution as the results are obtained at different investigational sites using different equipment.

In Japanese subjects with T1DM, the glucose-lowering effect of IDeg was slightly lower compared to Caucasian subjects. This was supported by descriptive statistics. The shape of the mean glucose infusion rate profiles was similar in Japanese and Caucasian subjects. The data, however, does not indicate any clinically relevant differences between Japanese and Caucasian subjects.

2.4.4. Discussion on clinical pharmacology

IDegAsp is a combination of a new long acting insulin analogue and a well-known fast acting insulin analogue. The IDeg component of the product needs to be described to an extent expected for a new chemical entity. This could be done using either only IDeg or IDeg as part of the combination depending on the situation.

The characterisation of IDeg is expected to include an evaluation of the influence of intrinsic factors (BMI, age, sex, race/ethnicity, renal and hepatic function) and extrinsic factors (drug interactions) on its PK. Moreover, it is anticipated that new insulin analogues are documented in comparison to other insulin analogues with similar pharmacological profiles. One specific aspect of interest in this comparison is how variable the new analogue is (intra-individual variability). The influence on PK due to different injection sites and different injection volumes are also expected to be studied.

The IDegAsp consists of 30% IAsp and 70% IDeg, IDeg being a new long-acting insulin analogue. At the target tissues, IDeg and IAsp monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake as confirmed by the non-clinical data. The mechanism of action of IDeg is similar to that of other insulins, only with a slightly lower activity and prolonged duration of action.

The pharmacodynamic profile of IDegAsp and IDeg has been investigated through a well-designed development program including studies in both T1DM and T2DM patients as well as healthy volunteers. The PD profile was similar for the mixed formulation and when IDeg and Asp was given as separate doses. A proportional dose-response relationship was shown for IDegAsp in patients with T1DM whereas a linear dose-response was observed in patients with T2DM.

When compared to a single dose of BIAsp, a lower peak of the short-acting component and longer duration of action were observed both in T1DM and T2DM patients. The effect of the Asp component also appears to decline faster for IDegAsp than for BIAsp. Individual data indicate that the inter-individual variability may be lower with IDegAsp than with BIAsp. In T1DM, the dose adjusted data across trials for AUC_{GIR} and GIR_{max} were consistent although with some variation.

In addition to the PD data on IDegAsp, data from studies performed with the long-acting component IDeg has also been provided. Data has been provided to supports that the molar dose is equipotent and that one unit of IDeg corresponds to one unit of IGlar. These data are deemed sufficient to conclude that 1 U of IDeg 100 U/mL corresponds to 1 U of all other insulin analogues and to 1 IU of human insulin.

Data in both T1DM and T2DM patients show that IDeg has a flatter profile than IGlar, with a slight peak observed about 10-12 hours after dosing especially at higher doses. In T1DM, the dose adjusted data across trials for AUC_{GIR} and GIR_{max} were consistent although with some variation especially within trial 1993. Due to the long duration of action for IDeg, an exact duration of action could not be estimated. At the dose levels investigated (0.4-0.8 U/kg) the effect well exceeds 24 hours, however, the duration of action appears to be dose dependent with some T1DM subjects experiencing an escape after approximately 30 hours at the lowest dose. Additional PD data provided by the Applicant show that the duration of action exceeded 24 hours when a dose of 0.28 U/kg was tested. Further to this, a subgroup analysis in T1DM patients treated with doses ≤ 0.2 U/kg OD within the clinical trial program support a 24-hour coverage with once daily dosing. Since insulin requirements are usually higher in T2DM, 24-hour coverage with IDeg would be expected in clinical use.

In a study dedicated to investigate the intra-individual variability it was shown that the variability, both with regards to $AUC_{GIR,\tau,SS}$ and GIR_{max} was significantly lower for IDeg compared to IGlar. The Applicant hypothesises a decreased risk for both hyperglycaemia and hypoglycaemia with IDeg compared to IGlar. However, whether this lower variability actually transforms into a clinical benefit remains to be seen and it is considered premature to make clinical claims solely on the PD observations.

Very similar PD profiles were obtained for IDeg irrespective of injection site. A slight difference in AUC and GIR was observed with the largest difference seen between "thigh" and "deltoid". Data has been provided, showing that these differences will diminish at steady state. The information included in the SmPC is considered adequate. Although the PD profile was essentially similar with i.m. and s.c. injection, a higher peak was observed with i.m. injection together with higher AUC and GIR. Therefore i.m. injections should be avoided and adequate warnings are included in section 4.2 of the SmPC.

Considering the long duration of action of IDeg, it is of importance that the response to hypoglycaemia is adequate. The data obtained by the hypoglycaemic clamp did not reveal any attenuation of the counter-regulation in response to hypoglycaemia with IDeg as compared to IGlar. Less glucose was needed to reverse the hypoglycaemia induced by IDeg, the clinical relevance of this finding is unknown.

The influence of age on the effect of IDegAsp was investigated in dedicated trials. The differences in the PD profile were greater for BIAsp between geriatric patients and younger adults than for IDegAsp. A slightly lower glucose-lowering effect of IDegAsp was observed for geriatric subjects at steady state, in line with the decreasing insulin sensitivity with age. The results from study 1982 indicate that the glucose lowering effect of the prandial component of IDegAsp is similar in children, adolescents and adults. Thus, the greater exposure of IAsp seen in children with IDegAsp, were not reflected in the pharmacodynamic results.

The influence of BMI and sex and IDeg was investigated in across trial analyses. As expected, the glucose-lowering effect of IDeg and IDegAsp decreased with increasing BMI. After a single dose, no significant differences were observed between sexes. At steady state the glucose-lowering effect of IDeg was higher in women compared to men. This is as expected and in line with previous studies showing that insulin sensitivity is either similar or greater in women compared to men.

No statistically or clinically relevant differences were observed in the PD profile for patients of different ethnic origin.

No discussion on pharmacodynamic interactions has been provided by the Applicant. This is acceptable considering the mechanism of action. Pharmacodynamic interactions known for other insulins are expected to occur also for IDegAsp and these interactions are sufficiently reflected in section 4.5 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The applicant has performed a very comprehensive development program which in part is based on studies with only IDeg and in part from studies with IDegAsp. The studies performed clearly covers more than what could be considered the minimum requirements regarding PK characterisation.

The pharmacodynamic properties of IDegAsp has been adequately characterised in a well-designed program. IDegAsp has been shown to have a clear distinction between the short-acting component and the long-acting component, which has a flatter profile than currently available long-acting insulins. There are indications that the long-acting component has less intra-individual variability than IGlar, the clinical benefit of this finding remains to be seen.

2.5. Clinical efficacy

The clinical development programme evaluating the efficacy and safety of IDegAsp includes five therapeutic confirmatory trials and 3 therapeutic exploratory trials conducted between 23 January 2008 and 23 December 2010 (see Table 10). In addition to the trials with IDegAsp, key results from two confirmatory clinical trials (Trials NN1250-3770 and NN1250-3668) in the IDeg development programme (NN1250) are discussed. The two trials explore extreme variation in injection time of IDeg and the data are included to support flexible dosing of IDegAsp with the understanding that flexibility of this product is restricted to the meals due to the presence of the bolus component of IAsp in the formulation.

Table 10 Overview of IDegAsp therapeutic Confirmatory Trials

Trial No.	Duration (Weeks)	Trial Description	OAD Combination	Population	Randomisation (IDegAsp: Comparator)	No. of Subjects Randomised	Antidiabetic Treatment at Screening	Stratification
T1DM								
3594	26 (+ 26-week extension, NN5401-3645)	IDegAsp OD + IAsp vs. IDet[†] + IAsp	None	Insulin-treated	2:1	IDegAsp: 366 IDet: 182	Basal–bolus insulin regimen or other mixed insulin regimen	Prior treatment: • basal–bolus insulin regimen • other insulin regimen
T2DM								
3590	26	IDegAsp OD vs. IGlar OD	Metformin	Insulin-naïve	1:1	IDegAsp: 266 IGlar: 263	Metformin and ≥1 other OAD except TZD	None
3593	26	IDegAsp OD vs. IGlar OD	Metformin ± pioglitazone ± DPP-4 inhibitor	Insulin-treated	1:1	IDegAsp : 230 IGlar: 233	Basal insulin OD and metformin ± other OADs	Prior treatment: • TZD Yes • TZD No
3592	26	IDegAsp BID vs. BIAsp 30 BID	± metformin ± pioglitazone ± DPP-4 inhibitor	Insulin-treated	1:1	IDegAsp: 224 BIAsp 30: 222	Premixed/self-mixed insulin OD or BID ± OADs	Prior treatment: • OD insulin regimen • BID insulin regimen
3597	26	IDegAsp BID vs. BIAsp 30 BID	± metformin	Insulin-treated	2:1	IDegAsp: 280 BIAsp 30: 142	Basal insulin OD or BID ± metformin or premixed/self-mixed insulin OD or BID ± metformin	Prior treatment: • basal without metformin • basal with metformin • premix without metformin • premix with metformin

[†]OD from start, but a second IDet dose could be added after 8 weeks in case of inadequate glycaemic control.

BIAsp: biphasic insulin aspart; BID: twice daily; DPP-4: di-peptidyl peptidase-4; IAsp: insulin aspart; IDet: insulin detemir; IGlar: insulin glargine; OAD: oral antidiabetic drug; OD: once daily; TZD: thiazolidinedione.

2.5.1. Dose response studies

For dose-response studies, please refer to the pharmacodynamic part of this report.

2.5.2. Main studies

Methods

The therapeutic confirmatory trials were similar in design. All the trials were randomised, controlled, parallel-group, open label, multicentre, multinational trials, in which IDegAsp was compared with an active comparator. The comparators represent the currently available insulin analogues and included IDet, BIAsp 30 BID or IGlar OD. The trial duration was 26 weeks to ensure that stable glycaemic control was maintained for a sufficient time period. To evaluate long-term safety of IDegAsp, Trials 3594 and 3590 were extended by an additional trial period of 26 weeks (Table 10).

All the therapeutic confirmatory trials were conducted with a treat-to-target principle; the insulin dose was adjusted for each individual subject with the aim of achieving identical glycaemic targets for IDegAsp and comparator products. Because both the IDegAsp and the comparator treatment were

adjusted to achieve glycaemic targets, a non-inferiority design was applied for all studies. Focus was thus also on other parameters, for instance the rate of hypoglycaemia. The clinical program is considered adequate as well as the overall design of the studies.

All trials included a 1-week follow-up period after completion of the treatment period.

All trials were conducted at sites across different continents except therapeutic confirmatory Trial 3597, which included sites in Japan, South Korea, Hong Kong, Malaysia and Taiwan only.

Study Participants

Inclusion Criteria

The inclusion criteria regarding diabetes duration and current anti-diabetic treatment were set to ensure that all subjects qualified for intensified treatment and thus reflected the intended diabetes population. An upper HbA_{1c} limit of 10.0% was introduced in all except one trial to ensure that noncompliant subjects were excluded. Subjects with an HbA_{1c} of 7.0–10.0% (both inclusive) were eligible, whereas for insulin-naïve subjects (Trial 3590) an HbA_{1c} of 7.5–11% (both inclusive) was required for inclusion.

Exclusion Criteria

The exclusion criteria were set to ensure a trial population in a stable disease state who were able to adhere to trial procedures. Subjects with significant concomitant illness, including renal impairment, were excluded, as they may need individualised therapy with less stringent treatment goals. Anti-diabetic treatments that may interfere significantly with trial endpoints were not allowed 3 months before screening, allowing an appropriate time for wash-out of such treatments before the trial.

Treatments

The drug product IDegAsp (100 U/mL, corresponding to 600 nmol/mL) contains the drug substances IDeg and IAsp. This product contains the drug substances IDeg and IAsp in the ratio 70/30. The FlexPen, currently used with Novo Nordisk A/S marketed products, was used for IDegAsp administration in Trials 1791, 1792, 3594, 3592, 3597 and 3593. The PDS290 prefilled pen-injector, used for IDegAsp administration in Trial 3590, is currently under development for use with IDeg/IDegAsp.

In T1DM (Trial 3594), subjects were transferred unit-to-unit from their pre-trial insulin treatment to IDegAsp OD + IAsp at remaining meals or IDet OD + IAsp at all meals. Insulin-naïve subjects with T2DM (Trial 3590) were initiated on once-daily insulin treatment with 10 U IDegAsp or IGlar. In the other T2DM trials (Trials 3593, 3592 and 3597), subjects switching from basal, premix or self-mixed insulin therapy were transferred to IDegAsp or comparator at the identical total insulin doses (unit-to-unit) as the subject's previous total daily insulin dose.

The starting doses for insulin-naïve subjects in the therapeutic exploratory trials were 10 U administered before dinner (Trial 1791) or 6 U for breakfast and 6 U for dinner (Trial 1792).

The initiation of IDegAsp or switch to IDegAsp was followed by dose optimisation and titration.

All the therapeutic confirmatory trials were conducted with a treat-to-target principle; the dose was adjusted for each individual subject with the aim of achieving identical glycaemic targets for IDegAsp and comparator products. The overall treatment goal in all therapeutic confirmatory trials was to achieve HbA_{1c} <7% and a pre-breakfast (fasting) SMPG <5.0 mmol/L (90 mg/dL). In trials with BID dosing an additional titration target of SMPG <5.0 mmol/L before the main evening meal was applied

for adjustment of the morning dose. The titration algorithm specified the recommended dose adjustments for IDegAsp and comparator at different PG levels.

Across the trials, various dosing times of IDegAsp were investigated. IDegAsp was dosed either OD or BID; please see Table 11.

Table 11 Dosing Schedules – Therapeutic Confirmatory Trials

Trial	IDegAsp dosing interval	IDegAsp dosing time	Comparator
T1DM			
3594	OD	with any main meal of the day (injection time could be moved to another meal at any time during the trial)	IDet[a] at the same time each day
T2DM			
3592	BID	with breakfast meal and main evening meal	BIAsp 30 BID with breakfast meal and main evening meal
3597	BID	with breakfast meal and main evening meal	BIAsp 30 BID with breakfast meal and main evening meal
3593	OD	with any meal[b] (same meal throughout trial)	IGlar OD according to label
3590	OD	with breakfast meal	IGlar OD according to label

[a]Dosed OD at evening meal or bedtime with the option of BID dosing after 8 weeks (i.e. a second IDet dose could be added after 8 weeks in case of inadequate glycaemic control). [b]Evening meal or the largest meal.

Concomitant Antidiabetic Treatment

Prandial bolus IAsp was used as concomitant treatment in Trial 3594 involving subjects with T1DM. IAsp was administered with all insulin requiring meals in the IDet arm and with the remaining insulin-requiring meals not covered by IDegAsp in the IDegAsp arm. No other concomitant antidiabetic treatment was allowed for subjects with T1DM.

The therapeutic confirmatory trials investigated the efficacy and safety of IDegAsp in combination with various types of OADs. It was required that subjects had been treated with the mandatory or allowed OADs for at least 3 months before inclusion in the trials. Use of insulin secretagogues, alpha-glucosidase inhibitors and GLP-1 agonists were not allowed as concomitant medication in any of the trials.

Choice of Comparator

In the therapeutic confirmatory trials including subjects with T2DM, IGlar OD was chosen as comparator to IDegAsp dosed OD, and BIAsp 30 BID was chosen as comparator to IDegAsp dosed BID. IGlar OD was selected as it exhibits a duration of action of around 24 hours and is approved for OD dosing. Furthermore, IGlar OD is one of the most widely used basal insulin analogues world-wide and has a well-known efficacy and safety profile. IDegAsp dosed OD was not compared to basal insulin in combination with one bolus injection as such a regimen did not reflect clinical practice when the confirmatory trials were initiated. The comparator BIAsp 30 BID was chosen since it is the most widely used pre-mixed insulin worldwide and it contains a basal component (intermediate-acting protamine IAsp) and the same rapid-acting component (IAsp) as IDegAsp.

IDet was the comparator in the trial including subjects with T1DM as it is an approved, well-established and widely used treatment in all countries participating in the trial and has a well-known efficacy and safety profile.

Objectives and endpoints

Primary Objective/Endpoints

The primary objective in all of the therapeutic confirmatory trials was to confirm the efficacy of IDegAsp in controlling glycaemia as measured by change from baseline in glycosylated haemoglobin A_{1c} (HbA_{1c}) after 26 weeks of treatment in subjects with T1DM or T2DM. This was done by comparing the difference in change of HbA_{1c} from baseline to end-of-treatment between IDegAsp and the active comparator. One exception was the extension, Trial 3645, where the primary endpoint was related to safety.

Secondary Objectives/Endpoints

The secondary objectives of the therapeutic confirmatory trials were to compare efficacy of IDegAsp to the active comparator in terms of:

- Proportion of subjects reaching prespecified HbA1c targets with or without hypoglycaemic episodes. Subjects achieving the predefined HbA1c targets at end of trial are designated as 'responders', and were recorded at end of trial.
- Laboratory-measured fasting plasma glucose (FPG). Blood samples were taken in fasting state before breakfast at baseline and after 12, 16 and 26 weeks of treatment, and after 27, 39 and 53 weeks in the extension to Trial 3594 (Trial 3645).
- 9-point self-measured plasma glucose (SMPG) profiles. In all trials, 9-point SMPG profiles were measured at baseline and after 12, 16 and 26 weeks of treatment.
- SMPG profiles for dose adjustments.
- Interstitial glucose (IG) profiles measured by continuous glucose monitoring (CGM) in a Interstitial glucose (IG) profiles measured by continuous glucose monitoring (CGM) in a subpopulation of subjects in selected trials. Continuous glucose monitoring (CGM) was employed in a subset of subjects at selected sites, in Trials 3593 and 3590. Measurements were made during a period up to 72 hours just before randomisation and 3–4 days before the last clinic visit of the trial.
- Patient-reported outcome (PRO). A self-completed patient-reported outcome (PRO) battery containing several questionnaires was used to investigate the subject's treatment satisfaction, productivity and health-related quality of life in relation to IDegAsp and comparator products during the course of the trials.

The safety objectives of importance for the efficacy evaluation were to compare IDegAsp to the active comparator in terms of:

- Hypoglycaemic episodes: severe, all confirmed (severe or plasma glucose < 3.1 mmol/L [56 mg/dL]), nocturnal confirmed. Throughout the trials, subjects recorded hypoglycaemic episodes in their diary, and the information was transferred to the case report forms. Confirmed hypoglycaemic episodes (severe or plasma glucose <3.1 mmol/L [56 mg/dL]) with an onset between 00:01 and 05:59 (both inclusive) were considered nocturnal.
- Body weight was measured at screening and at Weeks 0, 12, 16 and 26, and for trials of 52 weeks' duration, also at Weeks 40 and 52.
- Insulin dose. Starting at first visit after the randomisation visit, subjects were to report the insulin dose in the diary on three consecutive days before each visit, on the same days as the SMPG measurements, throughout the trial.

- Insulin antibodies. Specific insulin antibodies (IDeg, IAsp, IDet and/or IGlar specific antibodies) as well as insulin antibodies cross-reacting to human insulin were measured in T1DM Trial 3594/3645 and T2DM Trials 3590 and 3597.

Other important safety objectives in all trials were to compare safety in terms of adverse events (AEs) and clinical laboratory assessments.

Randomisation/Blinding (masking)

Participants were randomised 1:1 or 2:1 to each of the treatment arms. The unequal 2:1 randomisation was employed in two of the confirmatory trials in order to ensure an adequate total number of subjects exposed to IDegAsp in the development programme. Stratification was implemented in some but not all trials. In trials using stratification, participants were stratified according to prior anti-diabetic treatment (Table 10).

The various pen systems used for IDegAsp, IDet, BIAsp 30 and IGlar, as well as the different timing and frequency of dosing between treatment arms in some of the trials necessitated an open-label trial design in all trials. Use of a double-dummy design was considered unethical and not feasible because of the increased number of injections, risk of overdose and risk of mix-ups of insulin products. This justification is acceptable. The titration committee and most Novo Nordisk personnel involved in the trial conduct were blinded, but investigators were not.

Statistical methods

Adequate statistical methods were applied. Analysis of the endpoints evaluating the objectives was pre-planned for all trials. Some endpoints were prioritised as confirmatory endpoints in the individual trials and tested in a hierarchical manner.

Results

Participant flow

A total of 548 subjects with T1DM were randomised, and 542 were exposed to treatment (Table 12). In Trial 3594 and extension Trial 3645, T1DM subjects had a high completion rate and the proportion of withdrawals was comparable between the treatment groups. The withdrawal rate was similar in the treatment groups with the majority being due to 'Other' reasons. The reason most frequently stated in the category 'Other' was withdrawal at the subjects' own initiative. Few subject withdrawals were due to ineffective therapy (IDegAsp: 2; IDet: 0 subjects) or lack of effect within the category of subjects meeting withdrawal criteria (IDegAsp: 2; IDet: 0 subjects) in Trial 3594/3645 (Table 12).

Table 12 Subject Disposition – T1DM

Trial (wks)	IDegAsp OD N	(%)	IDet N	(%)	Total N	(%)
3594 (26)						
Randomised	366	(100.0)	182	(100.0)	548	(100.0)
Exposed	362	(98.9)	180	(98.9)	542	(98.9)
Withdrawn at/after Randomisation	46	(12.6)	26	(14.3)	72	(13.1)
Adverse Event	4	(1.1)	3	(1.6)	7	(1.3)
Ineffective Therapy	2	(0.5)			2	(0.4)
Non-Compliance With Protocol	8	(2.2)	6	(3.3)	14	(2.6)
Withdrawal Criteria	7	(1.9)	5	(2.7)	12	(2.2)
Other	25	(6.8)	12	(6.6)	37	(6.8)
Completed trial	320	(87.4)	156	(85.7)	476	(86.9)
Extension (3594/3645 (52))						
Included in Extension	254	(69.4)	122	(67.0)	376	(68.6)
Withdrawn during Extension	21	(5.7)	9	(4.9)	30	(5.5)
Adverse Event	3	(0.8)			3	(0.5)
Non-Compliance With Protocol	4	(1.1)	1	(0.5)	5	(0.9)
Withdrawal Criteria	2	(0.5)	1	(0.5)	3	(0.5)
Other	12	(3.3)	7	(3.8)	19	(3.5)
Completed Extension Trial	233	(63.7)	113	(62.1)	346	(63.1)
Full Analysis Set	366	(100.0)	182	(100.0)	548	(100.0)
PP Analysis Set	336	(91.8)	168	(92.3)	504	(92.0)

N: Number of subjects; %: Proportion of randomised subjects; Ineffective Therapy: Either documented by HbA_{1c} or undocumented at investigator discretion; PP: Per Protocol

In the four therapeutic confirmatory trials with T2DM subjects (Trials 3592, 3597, 3593 and 3590), a total of 1866 subjects were randomised and 1855 were exposed to treatment (Table 13). All therapeutic confirmatory trials in T2DM subjects had a high completion rate (85–88%), and the overall number of withdrawals within each trial was generally comparable among treatment groups with minor variations in the reasons for withdrawal (Table 13). The majority of the withdrawals both in the IDegAsp and comparator groups were due to subjects meeting a withdrawal criterion or 'Other' reasons. The reason most frequently stated in the category 'Other' was withdrawal of consent by the subject or violation of inclusion/exclusion criteria. The most common withdrawal criteria met were protocol deviations. In the four T2DM trials few subjects were withdrawn due to ineffective therapy (IDegAsp: 9; Comparator: 6 subjects) or lack of effect within the category of subjects meeting the withdrawal criteria (IDegAsp: 2; Comparator: 0 subjects); please see Table 13.

Table 13 Subject Disposition – T2DM

	IDegAsp N (%)	Comparator N (%)	Total N (%)
T2DM, Pooled Trials			
Randomised	1004 (100.0)	862 (100.0)	1866 (100.0)
Exposed	998 (99.4)	857 (99.4)	1855 (99.4)
Withdrawn at/after Randomisation	147 (14.6)	111 (12.9)	258 (13.8)
Adverse Event	18 (1.8)	13 (1.5)	31 (1.7)
Ineffective Therapy	9 (0.9)	6 (0.7)	15 (0.8)
Non-Compliance With Protocol	17 (1.7)	12 (1.4)	29 (1.6)
Withdrawal Criteria	45 (4.5)	31 (3.6)	76 (4.1)
Other	58 (5.8)	49 (5.7)	107 (5.7)
Completed	857 (85.4)	751 (87.1)	1608 (86.2)
Full Analysis Set	1000 (99.6)	860 (99.8)	1860 (99.7)
PP Analysis Set	895 (89.1)	776 (90.0)	1671 (89.5)

N: Number of subjects; %: Proportion of randomised subjects; Ineffective Therapy: Either documented by HbA1c or undocumented at investigator discretion; PP: Per Protocol; T2DM Pooled Trials: 3593, 3590, 3592 and 3597; Comparator: IGlar OD (3593, 3590) and BIAsp 30 BID (3592, 3597)

The time of withdrawal was comparable between treatment arms in each of the therapeutic confirmatory trial. In general, more subjects withdrew in the first half of the trials (0–12 weeks) compared to the second half of the trials (≥13 weeks).

Six subjects in the five therapeutic confirmatory trials were randomised in error and therefore not included in the FAS. The exclusion of these subjects from the FAS was documented with an appropriate justification in the individual CTRs.

Conduct of the study

One trial site was closed due to data quality issues, discovered before database lock. The site closure involved 11 subjects in Trial 3580 (IDeg 4, comparator 7), and 14 subjects in Trial 3582 (IDeg 11, comparator 3). In addition, 2 subjects in Trial 3579 (IDeg OD) were withdrawn before the site was closed. The actions taken with regards to handling of data from this site were acceptable.

In December 2010, Abbott recalled certain lots of Precision glucose test strips due to an error that potentially caused readings to be too low. The defect strips were used at some U.S. sites in Trials 3583, 3672, 3770 and 3839. The risk of experiencing too low readings was very low (maximally 0.099% of measurements) and the recall did not have any impact on the data quality and outcome of any of the Novo Nordisk A/S trials.

Baseline data

The groups were generally well balanced. The age in subjects with T1DM (Trial 3594/3645) was lower in the IDegAsp group than IDet group (40.7 vs. 42.6 years, mean age 41.3 years), while the age was similar between the treatment groups in subjects with T2DM (pooled Trials 3592, 3597, 3593 and 3590). The mean age in the T2DM trials was higher, 58.3 years. In total, 501 subjects were over 65 years of age and 66 subjects were over 75 years. In the pooled population including all IDegAsp + IDeg treated subjects, 86 elderly (>65 years) and 13 very elderly (>75 years) subjects with T1DM and 1034 elderly and 126 very elderly subjects with T2DM were exposed.

In the T1DM trial there was an overall equal distribution between male and females, while a somewhat lower proportion of males were seen in the comparator group (52 % IDegAsp vs. 45 % for comparator). In the T2DM trials slightly more than 50% of the all randomised subjects were males. In

general, men and women were equally distributed between the treatment groups with 47.0–58.7% male subjects in each of the T2DM trials. The potential effects of unequal male: female distribution is accounted for in the results, as sex was included as a covariate in the statistical analysis.

In the T1DM trial, 57.7% were from Europe, 30.5% from North America and 11.9% from Australia, and in the T2DM trials, 37.9% of the subjects were from Asia, 32.7% from Europe, 16.0% from North America, 9.6% from Japan, 2.5% from Australia and 1.3% from South Africa. Thus European patients were well represented in both T1DM and T2DM trials.

- *Baseline Diabetes Characteristics*

Diabetes characteristics were generally well balanced and representative for the target population. In the T1DM trial, mean HbA_{1c} was 8.3% in both treatment arms. The mean HbA_{1c} varied between 8.3 to 8.9% in the T2DM trials and was comparable between treatment groups.

Within the five therapeutic confirmatory trials the pretrial anti-diabetic treatment regiments were comparable between the treatment arms (Table 14). Participants were stratified according to prior anti-diabetic treatment in some of the trials (Table 10).

Table 14 Pretrial OAD Treatment – T2DM Pooled Trials

Trial (wks)	IDegAsp N	(%)	Comparator N	(%)	Total N	(%)
Alpha-glucosidase inhibitor	29	(2.9)	31	(3.6)	60	(3.2)
Acarbose	24	(2.4)	23	(2.7)	47	(2.5)
Miglitol	2	(0.2)	2	(0.2)	4	(0.2)
Voglibose	3	(0.3)	6	(0.7)	9	(0.5)
Biguanide	826	(82.6)	747	(86.9)	1573	(84.6)
Metformin	826	(82.6)	747	(86.9)	1573	(84.6)
DPP-4 inhibitor	50	(5.0)	66	(7.7)	116	(6.2)
Sitagliptin	38	(3.8)	53	(6.2)	91	(4.9)
Vildagliptin	10	(1.0)	13	(1.5)	23	(1.2)
Saxagliptin	2	(0.2)			2	(0.1)
Glinide	29	(2.9)	33	(3.8)	62	(3.3)
Repaglinide	21	(2.1)	27	(3.1)	48	(2.6)
Nateglinide	8	(0.8)	5	(0.6)	13	(0.7)
Mitiglinide			1	(0.1)	1	(0.1)
Sulphonylurea	401	(40.1)	378	(44.0)	779	(41.9)
Glibenclamide	112	(11.2)	103	(12.0)	215	(11.6)
Gliclazide	74	(7.4)	55	(6.4)	129	(6.9)
Glimepiride	173	(17.3)	172	(20.0)	345	(18.5)
Glipizide	40	(4.0)	47	(5.5)	87	(4.7)
Glyburide	2	(0.2)	1	(0.1)	3	(0.2)
Tolazamide	1	(0.1)			1	(0.1)
Thiazolidinedione	39	(3.9)	37	(4.3)	76	(4.1)
Pioglitazone	39	(3.9)	37	(4.3)	76	(4.1)

A subject can be on more than one OAD. IDegAsp: OD (3593, 3590) and BID (3592, 3597); Comparator: IGlar OD (3593, 3590) and BIAsp 30 BID (3592, 3597)

Overall, approximately 90% of the subjects in each treatment arms reported at least one concomitant illness at baseline. The most common concomitant illness reported was hypertension, with a lower incidence in the IDegAsp group (32.0%) than comparator group (40.0%). Other concomitant illnesses reported at baseline for at least 10% of the subjects were: diabetic retinopathy (26.9%), diabetic

neuropathy (17.9%), hypercholesterolaemia (12.9%), hyperlipidaemia (12.4%), hypothyroidism (10.9%), dyslipidaemia (10.3%) and depression (10.7%).

Around 97% of all subjects in the therapeutic confirmatory trials in subjects with T2DM had concomitant illness at baseline. The most common concomitant illness reported was hypertension (67.3%), with similar incidence across the IDegAsp and comparator group. Other concomitant illnesses reported at baseline for at least 10% of the subjects were hyperlipidaemia (27.2%), dyslipidaemia (23.8%), diabetic retinopathy (20.6%), diabetic neuropathy (15.0%) and cataract (12.1%).

Outcomes and estimation

Summary of Confirmatory Testing

- *Subjects with T1DM*

The conclusion of the confirmatory statistical analysis in Trial 3594 is presented in Table 15. IDegAsp improved long-term glycaemic control (HbA_{1c} non-inferior to IDet). Non-inferiority was shown both in the ITT and the PP population and the upper limit of the 95% CI was well below the predefined delta of 0.4 %. In terms of FPG reduction superiority of IDegAsp OD over IDet could not be confirmed (upper limit of 95% CI >0%), the hierarchical testing procedure was stopped and thus superiority could not be confirmed for the two remaining confirmatory secondary efficacy and safety endpoints.

No confirmatory analyses were done for the extension, Trial 3645.

Table 15 Conclusion of Confirmatory Statistical Analysis – T1DM – Trial 3594

	HbA_{1c} (%) (IDegAsp–IDet)	**FPG (mmol/L, *mg/dL*)** (IDegAsp–IDet)	**HbA_{1c} <7.0% without Severe Hypoglycaemia** (IDegAsp/IDet)	**Nocturnal Confirmed Hypoglycaemia** (IDegAsp/IDet)
Estimate [95% CI]:	-0.05 [-0.18;0.08]	0.23 [-0.46;0.91] *4.09 [-8.25; 16.43]*	1.24 [0.77;2.02]	0.63 [0.49;0.81]*
Test Conclusion:	**Non-inferiority**	Inconclusive	Testing Proc. Stopped	Testing Proc. Stopped

Columns appear in the order of the test priority. Data are estimated differences/ratios [95% CI]. Based on Full Analysis Set. *Difference statistically significant, but testing procedure was stopped.

- *Subjects with T2DM*

The conclusions of the confirmatory statistical analysis of Trials 3593 and 3590 with IDegAsp OD and Trials 3592 and 3597 with IDegAsp BID are presented in Table 16 and Table 17, respectively. Overall, IDegAsp improved long-term glycaemic control after 26 weeks when dosed both OD (HbA_{1c} non-inferior to IGlar OD, both in insulin-naïve subjects (Trial 3590) and subjects treated with insulin pretrial (Trial 3593)) and BID (HbA_{1c} non-inferior to BIAsp 30 BID).

The upper 95 % CI was well below the predefined delta of 0.4 % in all trials for both the ITT and the PP populations.

IDegAsp OD was superior to IGlar OD in terms of lowering prandial PG increment at breakfast (Trial 3590) and dinner (Trial 3593); please see Table 16. IDegAsp OD superiority to IGlar OD could not be confirmed for fluctuation in nocturnal IG (Trial 3590) or for subjects achieving HbA_{1c} <7.0% at end-of-trial without confirmed hypoglycaemia (Trial 3593) and thus the hierarchical testing procedure was stopped and superiority could not be confirmed for the remaining confirmatory secondary endpoints.

IDegAsp BID was superior to BIAsp 30 BID in terms of lowering FPG; please see Table 17. Furthermore, IDegAsp BID was superior to BIAsp 30 BID in terms of a lower rate of confirmed

hypoglycaemia in Trial 3592. Superiority could not be confirmed for the remaining confirmatory secondary endpoints.

Table 16 Conclusion of Confirmatory Statistical analysis – T2DM – IDegAsp OD

	HbA_{1c} (%) **(IDegAsp–IGlar)**	**Prandial PG Increment (mmol/L, *mg/dL*) Breakfast/Dinner[†] (IDegAsp–IGlar)**	**Fluctuation in Nocturnal IG (mmol/L, *mg/dL*) (IDegAsp/IGlar)**	**HbA_{1c} <7.0% without Confirmed Hypoglycaemia (IDegAsp/IGlar)**	**Nocturnal Confirmed Hypoglycaemia (IDegAsp/IGlar)**	**Body Weight (kg)** **(IDegAsp–IGlar)**
Trial 3593						
Estimate [95% CI]:	-0.03 [-0.20;0.14]	-1.32 [-1.93;-0.72] -23.86 [-34.74;-12.98]	0.97 [0.74;1.28] 0.97 [0.74;1.28]	0.80 [0.50;1.30]	0.80 [0.49;1.30]	0.33 [-0.17;0.83]
Test Conclusion:	**Non-inferiority**	**Superiority**	Testing Proc. Stopped	Inconclusive	Testing Proc. Stopped	Testing Proc. Stopped
Trial 3590						
Estimate [95% CI]:	0.03 [-0.14;0.20]	-1.40 [-1.92;-0.88] -25.22 [-34.52;-15.92]	0.69 [0.25;1.92] 0.69 [0.25;1.92]	0.61 [0.40;0.94]	0.29 [0.13;0.65]*	1.31 [0.72;1.89]
Test Conclusion:	**Non-inferiority**	**Superiority**	Inconclusive	Testing Proc. Stopped	Testing Proc. Stopped	Testing Proc. Stopped

Note: Columns appear in the order of the test priority for Trial 3590, in Trial 3593 the endpoint HbA_{1c} <7.0% without confirmed hypoglycaemia was tested before fluctuation in nocturnal IG. IG: interstitial glucose; IGlar: IGlar OD; PG: plasma glucose. Data are estimated difference [95% CI] or ratio [95% CI]. Based on Full Analysis Set. [†]At breakfast for Trial 3590, at dinner for Trial 3593.*Difference statistically significant.

Table 17 Conclusion of Confirmatory Statistical analysis – T2DM – IDegAsp BID

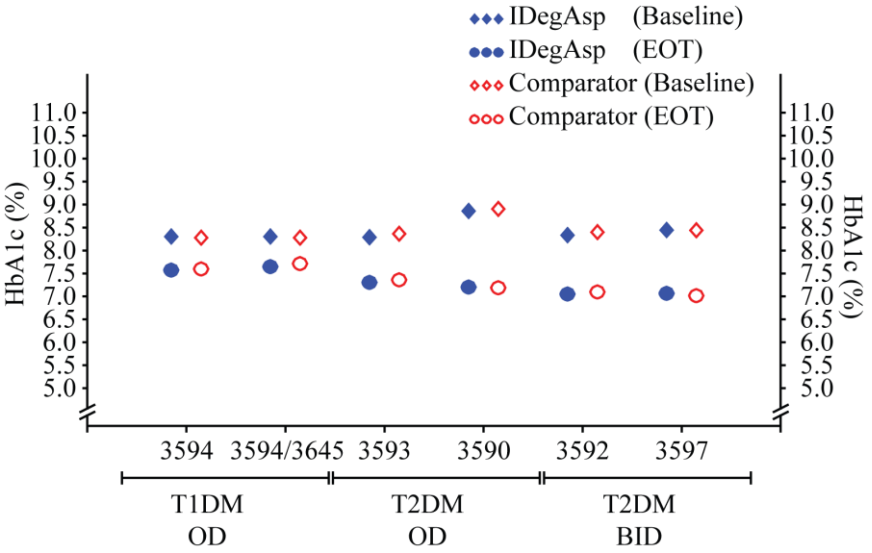
	HbA_{1c} (%) **(IDegAsp–BIAsp)**	**FPG (mmol/L, *mg/dL*)** **(IDegAsp–BIAsp)**	**Confirmed Hypo-glycaemia** **(IDegAsp-BIAsp)**	**HbA_{1c} <7.0% without Confirmed Hypo-glycaemia (IDegAsp-BIAsp)**	**Body Weight (kg)** **(IDegAsp–BIAsp)**	**Nocturnal Confirmed Hypo-glycaemia (IDegAsp-BIAsp)**
Trial 3592						
Estimate [95% CI]:	-0.03 [-0.18;0.13]	-1.14 [-1.53;-0.76] -20.57 [-27.51;-13.63]	0.68 [0.52;0.89]	1.60 [0.94;2.72]	-0.62 [-1.15;-0.10]*	0.27 [0.18;0.41]*
Test Conclusion:	**Non-inferiority**	**Superiority**	**Superiority**	Inconclusive	Testing Proc. Stopped	Testing Proc. Stopped
Trial 3597						
Estimate [95% CI]:	0.05 [-0.10;0.20]	-1.06 [-1.43;-0.70] -19.15 [-25.69;-12.62]	1.00 [0.76;1.32]	1.77 [0.97;3.25]	-0.38 [-0.96;0.21]	0.67 [0.43;1.06]
Test Conclusion:	**Non-inferiority**	**Superiority**	Inconclusive	Testing Proc. Stopped	Testing Proc. Stopped	Testing Proc. Stopped

Note: Columns appear in the order of the test priority. Data are estimated difference [95% CI] or ratio [95% CI]. BIAsp: BIAsp 30 BID; FPG: fasting plasma glucose (central lab). Based on Full Analysis Set. *Difference statistically significant.

Primary Efficacy Endpoint: Change in HbA1c

The change in HbA1c for all trials is summarised in Figure 12. For trials with T2DM the end-of-trial mean HbA1c values were close to the ADA recommended target of 7%.

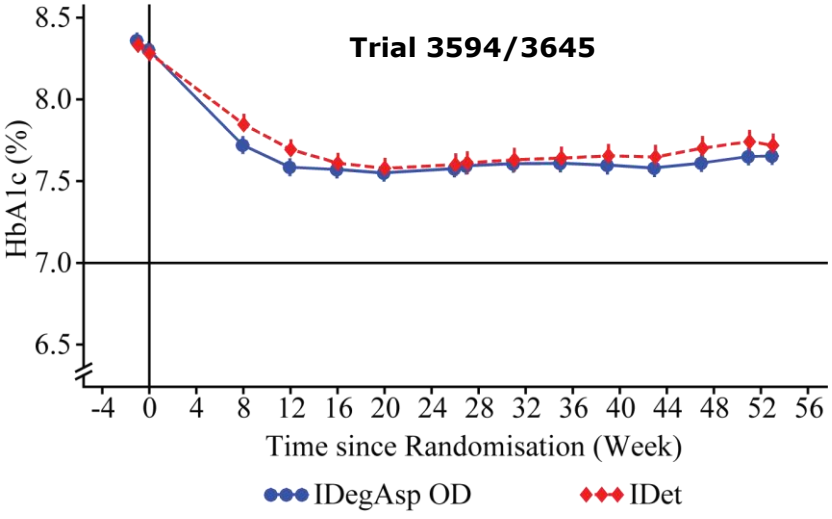
Figure 12 Mean HbA1c (%) at Baseline and End-of-trial



EOT: End-of-trial; Comparator: IDet (Trial 3594/3645) IGlar OD (Trials 3593 and 3590) and BIAsp 30 BID (Trials 3592 and 3597). LOCF imputed. Based on Full Analysis Set

Subjects with T1DM treated with IDegAsp OD in combination with IAsp improved long-term glycaemic control after 26 and 52 weeks of treatment. Mean HbA_{1c} decreased during the trial in the IDegAsp OD group and the comparator group treated with IDet (Figure 13). The reduction in HbA_{1c} was evident after the first 8 weeks of treatment, and after 26 weeks the observed HbA_{1c} reduction was 0.73 %-points in the IDegAsp group, comparable to the 0.68 %-point reduction in the IDet group. The reduction was still evident after 52 weeks in both treatment groups.

Figure 13 Mean HbA1c (± SEM) over Time – T1DM



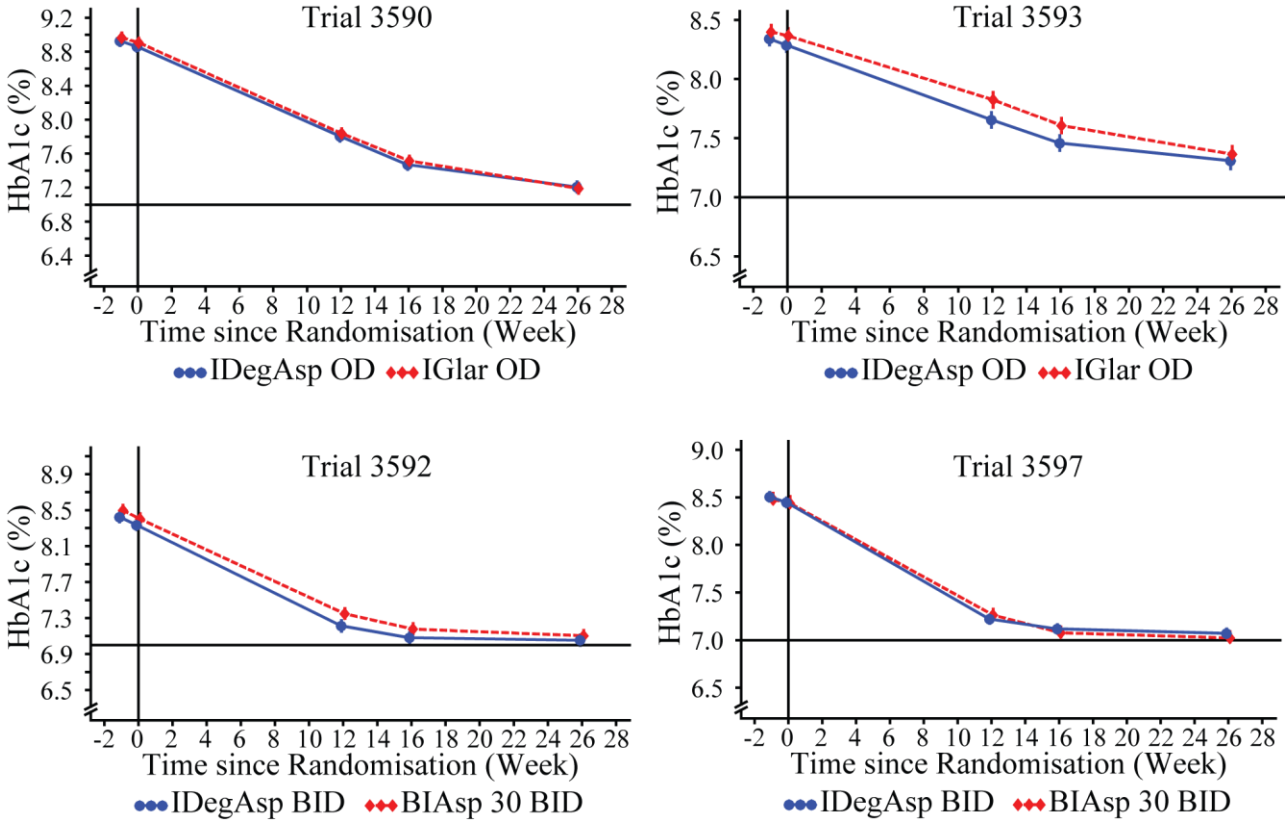
LOCF imputed data. Based on Full Analysis Set.

The reduction in HbA_{1c} was similar after 26 weeks and 52 weeks of IDegAsp OD treatment, demonstrating that the initial improvement in HbA_{1c} could be maintained for one year. There was no statistically significant difference in the lowering of HbA_{1c} in the IDegAsp OD group compared with the IDet group after 52 weeks of treatment.

For subjects completing the full 52 weeks the results were in the same direction as after 26 weeks and the larger HbA_{1c} reduction for IDegAsp than IDet was now statistically significant (estimated treatment difference: -0.16 $[-0.30; -0.02]_{95\%CI}$).

IDegAsp OD and BID effectively improved long-term glycaemic control in subjects with T2DM. Mean HbA_{1c} decreased throughout the trials in all IDegAsp treatment groups (Figure 14).

Figure 14 Mean HbA1c (± SEM) over Time for IDegAsp and Comparator – T2DM



LOCF imputed data. Based on Full Analysis Set.

After 26 weeks of IDegAsp OD treatment, the mean HbA_{1c} was 7.21% in Trial 3590 and 7.31% in Trial 3593. The observed mean reduction from baseline after IDegAsp OD treatment was higher in the insulin-naïve subjects of Trial 3590 (1.65 %-points) than the subjects treated with insulin pretrial in Trial 3593 (0.98 %-points). These reductions were comparable to the HbA_{1c} reduction in the IGlar OD group of each trial.

Treatment with IDegAsp BID for 26 weeks led to an observed mean HbA_{1c} of 7.05% and 7.07% in Trials 3592 and 3597, respectively. The observed mean reduction from baseline to end-of-trial in the IDegAsp group was 1.28 %-point in Trial 3592 and 1.38 %-point in Trial 3597, similar to the reduction after BIAsp 30 BID treatment.

Secondary Efficacy Endpoints

- *Subjects with T1DM Achieving HbA1c Targets*

The proportion of subjects reaching HbA_{1c} <7.0% after 26 weeks treatment was higher for IDegAsp OD-treated subjects (24.6%) compared with IDet-treated subjects (20.3%) in Trial 3594. After 52 weeks of treatment (Trial 3594/3645) the proportion of subjects reaching the ADA target remained higher for IDegAsp OD, 22.4% compared with 17.0% for IDet. The treatment differences were not statistically significant.

The proportion of subjects achieving HbA_{1c} <7.0% without severe hypoglycaemia was higher for IDegAsp OD compared with IDet treated subjects both after 26 weeks and 52 weeks of treatment: IDegAsp OD 24.3% (26 weeks) and 22.0% (52 weeks), IDet 20.7% (26 weeks) and 16.6% (52 weeks). As these subjects had to be exposed for 12 weeks, the proportions can be higher compared with the proportions of subjects achieving HbA_{1c} <7.0%. The treatment differences were not statistically significant.

The proportion of subjects achieving HbA_{1c} <7.0% without confirmed hypoglycaemia was low, both in the IDegAsp OD group (26 weeks: 4.5%; 52 weeks: 5.3%) and the IDet group (26 weeks: 3.0%; 52 weeks: 3.6%), as might be predicted in individuals with T1DM on basal–bolus insulin therapy. The treatment differences were not statistically significant.

- *Subjects Reaching HbA1c Targets in T2DM*

After 26 weeks of IDegAsp OD treatment, 45.9% of the subject in Trial 3590 and 40.0% of the subjects in Trial 3593 reached HbA_{1c} <7.0%, comparable to the results from the IGlar OD groups (45.6% in Trial 3590 and 36.5% in Trial 3593). There were no statistically significant differences between IDegAsp OD and IGlar OD in any of the trials.

The proportion of subjects reaching the ADA target of HbA_{1c} <7.0% after IDegAsp BID treatment was 50.4% (Trial 3592) and 48.2% (Trial 3597), comparable to BIAsp 30 BID treatment results, 48.6% and 49.3%. There were no statistically significant differences between the IDegAsp BID and BIAsp 30 BID groups.

The proportion of subjects who achieved HbA_{1c} <7.0% without confirmed hypoglycaemia was lower for IDegAsp OD (23.6 and 20.9%) compared with IGlar OD (30.7 and 23.5%) in Trials 3590 and 3593, respectively. This difference was statistically significant in Trial 3590 with pretrial insulin-naïve subjects, but not in Trial 3593.

In Trials 3592 and 3597 the proportion of subjects achieving HbA_{1c} <7.0% without confirmed hypoglycaemia was higher for IDegAsp BID (21.8 and 21.9%) compared with BIAsp 30 BID (14.9 and 13.2%). These differences were not statistically significant.

The proportion of subjects achieving HbA_{1c} <7.0% without severe hypoglycaemia in T2DM were high in all treatment groups, reflecting the low incidence of severe hypoglycaemia and overall the proportion was. There were no statistically significant differences between IDegAsp OD or BID and comparator in any of the T2DM trials.

- *FPG (Central Laboratory)*

FPG decreased with both IDegAsp and comparator in all trials. The FPG values at end-of-trial were lower with IDegAsp BID than with BIAsp 30 BID in subjects with T2DM, and the FPG was similar or higher with IDegAsp OD than with comparators at end-of-trial in subjects with T1DM and T2DM.

- *9-Point SMPG Profiles*

In T1DM subjects, the 9-point profiles were lower than baseline after 26 and 52 weeks of IDegAsp OD and IDet treatment, both in combination with IAsp. The 9-point profile was similar between IDegAsp OD and IDet treatment after 52 weeks, except before lunch and the evening meal where the mean PG value was lower for IDegAsp OD than for IDet. A similar pattern was seen after 26 weeks.

In all T2DM trials, the 9-point profiles improved after 26 weeks compared to baseline. No differences were observed between IDegAsp and the comparators.

- *SMPG Used for Dose Adjustments*

In T1DM subjects, the pre-breakfast titration target of SMPG <5 mmol/L (90 mg/dL) was met by a similar proportion of subjects in the IDegAsp OD group and IDet group after 26 weeks (IDegAsp OD: 16.9%; IDet: 16.0%) and 52 weeks (IDegAsp OD: 15.0%; IDet: 17.7%). The median time to reach titration target for the first time was 9 weeks for IDegAsp OD and 12 weeks for IGlar OD treated subjects. There were no statistically significant differences.

In T2DM subjects, the pre-breakfast titration target of SMPG <5 mmol/L (90 mg/dL) was met by a lower proportion of subjects in the IDegAsp OD group compared with the IGlar OD group after 26 weeks in both Trial 3590 (IDegAsp OD: 13.9%; IGlar OD: 28.5%) and Trial 3593 (IDegAsp OD: 23.0%; IGlar OD: 36.1%). The median time to achieving the pre-breakfast SMPG titration target of <5 mmol/L for the first time was longer for IDegAsp OD than IGlar OD in Trial 3590 (23 versus 13 weeks) and 3593 (11 versus 9 weeks).

The pre-breakfast titration target of SMPG <5 mmol/L (90 mg/dL) was met by a higher proportion of subjects in the IDegAsp BID group compared with the BIAsp 30 BID group after 26 weeks in both Trial 3592 (IDegAsp BID: 37.9%; BIAsp 30 BID: 23.0%) and Trial 3597 (IDegAsp BID: 33.9%; BIAsp 30 BID: 14.2%). The before main meal target of SMPG <5 mmol/L was met by 13.6 to 14.7% in the IDegAsp BID group and 8.5 to 13.1% in the BIAsp 30 BID group in Trials 3592 and 3597. The median time to achieving the pre-breakfast SMPG titration target of <5 mmol/L for the first time was shorter for IDegAsp BID than BIAsp 30 in both Trial 3592 (5 versus 13 weeks) and Trial 3597 (5 versus 21 weeks).

- *Interstitial Glucose Profiles by Continuous Glucose Monitoring*

In the subgroup of T2DM subjects who underwent CGM, fluctuation of the nocturnal IG profiles was reduced after 26 weeks treatment in Trial 3593 with both IDegAsp OD and IGlar OD and slightly reduced in the IDegAsp OD group of Trial 3590.

- *Patient-reported Outcome*

In general only modest changes were observed in the quality of life assessment. In subjects with T1DM, mean physical and mental scores in the SF-36 v2 were unchanged during Trial 3594, both with IDegAsp OD and IDet. In subjects with T2DM, physical and mental scores measured by SF-36v2 changed marginally from baseline to end-of-trial with IDegAsp OD, IDegAsp BID and comparators.

Safety Endpoints as Part of Efficacy Evaluation

Across the therapeutic confirmatory trials, subjects treated with IDegAsp experienced fewer nocturnal hypoglycaemic episodes than with comparators; please see Figure 15. Overall rates of confirmed hypoglycaemic episodes were similar or higher with IDegAsp OD than with comparator in subjects with T1DM and T2DM, while T2DM subjects treated with IDegAsp BID experienced fewer confirmed hypoglycaemic episodes than with BIAsp 30 BID (data are summarized in Table 18, Table 19 and Table 20).

Table 18 Hypoglycaemic Episodes by Classification – T1DM – IDegAsp OD – SAS

	IDegAsp				Comparator			
Trial	N	(%)	E	R	N	(%)	E	R
3594/3645 Number of Subjects	362				180			
3594/3645 Severe	48	(13.3)	79	26.6	33	(18.3)	65	44.7
3594/3645 Confirmed	344	(95.0)	9450	3183.1	169	(93.9)	5342	3672.6
3594/3645 Nocturnal severe	13	(3.6)	14	4.7	14	(7.8)	28	19.2
3594/3645 Nocturnal confirmed	221	(61.0)	918	309.2	135	(75.0)	787	541.1

N: number of subjects;%: percentage of subjects; E: number of events; R: event rate per 100 exposure years; confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG <3.1 mmol/L (56 mg/dL); Nocturnal: the period between 00:01 and 05:59 (both included)3594/3645: 3594 including extension part 3645; Comparator: IDet

Table 19 Hypoglycaemic Episodes by Classification – T2DM – IDegAsp OD – SAS

	IDegAsp				Comparator			
Trial	N	(%)	E	R	N	(%)	E	R
3590 Number of Subjects	265				261			
3593 Number of Subjects	230				233			
3590 Severe	1	(0.4)	1	0.8	1	(0.4)	1	0.8
3593 Severe	0		0		3	(1.3)	4	3.7
3590 Confirmed	132	(49.8)	500	422.8	96	(36.8)	226	185.3
3593 Confirmed	121	(52.6)	451	431.4	112	(48.1)	344	320.1
3590 Nocturnal severe	0		0		0		0	
3593 Nocturnal severe	0		0		0		0	
3590 Nocturnal confirmed	13	(4.9)	22	18.6	30	(11.5)	56	45.9
3593 Nocturnal confirmed	44	(19.1)	86	82.3	49	(21.0)	108	100.5

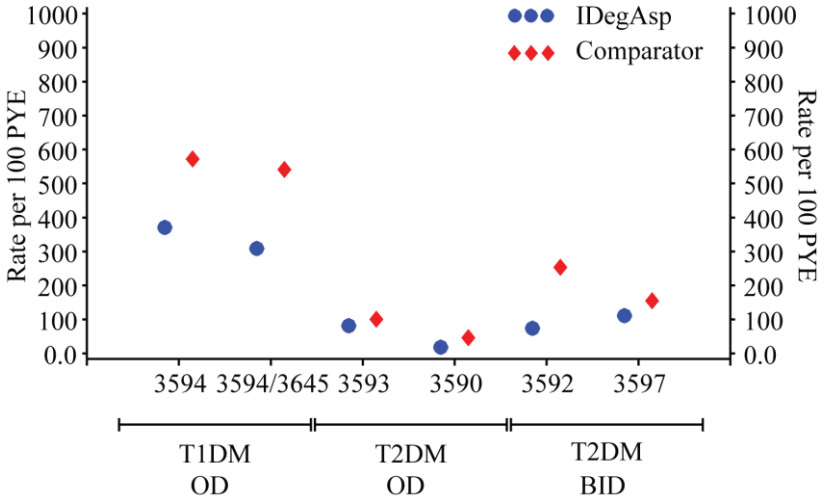
N: number of subjects;%: percentage of subjects; E: number of events; R: event rate per 100 exposure years; Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG <3.1 mmol/L (56 mg/dL); Nocturnal: the period between 00:01 and 05:59 (both included); Comparator: IGlar

Table 20 Hypoglycaemic Episodes by Classification – Treatment Emergent – T2DM – IDegAsp BID – SAS

	IDegAsp				Comparator			
Trial	N	(%)	E	R	N	(%)	E	R
3592 Number of Subjects	224				222			
3597 Number of subjects	279				141			
3592 Severe	7	(3.1)	9	8.8	16	(7.2)	25	25.3
3597 Severe	4	(1.4)	6	4.7	2	(1.4)	2	3.1
3592 Confirmed	148	(66.1)	993	971.7	153	(68.9)	1379	1396.3
3597 Confirmed	205	(73.5)	1227	956.0	107	(75.9)	621	952.3
3592 Nocturnal severe	1	(0.4)	1	1.0	8	(3.6)	9	9.1
3597 Nocturnal severe	1	(0.4)	1	0.8				
3592 Nocturnal confirmed	52	(23.2)	76	74.4	80	(36.0)	250	53.1
3597 Nocturnal confirmed	70	(25.1)	143	111.4	44	(31.2)	101	154.9

N: number of subjects;%: percentage of subjects; E: number of events; R: event rate per 100 exposure years;. Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG <3.1 mmol/L (56 mg/dL); Nocturnal: the period between 00:01 and 05:59 (both included); Comparator BiAsp 30

Figure 15 Nocturnal Confirmed Hypoglycaemic Episodes – Plot of Rates



Comparator: IDet (Trial 3594/3645) IGlar OD (Trials 3593 and 3590) and BIAsp 30 BID (Trials 3592 and 3597)
Based on Safety Analysis Set.

Confirmed Hypoglycaemia: Subjects with T1DM – IDegAsp OD

The majority of subjects (approximately 95%) treated with IDegAsp OD or IDet both in combination with mealtime IAsp for 52 weeks experienced at least one episode of confirmed hypoglycaemia. Most (up to 90%) episodes of confirmed hypoglycaemia occur during daytime (from 06:00 to 00:00). There was no statistically significant difference between treatment groups; estimated rate ratio (IDegAsp OD/IDet) 0.95 $[0.79; 1.14]_{95\%CI}$. The confirmed hypoglycaemic episodes was also analysed using the extension trial set (i.e. all subjects receiving at least one dose of the investigational product or its comparator in the extension part), results were in accordance with those from the FAS.

Nocturnal Confirmed Hypoglycaemia: Subjects with T1DM – IDegAsp OD

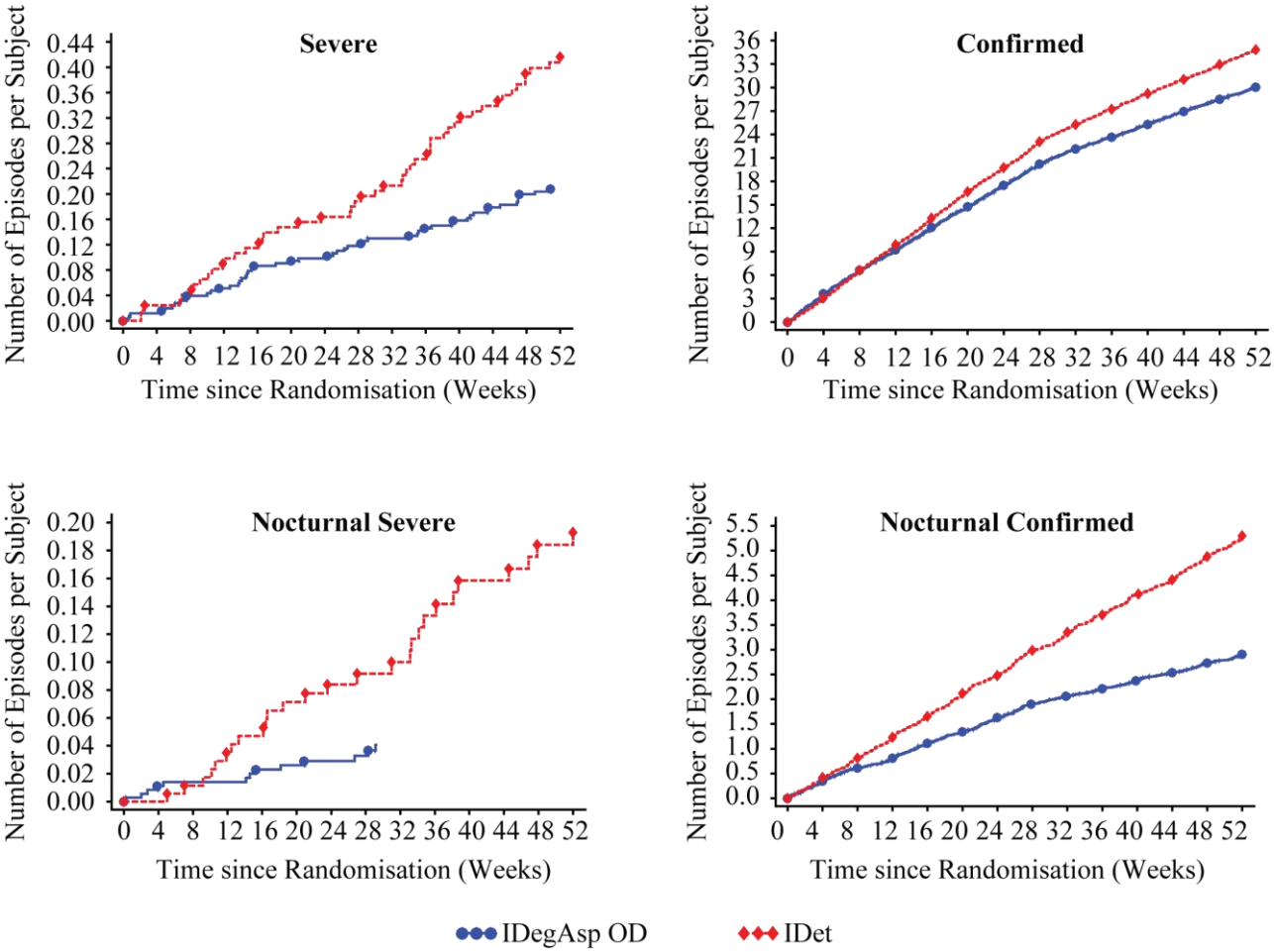
Subjects treated with IDegAsp OD in combination with mealtime IAsp experienced fewer nocturnal confirmed and nocturnal severe hypoglycaemic episodes than IDet + IAsp in Trial 3594/3645. The estimated rate of nocturnal confirmed hypoglycaemia was 38% lower with IDegAsp OD than with IDet after 52 weeks' treatment, and this was statistically significant. Nocturnal confirmed hypoglycaemia was a confirmatory endpoint in Trial 3594, and superiority based on hierarchical testing could not be formally confirmed as the testing procedure was stopped prior to testing this endpoint.

For nocturnal severe hypoglycaemia, the estimated rate was 65% lower with IDegAsp OD than with IDet, and the difference was statistically significant with an estimated rate ratio of $0.35\ [0.14; 0.87]_{95\%CI}$.

Treatment Emergent Hypoglycaemia over Time: Subjects with T1DM – IDegAsp OD

After the initial 12–16 weeks of treatment, the number of hypoglycaemic episodes tapered off in the IDegAsp OD group compared with the IDet group; please see Figure 16.

Figure 16 Hypoglycaemic Episodes – Mean Cumulative Function – T1DM – Trial 3594/3645



Based on Safety Analysis Set. No nocturnal severe hypoglycaemic episodes were reported in the IDegAsp OD group between Week 30 and end-of-trial, explaining why the line for nocturnal severe hypoglycaemia stops at Week 30.

Severe and Confirmed Hypoglycaemia: Subjects with T2DM – IDegAsp OD

In the trials utilizing once daily IDegAsp or IGlar (Trials 3590 and 3593) few or no events of severe hypoglycaemia were reported in the IDegAsp OD and IGlar OD treatment groups. The rate of SAEs related to hypoglycaemia was similar in the IDegAsp and the comparator groups for subjects with T2DM. No subjects with T2DM withdrew from the trials due to hypoglycaemia reported as 'adverse event'. Few subjects (IDegAsp OD: 2 subjects; IGlar: 0 subjects) withdrew due to the withdrawal criterion "Hypoglycaemia causing a safety problem". In addition, 1 subject in the IDegAsp OD group and none in the comparator group withdrew from the trial due to the withdrawal category 'Other' including a comment mentioning hypoglycaemia. None of these withdrawals occurred within the first month of treatment. With reference to the low number of events, withdrawal of subjects due to hypoglycaemia did not affect conclusions on hypoglycaemia.

A similar proportion of subjects (~50%) in the two treatment groups did not experience confirmed hypoglycaemic episodes in Trial 3593. In Trial 3590, the proportion of subjects experiencing confirmed hypoglycaemic episodes was higher in the IDegAsp OD group compared with IGlar. Also, the rate of confirmed hypoglycaemic episodes was statistically significantly higher with IDegAsp than IGlar; estimated treatment ratio 2.17 $[1.59; 2.94]_{95\%CI}$ and 1.43 $[1.07; 1.92]_{95\%CI}$ in Trials 3590 and 3593, respectively. This imbalance in hypoglycaemias was raised as a major objection in the Day 120 LoQ, together with the significantly higher increase in body weight was observed with IDegAsp treatment than with the comparator in study 3590. In the responses the Applicant demonstrated that the

increased rates of hypoglycaemias and body weight in studies 3590 and 3593 were related to the study design rather than to IDegAsp per se. The Applicant has also provided new data supporting the recommendation given in the SmPC to take IDegAsp with the largest meal of the day.

In Trial 3590 IDegAsp OD was dosed with the morning meal, whereas subjects in Trial 3593 administered IDegAsp OD at their main evening meal or largest meal of the day, thereby accommodating individual lifestyles and dietary patterns. The data on confirmed hypoglycaemia and timing of hypoglycaemia in the two trials reflected the time of injection. In Trial 3590 most confirmed hypoglycaemic episodes (~70%) occurred between 8:00 and 14:00 in Trial 3590, whereas the confirmed episodes in Trial 3593 occurred evenly throughout the day. The results point to the importance of administrating IDegAsp OD with the largest meal of the day, customised to the individual.

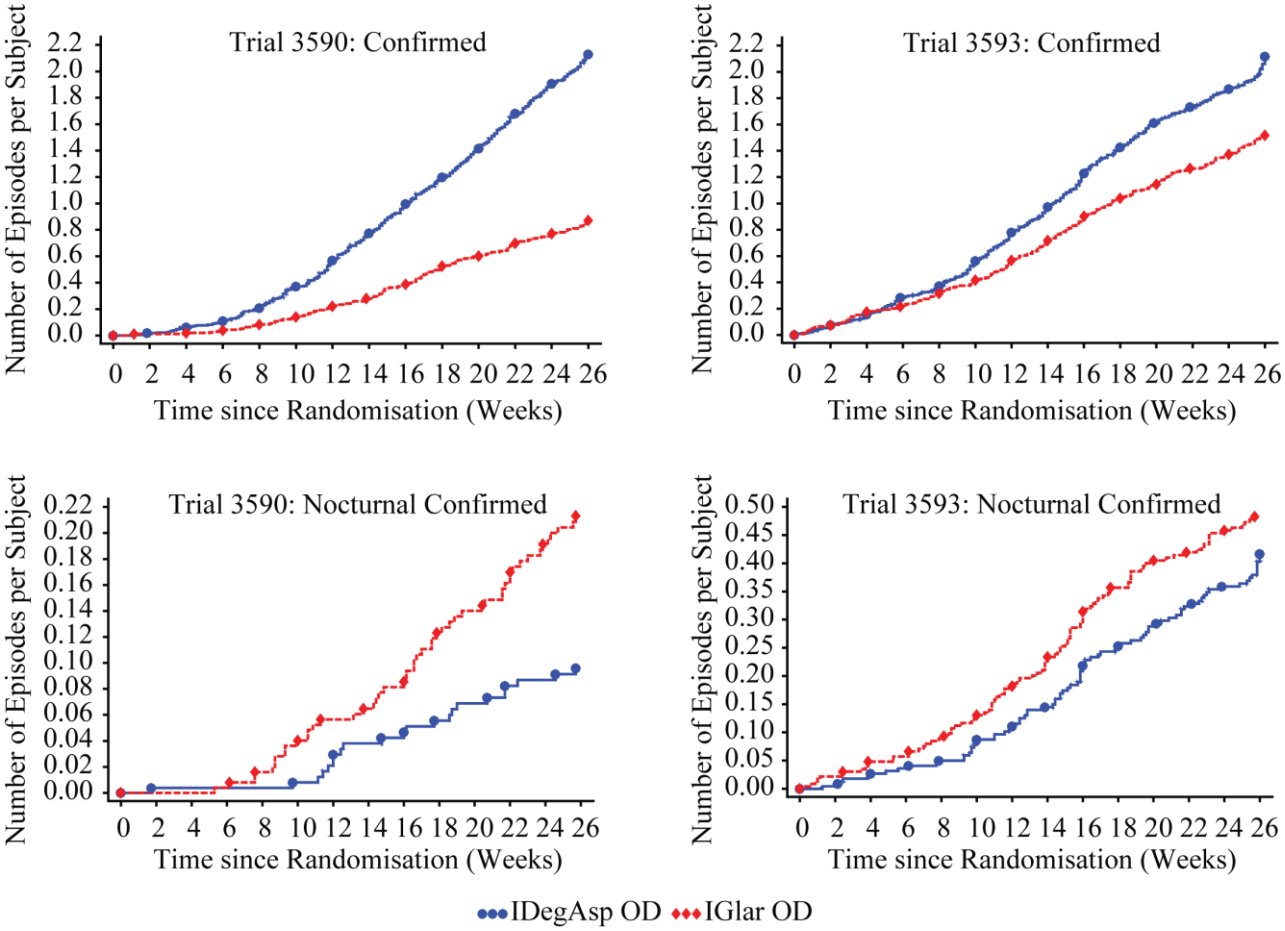
Nocturnal Confirmed Hypoglycaemia: Subjects with T2DM – IDegAsp OD

Subjects treated with IDegAsp OD experienced fewer episodes of nocturnal confirmed hypoglycaemia compared to subjects treated with IGlar in both Trials 3590 and 3593. The rate of nocturnal confirmed hypoglycaemia was statistically significantly lower with IDegAsp OD compared with IGlar. Nocturnal confirmed hypoglycaemia was a confirmatory endpoint. Superiority based on hierarchical testing could not be formally demonstrated as the testing procedure was stopped prior to testing this endpoint. In Trial 3593, the estimated rate of nocturnal confirmed hypoglycaemia was 20% lower for IDegAsp OD compared with IGlar OD. The difference was not statistically significant. No nocturnal severe episodes were reported during the trials.

Treatment Emergent Hypoglycaemia over Time: Subjects with T2DM – IDegAsp OD

A lower rate of nocturnal confirmed hypoglycaemic episodes was observed for IDegAsp OD compared with IGlar over time during Trials 3590 and 3593; please see Figure 17. The difference in the rate of confirmed hypoglycaemic episodes between treatment groups was less pronounced during the first part (from Week 1 to Week 8) of Trials 3593 and 3590, followed by a higher rate of hypoglycaemic episodes in the IDegAsp OD group than the IGlar group during the latter part of the trials.

Figure 17 Hypoglycaemic Episodes – Mean Cumulative Function – T2DM – IDegAsp OD



Based on the Safety Analysis Set

Severe and Confirmed Hypoglycaemia: Subjects with T2DM – IDegAsp BID

The rate of severe hypoglycaemia was numerically lower with IDegAsp BID than BIAsp 30 BID in Trial 3592 and similar in Trial 3597. The rate of SAEs related to hypoglycaemia was similar in the IDegAsp and the comparator groups for subjects with T2DM. No subjects with T2DM withdrew from the trials due to hypoglycaemia reported as 'adverse event'. Few subjects (IDegAsp BID: 3 subjects; BIAsp 30 BID: 1 subject) withdrew due to the withdrawal criterion "Hypoglycaemia causing a safety problem". One of the withdrawals in the IDegAsp group occurred within the first month of treatment (in Trial 3597). In addition, 3 subjects in the BIAsp 30 BID group and none in the IDegAsp group withdrew from the trial due to the withdrawal category 'Other' including a comment mentioning hypoglycaemia. Taken together, withdrawal of subjects due to hypoglycaemia did not affect the conclusions on hypoglycaemia.

IDegAsp BID was superior to BIAsp 30 BID in terms of a 32% lower rate of confirmed hypoglycaemic episodes in Trial 3592 (estimated rate ratio (IDegAsp BID/BIAsp 30 BID): 0.68 $[0.52; 0.89]_{95\%CI}$); please see Table 17. Confirmed hypoglycaemia was a confirmatory endpoint in Trial 3592, and superiority based on hierarchical testing was demonstrated.

The rate of confirmed hypoglycaemia in the IDegAsp BID group was comparable across trials (3592, 3597 and 1792). In Trial 3597, conducted in Asian countries where BIAsp 30 BID is the standard of care for subjects with T2DM, rates of confirmed hypoglycaemia with BIAsp 30 BID were as low as for IDegAsp BID, and there were no statistically significant treatment differences; estimated rate ratio: 1.00 $[0.76; 1.32]_{95\%CI}$.

Over 24 hours, the highest rate of confirmed hypoglycaemic episodes was observed during 06:00 to 14:00 with both IDegAsp BID and BIAsp 30 BID.

Nocturnal Confirmed Hypoglycaemia: Subjects with T2DM – IDegAsp BID

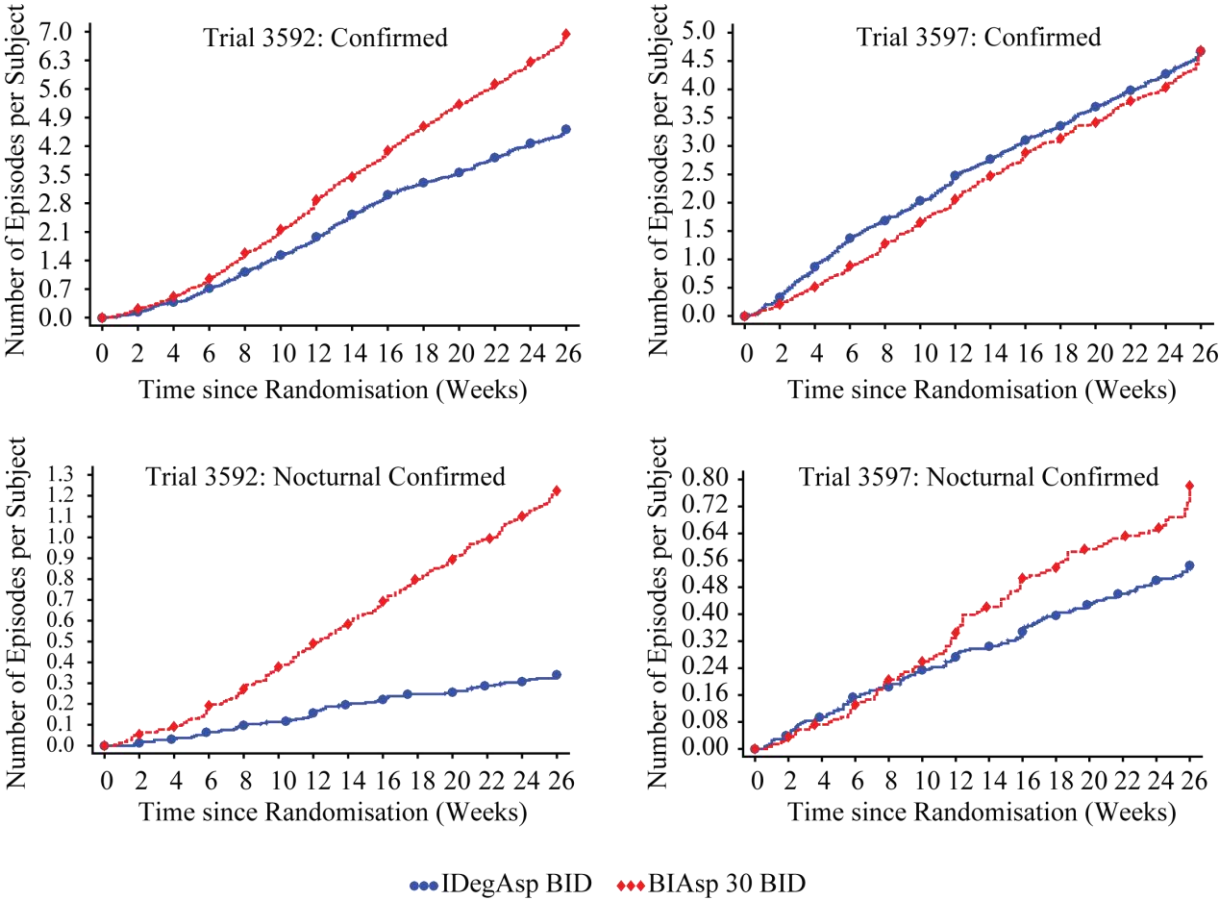
Across Trials 3592 and 3597, subjects treated with IDegAsp BID experienced fewer episodes of nocturnal confirmed hypoglycaemia than on BIAsp 30 BID. The 73% lower rate of nocturnal confirmed hypoglycaemia with IDegAsp BID treatment was statistically significant different from BIAsp 30 BID in Trial 3592. Nocturnal confirmed hypoglycaemia was a confirmatory endpoint in Trial 3592 and based on hierarchical testing superiority could not be formally confirmed as the testing procedure was stopped prior to testing this endpoint. In Trial 3597 with Asian subjects the estimated ratio was 33% lower for IDegAsp BID compared with BIAsp 30 BID. The difference was not statistically significant.

The lower nocturnal confirmed hypoglycaemia rates were achieved in the presence of a statistically significantly lower mean FPG at end-of-trial in both Trials 3592 and 3597 and use of a similar or lower total daily insulin dose. Few nocturnal severe episodes were reported during the trials.

Treatment Emergent Hypoglycaemia over Time: Subjects with T2DM – IDegAsp BID

The lower rate of confirmed hypoglycaemia with IDegAsp BID compared with BIAsp 30 BID in Trial 3592 became evident after 4 weeks of treatment (Figure 18). In Trial 3597, the rate of confirmed hypoglycaemic episodes was rather constant throughout the trial in both treatment groups. The number of nocturnal confirmed hypoglycaemic episodes tapered off in the IDegAsp BID group compared with the BIAsp 30 BID group after the initial 4–12 weeks of treatment (Figure 18).

Figure 18 Hypoglycaemic Episodes – Mean Cumulative Function – T2DM – IDegAsp BID



Based on Safety Analysis Set.

Body Weight

Subjects with T1DM – IDegAsp OD

Body weight increased in both treatment groups as can be expected with an intensive basal–bolus insulin therapy. In the IDegAsp OD group, the change in body weight was approximately 1 kg greater than with IDet after 26 weeks. The observed weight gain was 2.3 kg (IDegAsp OD) and 1.3 kg (IDet) after 26 weeks and 2.8 kg (IDegAsp OD) and 1.2 kg (IDet) after 52 weeks of treatment. The treatment differences were statistically significant at both time points. The analysis results were supported by the analysis done on the basis of the completer analysis set.

Subjects with T2DM – IDegAsp OD

Body weight was a confirmatory endpoint and included in the testing hierarchy in the two 26-week Trials 3590 and 3593 (Table 16). In these trials, the observed mean weight gain ranged from 1.2 to 2.5 kg with IDegAsp OD and 1.0 to 1.2 kg with IGlar. In Trial 3590 with pretrial insulin-naïve subjects, the increase in weight was statistically significantly greater with IDegAsp OD compared with IGlar. In this trial, subjects in the IDegAsp group were instructed to take IDegAsp OD with breakfast. In Trial 3593, where the majority of subjects used IDegAsp with the main evening meal, there was no statistically significant difference in the weight change between treatments. The two analysis results were supported by the analyses done based on the completer analysis set. When evaluating the change in body weight by injection time in Trial 3593 (dosing at breakfast, lunch or the main evening meal), there was no evidence to suggest that treatment with IDegAsp dosed with breakfast was accompanied by more weight gain than dosing at lunch or the main evening meal.

Subjects with T2DM – IDegAsp BID

Treatment with IDegAsp BID resulted in less weight gain than with BIAsp 30 BID in the two therapeutic confirmatory Trials 3597 and 3592. The observed mean increase in weight ranged from 1.1 kg to 1.7 kg with IDegAsp BID and from 1.4 kg to 2.2 kg with BIAsp 30 BID. In Trial 3592, smaller weight gain with IDegAsp BID compared with BIAsp 30 BID was statistically significant. Body weight was a confirmatory endpoint in Trial 3592. Superiority of IDegAsp BID based on hierarchical testing could not be formally confirmed as the testing procedure was stopped prior to testing this endpoint. There was no statistically significant difference between treatments in Trial 3597, in which only subjects from Asian countries with a low observed mean body weight at baseline (66.1 kg compared with 81.5 kg in Trial 3592) were included. All analysis results above were supported by the analyses done on the basis of the completer analysis set.

Ancillary analyses

Comparison of Results in Subpopulations

Comparison of HbA_{1c} and confirmed hypoglycaemic episodes of IDegAsp in subpopulations were assessed through statistical analysis of potential interaction between treatment effect and intrinsic and extrinsic factors. In T2DM, these interaction analyses were based on pooled data from the four therapeutic confirmatory trials (Trials 3593, 3590, 3592 and 3597). The intrinsic factors were demographic (age, sex, BMI, race and ethnicity) and disease-related (diabetes duration, baseline HbA_{1c}, estimated creatinine clearance, ALAT and serum creatinine). The extrinsic factors comprised pretrial antidiabetic treatment and concomitant medication (glucose-increasing drugs, glucose-lowering drugs, OAD medication class and monotherapy). The analyses were performed in order to evaluate whether the treatment differences (measured by HbA_{1c} and confirmed hypoglycaemic episodes) depended on any of the intrinsic or extrinsic factors. It should be noted that the results from some of the

subpopulation analyses of confirmed hypoglycaemic episodes in T2DM should be interpreted with caution due to the heterogeneity between trials in terms of race, ethnicity, region, pretrial antidiabetic treatment and the different treatment effects seen with respect to confirmed hypoglycaemia.

In summary, the comparison of HbA_{1c} in subjects with T2DM showed a statistically significant treatment-by-hepatic function (ALAT) and treatment-by-concomitant medication (thiazolidindione) interaction. These findings were not considered of clinical relevance and overall the treatment difference (IDegAsp – Comparator) in HbA_{1c} and confirmed hypoglycaemic episodes was independent of demographic factors, disease factors, pretrial antidiabetic treatment and concomitant medication.

Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing recommendations for the proposed labelling of IDegAsp are based on results from the therapeutic confirmatory trials, therapeutic exploratory trials, including dose-concentration and dose-response information, as well as other dosing results obtained in clinical pharmacology trials. In clinical practice, insulin dose is determined by individual need, considering the balance between the level of glycaemic control and the risk of hypoglycaemia. As the dose required to achieve similar glycaemic targets varies widely from patient to patient, no formal dose-response assessments have been made in terms of clinical efficacy.

In summary, the results from the therapeutic confirmatory Trial 3590 and the exploratory trials showed that it was safe to initiate IDegAsp at a dose of 10 U OD in insulin-naïve subjects with T2DM. Data on hypoglycaemia during the first month of treatment from the global Trials 3592 and 3593 support that subjects previously treated with basal insulin or premix/self-mix insulin can safely transfer to IDegAsp OD or BID on a unit-to-unit basis. Initiation of IDegAsp was followed by a safe dose optimisation and titration procedure.

The glycaemic response and the risk of hypoglycaemia were not linked to IDegAsp dosing at a specific main meal. The results from the IDegAsp therapeutic confirmatory trials and the trials with IDeg administered with extreme variation in dosing time from day-to-day support that treatment with IDegAsp OD can be dosed with the main evening meal or largest meal of the day customised to the individual's lifestyle needs in both T1DM and T2DM. If needed subjects treated with IDegAsp can advance or delay the dosing of IDegAsp to a different meal on the same day and thereafter resume their usual dosing schedule. Subjects should however not take an extra dose to make up for potential missed doses.

Change in Dose over Time versus Glycaemic Control

Doses of IDegAsp and comparators were titrated individually according to a predefined dosing guideline. The overall treatment goal in all therapeutic confirmatory trials was to achieve HbA_{1c} <7% and a prebreakfast (fasting) SMPG target of <5.0 mmol/L (90 mg/dL). In trials with BID dosing, an additional predinner SMPG target of <5.0 mmol/L was applied for adjustment of the morning dose.

In summary, the increase in total insulin dose from baseline to end-of-trial in T1DM and T2DM was a result of the insulin titration to achieve glycaemic targets. In T2DM, insulin doses increased primarily in the early part of the trials, and dose increments were not required to maintain glycaemic targets, nor was there any evidence of loss of efficacy over time.

Summary of main studies

The following tables 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).

IDegAsp – Therapeutic Confirmatory Trials

Summary of Efficacy for Trial 3594

Title: A 26-week, multinational, multi-centre, open-labelled, two-arm, parallel, randomised, treat-to-target trial comparing efficacy and safety of NN5401 once daily plus meal-time insulin aspart for the remaining meals vs. basal-bolus treatment with insulin detemir plus meal-time insulin aspart in subjects with type 1 diabetes mellitus			
Study identifier	Protocol number: NN5401-3594; EudraCT number: 2008-005769-71; Study identifier: NCT00978627.		
Design	This trial was a 26-week multinational, multi-centre, open-labelled, randomised (2:1), two-arm parallel group, treat-to-target trial comparing the efficacy and safety of IDegAsp once daily (OD) with IDet, both groups in combination with IAsp. Stratification was carried out according to previous insulin regimen with the categories basal bolus regimen or other insulin regimen (i.e. mixed insulin regimen). Trial population constituted a typical population with type 1 diabetes mellitus. During the one-week follow-up period, the subjects were treated with insulin NPH BID + IAsp.		
	Duration of main phase: Duration of extension phase:		26 weeks + 1 week follow-up 26 weeks + 1 week follow-up (see Trial 3594/3645)
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated treatment difference (IDegAsp OD-IDet) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). If non-inferiority was confirmed for the primary endpoint then superiority of a number of confirmatory secondary endpoints was tested using a hierarchical testing procedure to control the overall type I error rate: 1) Change from baseline in FPG; 2) HbA_{1c} <7.0% without severe hypoglycaemic episodes; 3) Number of nocturnal confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec/insulin aspart (IDegAsp) + insulin aspart (IAsp)		A total of 366 subjects were randomised to IDegAsp dosed OD at any of the main meals + IAsp at remaining meals. The total treatment duration was 26 weeks.
	Insulin detemir (IDet) + insulin aspart (IAsp)		A total of 182 subjects were randomised to IDet OD, dosed at the evening meal or at bed time + mealtime IAsp. A second dose of IDet could be added after 8 weeks of treatment in case of inadequate glycaemic control. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	see Hypothesis
	1) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp minus IDet) was entirely below zero.
	2) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without severe hypoglycaemia	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDegAsp/IDet) was entirely above one.
	3) Confirmatory secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDegAsp/IDet) was entirely below one.
	Supportive secondary endpoint	Number of confirmed hypoglycaemic episodes	The number of confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.

Database lock	22-June-2010		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		
Analysis population and time point description	The FAS included all randomised subjects. Analyses of efficacy endpoints, including analyses of confirmed hypoglycaemia and body weight and the confirmatory analyses on nocturnal confirmed hypoglycaemia, were based on the full analysis set (n=548). The per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The safety endpoints were summarized using the SAS (n=542). The SAS included all subjects receiving at least one dose of the investigational product or its comparator. The population consisted of male and female subjects with type 1 diabetes mellitus with a mean age of 41.3 years (ranging from 18.1 to 80.2 years), mean duration of diabetes of 17.4 years (ranging from 1.1 to 59.7 years), mean HbA_{1c} of 8.3 % and mean BMI of 26.4 kg/m^2. The time point duration for all analyses was 26 weeks. A total of 90.3% of subjects treated with a basal-bolus insulin regimen pre-trial. The majority were treated with IGlar (66.2%) pre-trial. A total of 87.4% and 85.7% completed the trial in the IDegAsp and IDet groups, respectively.		
Statistical Methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp**	**IDet**
	Number of subject	366	182
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean (SD), %	-0.73 (0.8)	-0.68 (0.8)
	HbA_{1c} at baseline mean (SD), %	8.30 (0.8)	8.28 (0.7)
	HbA_{1c} at Week 26 mean (SD), %	7.58 (0.9)	7.60 (0.8)
	Change from baseline in FPG after 26 weeks of treatment, mean (SD), mmol/L	-1.61 (5.4)	-2.41 (5.5)
	HbA_{1c} <7.0% without severe hypoglycaemia, N (%)	82 (24.3)	35 (20.7)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	3917	4434
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	371	572
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	2.29 (3.9)	1.29 (3.4)
	Total daily insulin dose mean units (SD) after 26 weeks of treatment	69 (40)	79 (49)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} after 26 weeks of treatment	Comparison groups	IDegAsp - IDet
		Treatment contrast	-0.05
		95% CI	[-0.18; 0.08][†]
	1) Confirmatory secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDegAsp - IDet
		Treatment contrast	0.23
		95% CI	[-0.46; 0.91]
	2) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without severe hypoglycaemia	Comparison groups	IDegAsp / IDet
		Odds ratio	1.24
		95% CI	[0.77; 2.02]
	3) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp / IDet
		Rate ratio	0.63 *
		95% CI	[0.49; 0.81]
	Supportive secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp / IDet
		Rate ratio	0.91
		95% CI	[0.76; 1.09]

	Supportive secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDegAsp - IDet
		Treatment contrast	1.04 *
		95% CI	[0.38; 1.69]
	Supportive secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.	
Notes			

BID: twice daily; BMI: body mass index; 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 A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 weeks of treatment; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; IDet: insulin detemir; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OD: once daily; SAS: safety analysis set; SD: standard deviation; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: Statistically significant

Summary of Efficacy for Trial 3594/3645

Title: A 26-week, multinational, multicentre, open-label, two-arm, parallel, randomised, treat-to-target extension trial comparing safety and efficacy of NN5401 once-daily plus meal-time insulin aspart for the remaining meals vs. basal-bolus treatment with insulin detemir plus meal-time insulin aspart in subjects with type 1 diabetes[#]			
Study identifier	Protocol number: NN5401-3645; EudraCT number: 2009-013412-13; Study identifier: NCT01087606.		
Design	The main trial (Trial 3594) was a 26-week multinational, multi-centre, open-labelled, randomised (2:1), treat-to-target,, parallel group trial comparing two treatment regimens in subjects with type 1 diabetes: IDegAsp OD + IAsp for the remaining meals and IDet + meal-time IAsp, This 26-week extension trial (Trial 3645) was with the same treatment regimen to ensure the most optimal coverage of both basal and bolus requirements. Subjects who consented to participate in the extension trial continued to receive treatment with either IDegAsp OD + IAsp for the remaining meals or IDet + meal-time IAsp as previously randomised in the main trial NN5401-3594. During the one-week follow-up period, the subjects were treated with insulin NPH BID + IAsp.		
	Duration of main phase: Duration of Extension phase:		26 weeks + 1 week follow-up (see Trial 3594) 26 weeks + 1 week follow-up
Hypothesis	No hypothesis was considered as this was an extension trial		
Treatments groups	Insulin degludec/insulin aspart (IDegAsp) OD + insulin aspart (IAsp)		A total of 366 subjects were randomised in the main trial and 254 were included in the extension trial to IDegAsp dosed OD at any of the main meals with IAsp at the remaining meals. The total treatment duration was 26 weeks (main trial) + 26 weeks (extension).
	Insulin detemir (IDet) + insulin aspart (IAsp)		A total of 182 subjects randomised in the main trial and 122 subjects in the extension trial to IDet, dosed at the evening meal or at the bed time + mealtime IAsp. A second dose of IDet could be added after 8 weeks of treatment in case of inadequate glycaemic control. The total treatment duration was 26 weeks (main trial) + 26 weeks.
	Primary endpoint	Adverse events	Adverse Events (AEs) were coded using the most recent version of MedDRA coding. All AEs were presented based on system organ class and preferred terms. The AEs were summarised descriptively according to treatment regimen.
	Primary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	A statistically significant difference was to be considered if the 95% CI for the relative risk (IDegAsp/IDet) was entirely below one.
	Primary endpoint	Number of confirmed hypoglycaemic episodes	A statistically significant difference was to be considered if the 95% CI for the relative risk (IDegAsp/IDet) was entirely below one.
	Primary endpoint	Change from baseline in body weight after 52 weeks of treatment	A statistically significant difference was to be considered if the 95% CI for the treatment difference (IDegAsp minus IDet) was entirely below zero.
	Primary endpoint	Total daily insulin dose after 52 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation..
	Supportive secondary endpoint	Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	Comparing the difference in change from baseline in HbA_{1c} after 52 weeks of treatment between IDegAsp and IDet to a non-inferiority limit of 0.4%.
	Supportive secondary endpoint	HbA_{1c} <7.0% at end of trial without severe hypoglycaemia	A statistically significant difference was to be considered if the 95% CI for the odds ratio (IDegAsp/IDet) was entirely above one.
	Supportive secondary endpoint	Change from baseline in FPG (central lab-measured) after 52 weeks of treatment	A statistically significant difference was to be considered if the 95% CI for the treatment difference (IDegAsp minus IDet) was entirely below zero.
Database lock	04-Jan-2011		
Results and Analysis			
Analysis description	**Primary Analysis and Key Supportive Secondary Endpoints**		

Analysis population and time point description	Analyses of all efficacy endpoints were based on the full analysis set (n=548) as were analyses of hypoglycaemia and body weight. All other endpoints related to safety were based on the safety analysis set (n=542). The population consisted of male and female subjects with type 1 diabetes mellitus with a mean age of 41.3 years (ranging from 18.1 to 80.2 years), mean duration of diabetes of 17.4 years (ranging from 1.0 to 59.7 years), mean HbA_{1c} of 8.3 % and mean BMI of 26.4 kg/m^2. The time point duration for all analyses was 52 weeks. Full analysis set included all randomised subjects. Per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. Safety analysis set included all subjects receiving at least one dose of the investigational product or its comparator. A total of 90.3% of subjects treated with a basal-bolus insulin regimen pre-trial. The majority were treated with IGlar (66.2%) pre-trial. A total of 87.4% and 85.7% completed the main trial and 63.7% and 62.1% completed extension trial in the IDegAsp and IDet groups, respectively.		
Statistical methods	Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes were presented as the event rate per 100 patient years of exposure (PYE). Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The responder analysis was based on a logistic regression model using the same factors and covariates as for the analysis of HbA_{1c}. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp**	**IDet**
	Number of subjects (FAS)	366	182
	Change from baseline in HbA_{1c} (%) after 52 weeks of treatment, mean (SD)	−0.65 (0.8)	−0.56 (0.8)
	HbA_{1c} at baseline mean (SD), %	8.30 (0.8)	8.28 (0.7)
	HbA_{1c} after Week 52, mean % (SD)	7.65 (0.9)	7.72 (0.9)
	HbA_{1c} <7.0% without severe hypoglycaemia, N (%)	74 (22.0)	28 (16.6)
	Change from baseline in FPG after 52 weeks of treatment, mean mmol/L (SD)	−1.83 (5.7)	−2.40 (5.9)
	Observed rate of adverse events per 100 PYE	408	442
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	3183	3673
	Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	309	541
	Change from baseline in body weight after 52 weeks of treatment, mean kg (SD)	2.78 (4.2)	1.15 (4.1)
	Total daily insulin dose after 52 weeks, mean units (SD)	72 (46)	82 (53)
Effect estimate per comparison	Primary endpoint: Adverse events	No statistical analysis was performed.	
	Primary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp/IDet
		Rate ratio	0.95
		95% CI	[0.79; 1.14]
	Primary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp/IDet
		Rate ratio	0.62
		95% CI	[0.48;0.79]*
	Primary endpoint: Change from baseline in body weight after 52 weeks of treatment	Comparison groups	IDegAsp - IDet
		Treatment contrast	1.64
		95% CI	[0.89; 2.38]
	Primary Endpoint: Total daily insulin dose after 52 weeks	No statistical analysis was performed.	
	Secondary endpoint: Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	Comparison groups	IDegAsp - IDet
		Treatment contrast	-0.10
		95% CI	[-0.24; 0.03]†

	Secondary endpoint: HbA_{1c} <7.0% at end of trial without severe hypoglycaemia	Comparison groups	IDegAsp/IDet
		Odds ratio	1.54
		95% CI	[0.90; 2.63]
	Secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDegAsp - IDet
		Treatment contrast	-0.07
		95% CI	[-0.79; 0.66]
Notes	#= This table contains the results after 52 weeks treatment (26 weeks in the main trial NN5401-3594 followed by 26 weeks in the present extension trial NN5401-3645)		

BID: twice daily; BMI: body mass index; 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 A_{1c}; HbA_{1c} < 7% : Endpoint was only defined for subjects exposed for at least 12 weeks of treatment; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; IDet: insulin detemir; MedDRA: Medical Dictionary for Regulatory Activities; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OD: once daily; SAS: safety analysis set; SD: standard deviation; †Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: Statistically significant

Summary of Efficacy for Trial 3590

Title: A 26-week, multinational, multi-centre, open-labelled, two-arm, parallel, randomised, treat-to-target, efficacy and safety comparison of NN5401 once daily (OD) with insulin glargine (IGlar) OD both in combination with metformin in insulin-naïve subjects with type 2 diabetes inadequately controlled on oral antidiabetic drugs			
Study identifier	Protocol number: NN5401-3590; EudraCT number: 2009-011271-78; Study identifier: NCT01045707.		
Design	This was a 26-week multinational, multi-centre, open-labelled, randomised (1:1), treat-to-target, two-arm parallel group trial comparing the efficacy and safety of IDegAsp OD + met with IGlar + met in insulin-naïve subjects diagnosed with type 2 diabetes mellitus. At randomisation, previous OAD treatment was discontinued except for met. During the one week follow-up subjects were treated with insulin NPH BID + met.		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated treatment difference (IDegAsp–IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). If non-inferiority was confirmed for the primary endpoint then superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Prandial PG increment at breakfast (measured by SMPG 90 min after start of meal); 2) Fluctuation in nocturnal IG as measured by CGM; 3) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes; 4) Number of nocturnal confirmed hypoglycaemic episodes; 5) Change from baseline in body weight		
Treatments groups	Insulin degludec/insulin aspart (IDegAsp)		A total of 266 subjects were randomised to IDegAsp dosed OD at the breakfast (morning meal) + metformin (met). The total treatment duration was 26 weeks.
	Insulin glargine (IGlar)		A total of 264 subjects randomised to IGlar, dosed OD according to the approved labelling + metformin (met). The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Prandial PG increment at breakfast meal after 26 weeks	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp minus IGlar) was entirely below zero.
	2) Confirmatory secondary endpoint	Fluctuations in nocturnal IG as measured by CGM (subpopulation only) after 26 weeks	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% confidence interval for the treatment ratio (IDegAsp/IGlar) was entirely below one.
	3) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDegAsp/IGlar) was entirely above one.
	4) Confirmatory secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority is confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDegAsp/IGlar) was entirely below one.
	5) Confirmatory secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp minus IGlar) was entirely below zero.
	Supportive secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	Comparing the change in FPG from baseline between IDegAsp and IGlar after 26 weeks of treatment.
	Supportive secondary endpoint	Number of confirmed hypoglycaemic episodes	The number of confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation
	Supportive secondary endpoint	Mean daily insulin dose after 26 weeks of treatment	The insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	23-Nov-2010		
Results and Analysis			

Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Analyses**		
Analysis population and time point description	The FAS included all randomised subjects. The per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. Analyses of efficacy endpoints including analyses of hypoglycaemia and body weight, were based on the FAS (n=529), while the safety endpoints were summarized using the SAS (n=526). The SAS included all subjects receiving at least one dose of the investigational product or its comparator. In total, 85.1% of the randomised subjects completed the trial. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 56.9 years (ranging from 21.8 to 78.4 years), mean duration of diabetes of 9.2 years (range 0.6 to 39.6 years), mean HbA_{1c} of 8.9% and mean BMI of 30.7 kg/m^2. The time point duration for all analyses was 26 weeks. The majority of subjects (84.1%) were on two OADs pre-trial. A total of 82.3% and 87.9% completed the trial in the IDegAsp OD and IGlar OD groups, respectively.		
Statistical methods	Change from baseline in HbA_{1c}, FPG, prandial plasma glucose increment at breakfast, log-transformed fluctuation in nocturnal interstitial glucose and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp**	**IDet**
	Number of subjects (FAS)	266	263
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-1.65 (1.3)	-1.72 (1.2)
	HbA_{1c} at baseline, mean % (SD)	8.86 (1.0)	8.91 (0.9)
	HbA_{1c} at Week 26, mean % (SD)	7.21 (1.0)	7.19 (1.0)
	HbA_{1c} <7.0% without confirmed hypoglycaemia, N (%)	55 (23.6)	75 (30.7)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-3.32 (3.4)	-4.02 (3.5)
	Prandial PG increment at breakfast, after 26 weeks of treatment, mean mmol/L (SD)	1.9 (3.0)	3.4 (2.9)
	Fluctuation in nocturnal IG after 26 weeks of treatment, mean mmol/L (SD)	0.93 (0.7)	0.90 (0.7)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	423	185
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	19	46
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	2.47 (3.4)	1.23 (3.5)
	Insulin daily dose after 26 weeks, mean units (SD)	66 (36)	59 (33)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	0.03
		95% CI	[-0.14; 0.20] †
	1) Confirmatory secondary endpoint: Prandial PG increment at breakfast after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	-1.40
		95% CI	[-1.92; -0.88]
	2) Confirmatory secondary endpoint: Fluctuation in nocturnal IG after 26 weeks of treatment	Comparison groups	IDegAsp/IGlar
		Treatment ratio	0.69
		95% CI	[0.25; 1.92]

	3) Confirmatory secondary endpoint: HbA_{1c} < 7.0% at end of trial without confirmed hypoglycaemia	Comparison groups	IDegAsp/IGlar
		Odds ratio	0.61
		95% CI	[0.40; 0.94]*
	4) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp/IGlar
		Rate ratio	0.29
		95% CI	[0.13; 0.65]*
	5) Confirmatory secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	1.31
		95% CI	[0.72; 1.89]*
	Supportive secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	0.51
		95% CI	[0.09; 0.93]*
	Supportive secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp/IGlar
		Rate ratio	2.17
		95% CI	[1.59; 2.94]*
	Supportive secondary endpoint: Insulin daily dose after 26 weeks of treatment	No statistical analysis was performed.	
Notes			

BMI: body mass index; CGM: continuous glucose monitoring; 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 A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 treatment weeks; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; IG: interstitial glucose; IGlar: insulin glargine; met: metformin; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; PG: plasma glucose; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: Statistically significant

Summary of Efficacy for Trial 3593

Title: A 26-week, randomised, open-labelled, two-armed, parallel-group, treat-to-target study comparing efficacy and safety of the NN5401 once daily (OD) with insulin glargine OD, both in combination with metformin ± pioglitazone ± DPP-4 inhibitors in subjects with type 2 diabetes inadequately controlled with basal insulin OD + oral antidiabetic drugs (OADs).			
Study identifier	Protocol number: NN5401-3593; EudraCT number: 2008-005767-34; Study identifier: NCT01045447		
Design	This was a 26-week, multicentre, multinational, open-labelled, randomised (1:1), treat-to-target, two-arm parallel-group trial comparing the efficacy and safety of IDegAsp and IGlar in a basal-bolus regimen ± met ± pioglitazone ± DPP-4 inhibitor in subjects with type 2 diabetes mellitus. After randomisation subjects were switched to trial products and continued with the OADs allowed in the trial at unchanged doses, other OADs were to be discontinued. The trial was stratified according to prior pioglitazone use.		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated treatment difference (IDegAsp OD-IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). If non-inferiority was confirmed for the primary endpoint then superiority of a number of confirmatory secondary endpoints was tested using a hierarchical testing procedure to control the overall type I error rate: 1) Prandial PG increment at main evening meal; 2) HbA_{1c} <7.0% without confirmed hypoglycaemic episodes; 3) Fluctuation in nocturnal IG; 4) Number of nocturnal confirmed hypoglycaemic episodes; 5) Change in baseline in body weight.		
Treatments groups	Insulin degludec/insulin aspart (IDegAsp) OD		A total of 232 subjects were randomised to IDegAsp dosed OD with dinner or the largest meal OD + metformin (met) ± pioglitazone (pio) ± dipeptidyl peptidase-4 (DPP-4) inhibitors. The total treatment duration was 26 weeks.
	Insulin glargine (IGlar)		A total of 233 subjects randomised to IGlar, dosed OD according to approved labelling + metformin (met) ± pioglitazone (pio) ± dipeptidyl peptidase-4 (DPP-4) inhibitors. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis
	1) Confirmatory secondary endpoint	Prandial PG increment at main evening meal from 9-point SMPG profile at end of treatment	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp minus IGlar) was entirely below zero.
	2) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDegAsp/IGlar) was entirely above one.
	3) Confirmatory secondary endpoint	Fluctuations in nocturnal IG at end of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint then superiority was confirmed for this endpoint if the 95% CI for the treatment ratio (IDegAsp/IGlar) was entirely below one.
	4) Confirmatory secondary endpoint	Number of treatment nocturnal confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDegAsp/IGlar) was entirely below one.
	5) Confirmatory secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint then superiority was confirmed for this endpoint if the 95% CI for treatment difference (IDegAsp minus IGlar) was entirely below zero.
	Supportive secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	Comparing the change in FPG from baseline between IDegAsp and IGlar after 26 weeks treatment.
	Supportive secondary endpoint	Number of confirmed hypoglycaemic episodes	The number of confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Mean daily insulin dose after 26 weeks of treatment	The mean daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.

Database lock	12-Nov-2010		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		
Analysis population and time point description	The FAS included all randomised subjects. The per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. All statistical analyses, including analyses of hypoglycaemia and body weight, were based on the FAS (n=463), while the safety endpoints were summarized using the SAS (n=463). The SAS included all subjects receiving at least one dose of the investigational product or its comparator. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 58.1 years (ranging from 27.9 to 84.3 years), mean duration of diabetes of 11.5 years (range 0.6 to 55.6 years), mean HbA_{1c} of 8.3% and mean BMI of 30.1 kg/m^2. The time point duration for all analyses was 26 weeks. The majority of subjects had been treated with IGlar pre-trial, 53.9% in the IDeg group and 61.4% in the IGlar group. A total of 84.5% and 88.0% completed the trial in the IDegAsp OD and IGlar groups, respectively.		
Statistical methods	Change from baseline in HbA_{1c}, FPG, prandial PG increment at evening meal, log-transformed fluctuation in nocturnal interstitial glucose and body weight at end of treatment was analysed using an analysis of variance (ANOVA) method with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp**	**IGlar**
	Number of subjects (FAS)	230	233
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean (SD), %	-0.98 (1.0)	-1.00 (1.1)
	HbA_{1c} at baseline mean (SD), %	8.29 (0.8)	8.36 (1.0)
	HbA_{1c} at Week 26 mean (SD), %	7.31 (1.1)	7.36 (1.0)
	HbA_{1c} <7.0% without confirmed hypoglycaemia, N (%)	44 (20.9)	50 (23.5)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-1.68 (3.0)	-1.88 (3.0)
	Prandial PG increment at main evening meal (from 9-point SMPG profile) after 26 weeks of treatment, mean (SD) mmol/L	1.2 (3.7)	2.6 (2.9)
	Fluctuation in nocturnal IG after 26 weeks of treatment, mean (SD) mmol/L	0.89 (0.7)	0.97 (0.7)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	431	320
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	82	101
	Change from baseline in body weight, mean (SD), kg	1.20 (2.7)	0.98 (3.0)
	Total daily IDegAsp and IGlar dose after 26 weeks mean units (SD),	60 (36)	60 (36)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	-0.03
		95% CI	[-0.20; 0.14] †
	1) Confirmatory secondary endpoint: Prandial PG increment at main evening meal from 9-point SMPG profile at end of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	-1.32
		95% CI	[-1.93; -0.72]
	2) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	Comparison groups	IDegAsp / IGlar
		Odds ratio	0.80
		95% CI	[0.50; 1.30]
	3) Confirmatory secondary endpoint:	Comparison groups	IDegAsp / IGlar

	Fluctuations in nocturnal IG at end of treatment	Treatment ratio	0.97
		95% CI	[0.74; 1.28]
	4) Confirmatory secondary endpoint: Number of treatment nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp / IGlar
		Rate ratio	0.80
		95% CI	[0.49; 1.30]
	5) Confirmatory secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	0.33
		95% CI	[-0.17; 0.83]
	Supportive secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDegAsp - IGlar
		Treatment contrast	0.33
		95% CI	[-0.11; 0.77]
	Supportive secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp / IGlar
		Rate ratio	1.43
		95% CI	[1.07; 1.92]*
	Supportive secondary endpoint: Mean daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.	
Notes			

BMI: body mass index; CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; DPP-4: dipeptidyl peptidase-4; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 treatment weeks; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; IG: interstitial glucose; IGlar: insulin glargine; met: metformin; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; PG: plasma glucose; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: Statistically significant

Summary of Efficacy for Trial 3592

Title: A 26-week, randomised, open-labelled, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of NN5401 twice daily (BID) with biphasic insulin aspart (BIAsp) 30 BID, with or without metformin, with or without DPP 4 inhibitor, with or without pioglitazone in subjects with type 2 diabetes in inadequate glycaemic control on once or twice daily premixed or self mixed insulin regimen with or without OADs			
Study identifier	Protocol number: NN5401-3592; EudraCT number: 2008-005768-15; Study identifier: NCT01009580.		
Design	This was a 26-week multinational, multi-centre, open-labelled, randomised (1:1), stratified, two-arm parallel group trial comparing the efficacy and safety of IDegAsp BID with the BIAsp 30 BID treatment, both ± met ± DPP-4 inhibitor ± pioglitazone, in subjects diagnosed with type 2 diabetes mellitus, not optimally controlled on once daily (OD) or BID premixed or self-mixed insulin regimen ± OADs. Stratification was carried out according to the number of daily injections at screening (1 insulin injection a day or 2 insulin injections a day).		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated treatment difference (IDegAsp–BIAsp 30) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). If non-inferiority was confirmed for the primary endpoint then superiority could be confirmed for a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Change from baseline in FPG; 2) Number of confirmed hypoglycaemic episodes; 3) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes; 4) Change from baseline in body weight; 5) Number of nocturnal confirmed hypoglycaemic episodes		
Treatments groups	Insulin degludec/insulin aspart (IDegAsp) BID		A total of 224 subjects were randomised to IDegAsp dosed BID at breakfast and the main evening meal ± metformin (met) ± dipeptidyl peptidase-4 (DPP-4) ± pioglitazone (pio) dosed as pre-trial. The total treatment duration was 26 weeks.
	Biphasic insulin aspart (BIAsp) 30 BID		A total of 223 subjects randomised to BIAsp 30 BID at breakfast and at the main evening meal ± metformin (met) ± dipeptidyl peptidase-4 (DPP-4) ± pioglitazone (pio). The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} after 26 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Change from baseline in FPG (central-lab measured) after 26 weeks of treatment	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp BID minus BIAsp 30 BID) was entirely below zero.
	2) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDegAsp BID/BIAsp 30 BID) was entirely below one.
	3) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDegAsp BID/BIAsp 30 BID) was entirely above one.
	4) Confirmatory secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp BID minus BIAsp 30 BID) was entirely below zero..
	5) Confirmatory secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment ratio (IDegAsp BID/BIAsp 30 BID) was entirely below one.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	23-Sept-2010		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. Analyses of efficacy endpoints including analyses of hypoglycaemia and body weight, were based on the FAS (n=446), while the safety endpoints were summarised using the safety analysis set (n=446). The safety analysis set included all subjects receiving at least one dose of the investigational product or its comparator. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 58.7 years (range 20.4 to 88.8 years), mean duration of diabetes of 13.0 years (ranging from 0.6 to 41.4 years), mean HbA_{1c} of 8.4 % and mean BMI of 29.3 kg/m^2. The time point duration for all analyses was 26 weeks. Pre-trial 49.1% of the subjects were treated with biphasic insulin aspart 30 and 42.6% were treated with biphasic human insulin. A total of 87.9% and 84.3% completed the trial in the IDegAsp BID and BIAsp 30 BID group, respectively.		
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp**	**BIAsp 30**
	Number of subjects (FAS)	224	222
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-1.28 (0.9)	-1.30 (1.0)
	HbA_{1c} at baseline, mean % (SD)	8.33 (0.8)	8.40 (0.9)
	HbA_{1c} at Week 26, mean % (SD)	7.05 (0.9)	7.10 (0.9)
	HbA_{1c} <7.0% without confirmed hypoglycaemia, N (%)	44 (21.8)	29 (14.9)
	Change in FPG, mean mmol/L (SD)	-3.09 (3.0)	-1.76 (2.8)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	972	1396
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	74	253
	Change in body weight after 26 weeks, mean kg (SD)	1.68 (3.0)	2.16 (2.7)
	Total daily insulin dose after 26 weeks, mean units (SD)	90 (50)	98 (54)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} after 26 weeks of treatment	Comparison groups	IDegAsp – BIAsp 30
		Treatment contrast	-0.03
		95% CI	[-0.18; 0.13]†
	1) Confirmatory secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDegAsp – BIAsp 30
		Treatment contrast	-1.14
		95% CI	[-1.53; -0.76]*
	2) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp/BIAsp 30
		Rate ratio	0.68
		95% CI	[0.52;0.89]*
	3) Confirmatory secondary endpoint: HbA_{1c} < 7.0% at end of trial without confirmed hypoglycaemia	Comparison groups	IDegAsp/BIAsp 30
		Odds ratio	1.60
		95% CI	[0.94; 2.72]
	4) Confirmatory secondary endpoint: Change in body weight after 26 weeks of treatment	Comparison groups	IDegAsp – BIAsp 30
		Treatment contrast	-0.62
		95% CI	[-1.15; -0.10]*
	5) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp/BIAsp 30
		Rate ratio	0.27
		95% CI	[0.18; 0.41]*
	Secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed	

BIAsp: biphasic insulin aspart; BID: twice daily; BMI: body mass index; CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; DPP-4: dipeptidyl peptidase-4; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 treatment weeks; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; IG: interstitial glucose; IGlar: insulin glargine; met: metformin; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; pio: pioglizatone; PG: plasma glucose; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: Statistically significant

Summary of Efficacy for Trial 3597

Title: A 26 week trial, randomised, open label, two arm, parallel group, treat to target study comparing efficacy and safety of the NN5401 twice daily with biphasic insulin aspart 30 twice daily, with or without metformin in subjects with type 2 diabetes in inadequate glycaemic control on once or twice daily insulin regimen with or without metformin			
Study identifier	Protocol number: NN5401-3597; EudraCT number: not applicable; Japanese Trial number: 21-2751; Study identifier: NCT01059812.		
Design	This was a 26-week Pan Asian, multi-centre, open-label, randomised, stratified, two-arm parallel group, treat-to-target trial comparing the efficacy and safety of IDegAsp BID ± met with BIAsp 30 BID ± met treatment. Subjects eligible for this trial were subject diagnosed with type 2 diabetes mellitus, not optimally controlled on OD or BID human or analogue basal insulin, premixed or self-mixed insulin regimen ± met. Stratification was to be performed according to previous insulin regimen and met treatment at screening. Randomisation was to be carried out in a 2:1 manner to IDegAsp : BIAsp 30, both BID. During the one week follow-up period subjects were treated with biphasic human insulin 30 (BHI).		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated treatment difference (IDegAsp–BIAsp 30) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). If non-inferiority was confirmed for the primary endpoint then superiority of a number of confirmatory secondary endpoints was tested using a hierarchical testing procedure to control the overall type I error rate: 1) Change from baseline in FPG; 2) Number of confirmed hypoglycaemic episodes; 3) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes; 4) Change from baseline in body weight; 5) Number of nocturnal confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec/insulin aspart (IDegAsp) BID		A total of 282 subjects were randomised to IDegAsp dosed BID with the breakfast meal and main evening meal metformin (met) dosed as pre-trial. The total treatment duration was 26 weeks.
	Biphasic insulin aspart (BIAsp) 30 BID		A total of 142 subjects randomised to BIAsp 30, dosed with the breakfast meal and main evening meal metformin (met) dosed as pre-trial. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp minus BIAsp) was entirely below zero.
	2) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDegAsp/BIAsp 30) was entirely below one.
	3) Confirmatory secondary endpoint	HbA_{1c} < 7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDegAsp/BIAsp 30) was entirely above one.
	4) Confirmatory secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDegAsp minus BIAsp) was entirely below zero.
	5) Confirmatory secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDegAsp/BIAsp 30) was entirely below one.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	17-Jan-2011		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. Analyses of efficacy endpoints including analyses of hypoglycaemia and body weight, were based on the FAS (n=422), while the safety endpoints were summarized using the SAS (n=420). The SAS included all subjects receiving at least one dose of the investigational product or its comparator. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 59.8 years (ranging from 30.0 to 88.5 years), mean duration of diabetes of 16.3 years (ranging from 0.7 to 47.8 years), mean HbA_{1c} of 8.4 % and mean BMI of 25.4 kg/m^2. The time point duration for all analyses was 26 weeks. A majority of subjects (69.4%) had been treated pre-trial on a premix/self-mix insulin regimen with or without OADs . Of these, 41.5% of the subjects were treated with biphasic insulin aspart 30 and 19.7% were treated with biphasic human insulin. A total of 86.9% and 88.7% completed the trial in the IDegAsp BID and BIAsp 30 BID groups, respectively.		
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp**	**BIAsp 30**
	Number of subjects (FAS)	280	142
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	−1.38 (0.9)	−1.42 (1.0)
	HbA_{1c} at baseline, mean % (SD)	8.45 (0.8)	8.44 (0.9)
	HbA_{1c} at Week 26,mean % (SD)	7.07 (0.8)	7.02 (0.8)
	HbA_{1c} <7.0% at the end of trial without confirmed hypoglycaemia, N (%)	56 (21.9)	17 (13.2)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	−2.55 (2.6)	−1.47 (2.6)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	956	952
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	111	155
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	1.14 (2.9)	1.43 (3.0)
	Total daily insulin dose after 26 weeks, mean units (SD)	55 (40)	68 (46)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDegAsp – BIAsp 30
		Treatment contrast	0.05
		95% CI	−0.10; 0.20[†]
	1) Confirmatory secondary endpoint: Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	Comparison groups	IDegAsp – BIAsp 30
		Treatment contrast	−1.06
		95% CI	[−1.43; −0.70]*
	2) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp /BIAsp 30
		Rate ratio	1.00
		95% CI	[0.76; 1.32]
	3) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	Comparison groups	IDegAsp /BIAsp 30
		Odds ratio	1.77
		95% CI	[0.97; 3.25]
	4) Confirmatory secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDegAsp – BIAsp 30
		Treatment contrast	−0.38
		95% CI	[−0.96; 0.21]
	5) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp /BIAsp 30
		Rate ratio	0.67
		95% CI	[0.43; 1.06]

	Supportive secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.

BIAsp: biphasic insulin aspart; BID: twice daily, BHI: biphasic human insulin; BMI: body mass index; 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 A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 treatment weeks; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; OD: once daily; SAS: safety analysis set; SD: standard deviation; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: Statistically significant

IDegAsp – Therapeutic Exploratory Trials

Summary of Efficacy for Trial 1791

Title: A 16 week randomised, open labelled, 3 armed, parallel group, treat-to-target trial comparing once daily injection of SIAC 30 (B), SIAC 45 (B) and insulin glargine, all in combination with metformin in subjects with type 2 diabetes failing on OAD treatment			
Study identifier	Protocol number: NN5401-1791; EudraCT number: 2007-002476-33; Study identifier: NCT00614055.		
Design	This was a 16-week randomised, stratified, open labelled, parallel group, multicentre, multinational, efficacy and safety, treat-to-target trial comparing glycaemic control as assessed by HbA_{1c} after treatment with IDegAsp 30, IDegAsp 45 or IGlar. All treatments were given once daily (OD) in combination with met, in subjects with type 2 diabetes mellitus, inadequately controlled on OAD treatment. Stratification was carried out according to previous OAD treatment. The suitability of the trial population was ensured by including an up-titration period prior to randomisation: the current anti-diabetes treatment was discontinued followed by a two-week up-titration period with met towards a final dose of 1500 or 2000 mg/day and an one-week maintenance period. IDegAsp 30 (B) is the formulation used in the confirmatory trials named insulin degludec/insulin aspart (IDegAsp). B refers to the pharmaceutical formulation. The development of the alternative formulation, IDegAsp 45 (B) has been discontinued and is therefore not shown in this table (for IDegAsp 45 (B) results, see trial report Trial 1791 (M 5.3.5.1)).		
	Duration of main phase:	16 weeks + 2 weeks follow-up	
Hypothesis	All pair-wise treatment differences between IDegAsp 30, IDegAsp 45 and IGlar were investigated. The aim of the primary analysis was to estimate the difference between treatments in HbA_{1c} after 16 weeks of treatment and not to show formal superiority or non-inferiority. Estimated treatment means and treatment differences with corresponding 95% confidence intervals were presented based on the estimates from the statistical models that were used. The primary endpoint was analysed using an analysis of variance (ANOVA) approach with treatment, country, sex and OAD treatment at screening as fixed factors, and age and baseline HbA_{1c} as covariates.		
Treatment groups	Insulin degludec/insulin aspart 30 B (IDegAsp 30 B)	A total of 59 subjects were randomised to IDegAsp 30 (B) dosed OD before dinner + metformin (met) at main meals. The total treatment duration was 16 weeks.	
	Insulin degludec/insulin aspart 45 B (IDegAsp 45 B)	A total of 59 subjects were randomised to IDegAsp 45 (B) dosed OD before dinner + metformin (met) at main meals. The total treatment duration was 16 weeks. Endpoints not described and results are not shown for this treatment arm as development discontinued.	
	Insulin glargine (IGlar)	A total of 60 subjects were randomised to IGlar dosed OD before dinner + metformin (met). The total treatment duration was 16 weeks.	
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} after 16 weeks of treatment	see Hypothesis
	Additional primary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycemic episodes	Summarising the proportion of subjects reaching HbA_{1c} <7.0% after 16 weeks of treatment without confirmed hypoglycemic episodes in the last 4 weeks of treatment. Comparison between IDegAsp 30 (B) and BIAsp 30, both in combination with met.
	Secondary endpoint	Change from baseline in FPG (central lab-measured) after 16 weeks of treatment	Comparing the difference in change from baseline in FPG after 16 weeks of treatment with IDegAsp 30 (B) and IGlar, both in combination with met.
	Secondary endpoint	Prandial PG increment after 16 weeks of treatment	Comparing the 9-point SMPG meal increments after 16 weeks of treatment with IDegAsp 30 (B) and IGlar, both in combination with met.
	Secondary endpoint	Number of confirmed[a] hypoglycaemic episodes	Comparing the number of confirmed[a] hypoglycaemic episodes between treatments groups was a safety endpoint and assessed by statistical analysis.
	Secondary endpoint	Number of nocturnal confirmed[a] hypoglycaemic episodes	Comparing the number of confirmed[a] nocturnal hypoglycaemic episodes between treatment groups was a safety endpoint and assessed by statistical analysis.
	Secondary endpoint	Change from baseline in body weight after 16 weeks of treatment	Comparing body weight change from baseline to 16 weeks of treatment between treatment groups was a safety endpoint and assessed by statistical analysis.

	Secondary endpoint	Total daily insulin dose after 16 weeks of treatment	The total daily insulin dose was summarised descriptively and compared between treatment groups.
Database lock	14–November–2008		
Results and Analysis			
Analysis description	**Primary and Secondary Analyses**		
Analysis population and time point description	Full analysis set included all randomised subjects. Per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. Analyses of efficacy endpoints including analyses of primary and secondary efficacy endpoints as well as confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia, were based on the full analysis set (n=178). In addition, the primary endpoint was also analysed based on the Per-protocol analysis set (n=143), while the safety endpoints were summarised using the safety analysis set (n=178). Safety analysis set included all subjects receiving at least one dose of the investigational product or its comparator. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 59.1 years (ranging from 34 to 74 years), mean duration of diabetes of 9.0 years (ranging from 0.7 to 43.1 years), mean HbA_{1c} of 8.5% and mean BMI of 30.3 kg/m^2. The time point duration for all analyses was 16 weeks. In total, 91.6% of randomised subjects completed the trial.		
Statistical methods	Change from baseline in HbA_{1c}, FPG, 9-point SMPG mean postprandial increments, mean IG after 16 weeks and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, country, sex and OAD treatment at screening as fixed factors, and age, baseline HbA_{1c} and relevant baseline value as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. Fluctuations of the IG profiles after 16 weeks of treatment were log transformed and analysed separately using ANOVA method with the addition of the profile mean as a covariate. The number of hypoglycaemic episodes was analysed using a negative binomial model with a log-link function and the logarithm of length of the profiles (in days) as offset. The model included treatment, OAD treatment at screening, sex and country as fixed factors, and age and baseline HbA_{1c} as covariates.		
Descriptive statistics and estimate variability	**Treatment group**	**IDegAsp 30 (B)**	**IGlar**
	Number of subjects (FAS)	59	60
	Change from baseline in HbA_{1c} after 16 weeks of treatment mean %(SD)	-1.31 (1.01)	-1.29 (1.10)
	HbA_{1c} at baseline, mean % (SD)	8.3 (1.2)	8.4 (1.3)
	HbA_{1c} at Week 16, mean % (SD)	7.0 (1.0)	7.1 (1.3)
	HbA_{1c} < 7.0% at end of trial, N (%)	33 (55.9)	31 (51.7)
	Change from baseline in FPG after 16 weeks of treatment, mean mmol/L (SD)	-4.30 (3.45)	-5.07 (3.85)
	Prandial PG increment, mean mmol/L (SD)	1.32 (1.51)	2.32 (1.99)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	115	67
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	6	17
	Change from baseline in body weight after 16 weeks of treatment, mean kg (SD)	-0.4 (2.3)	-0.1 (3.2)
	Total daily insulin dose after 16 weeks of treatment, mean units (SD)	33 (15)	40 (21)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) - IGlar
		Treatment contrast	-0.11
		95% CI	[-0.41; 0.19]
	Additional primary endpoint: HbA_{1c} <7.0% at end of trial	No statistical analysis was performed	
	Secondary endpoint: Change from baseline in FPG after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) - IGlar
		Treatment contrast	-0.13
		95% CI	[-1.03; 0.77]

	Secondary endpoint: Prandial PG increment after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) - IGlar
		Treatment contrast	-0.78
		95% CI	[-1.47;-0.09]
	Secondary endpoint: Number of confirmed hypoglycaemic episodes[a]	Comparison groups	IDegAsp 30 (B) / IGlar
		Rate ratio	2.30
		95% CI	[0.95; 5.58]
	Secondary endpoint: Number of confirmed nocturnal hypoglycaemic episodes[a]	Comparison groups	IDegAsp 30 (B) / IGlar
		Rate ratio	0.42
		95% CI	0.04; 4.84
	Secondary endpoint: Change from baseline in body weight after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) - IGlar
		Treatment contrast	-0.38
		95% CI	[-1.34; 0.58]
	Secondary endpoint: Total daily insulin dose after 16 weeks of treatment	No statistical analysis was performed.	
Notes	[a]Minor episodes same as confirmed hypoglycaemic episodes without major/severe episodes (no major/severe episodes reported in this trial, i.e., minor = confirmed).		

BMI: body mass index; CGM: continuous glucose monitoring; 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 A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 treatment weeks; IGlar: insulin glargine; IDegAsp: insulin degludec/insulin aspart; IG: interstitial glucose; IGlar: insulin glargine; met: metformin; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; PG: plasma glucose; SAS: safety analysis set; SD: standard deviation; SIAC - soluble insulin analogue combination was a name formerly used for insulin degludec/insulin aspart (IDegAsp); SMPG: self-measured plasma glucose;

Summary of Efficacy for Trial 1792

Title: A 16 week randomised, open labelled, 3-armed, parallel group, treat-to-target trial comparing twice daily (BID) injections of SIAC 30 (B), SIAC 45 (B) and NovoMix® 30, all in combination with metformin in subjects with type 2 diabetes failing on OAD treatment.			
Study identifier	Protocol number: NN5401-1792; EudraCT number: 2007-002462-35; Study identifier: NCT00613951.		
Design	This was a 16-week multinational, multicentre, open-labelled, randomised (1:1:1), stratified, three-armed parallel group, efficacy and safety, treat-to-target trial comparing glycaemic control as assessed by HbA_{1c} after treatment with IDegAsp 30 (B), IDegAsp 45 (B) and NovoMix30 (BIAsp 30), all treatments given twice daily (BID) in combination with met in subjects diagnosed with type 2 diabetes mellitus. Stratification was carried out according to previous OAD treatment. The suitability of the trial population was ensured by including an up-titration period prior to randomisation: the current anti-diabetes treatment was discontinued followed by a two-week up-titration period with met towards a final dose of 1500 or 2000 mg/day and an one-week maintenance period. IDegAsp 30 (B) is the formulation used in the confirmatory trials named insulin degludec/insulin aspart (IDegAsp). The development of the alternative formulation, IDegAsp 45 (B) has been discontinued and is therefore not shown in this table (for IDegAsp 45 (B) results see trial report Trial 1792 (M 5.3.5.1)).		
	Duration of main phase:	16 weeks + 2 week follow-up	
Hypothesis	All pair wise treatment differences between IDegAsp 30 (B), IDegAsp 45 (B) and BIAsp 30 concerning HbA_{1c} after 16 weeks of treatment were investigated. The aim of the trial was to estimate the difference between the treatments and not to show formal superiority or non-inferiority. Estimated treatment means and treatment differences with corresponding 95% confidence intervals were presented based on the estimates from the statistical models that were used. The primary endpoint was analysed using an analysis of variance (ANOVA) approach with treatment, country, sex and OAD treatment at screening as fixed factors, and age and baseline HbA_{1c} as covariates.		
Treatment groups	Insulin degludec/insulin aspart 30 B (IDegAsp 30 B)	A total of 61 subjects were randomised to IDegAsp 30 (B) dosed BID pre-breakfast and dinner + metformin (met) at main meals. The total treatment duration was 16 weeks.	
	Insulin degludec/insulin aspart 45 B (IDegAsp 45 B)	A total of 59 subjects were randomised to IDegAsp 45 (B), dosed BID pre-breakfast and dinner + metformin (met) at main meals. The total treatment duration was 16 weeks. Endpoints are not described and results are not shown for this treatment arm as development discontinued.	
	Biphasic human insulin 30 (BIAsp 30; NovoMix 30)	A total of 62 subjects were randomised to BIAsp 30, dosed BID pre-breakfast and dinner + metformin (met) at main meals. The total treatment duration was 16 weeks.	
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} after 16 weeks of treatment	See Hypothesis
	Additional primary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycemic episodes	Summarising the proportion of subjects reaching HbA_{1c} <7.0% after 16 weeks of treatment without confirmed hypoglycemic episodes in the last 4 weeks of treatment. Comparison between IDegAsp 30 (B) and BIAsp 30, both in combination with met.
	Secondary endpoint	Change from baseline in FPG (central lab-measured) after 16 weeks of treatment	Comparing the difference in change from baseline in FPG after 16 weeks of treatment with IDegAsp 30 (B) and BIAsp 30, both in combination with met.
	Secondary endpoint	Prandial PG increment after 16 weeks of treatment	Comparing the 9-point SMPG increments during 16 weeks of treatment with IDegAsp 30 (B) and BIAsp 30, both in combination with met.
	Secondary endpoint	Number of confirmed[a] hypoglycaemic episodes	Comparing the number of confirmed[a] hypoglycaemic episodes between treatment groups was a safety endpoint and assessed by statistical analysis.
	Secondary endpoint	Number of nocturnal confirmed[a] hypoglycaemic episodes	Comparing the number of confirmed[a] nocturnal hypoglycaemic episodes between treatment groups was a safety endpoint and assessed by statistical analysis.
	Secondary endpoint	Change from baseline in body weight after 16 weeks of treatment	Comparing body weight change from baseline to 16 weeks of treatment between treatment groups was a safety endpoint and assessed by statistical analysis.
	Secondary endpoint	Total daily insulin dose after 16 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups.

Database lock	14–November–2008		
Results and Analysis			
Analysis description	**Primary and Secondary Analyses**		
Analysis population and time point description	The full analysis set included all randomised subjects. The per protocol analysis set included subjects without any major protocol violations that may have affected the primary endpoint. Analyses of efficacy endpoints including analyses of primary and secondary efficacy endpoints as well as confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia, were based on the full analysis set (n= 182), while the safety endpoints were summarised using the safety analysis set (n=181). The safety analysis set included all subjects receiving at least one dose of the investigational product or its comparator. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 59.6 years (ranging from 34 to 75 years), mean duration of diabetes of 9.4 years (ranging from 0.6 to 36.2 years), mean HbA_{1c} of 8.5 % and mean BMI of 31.4 kg/m^2. The time point duration for all analyses was 16 weeks. The distribution of pre-trial OAD treatment regimen was similar in all three treatment groups because pre-trial OAD treatment was stratified at randomisation. A total of 88.5%, 91.5% and 91.9% completed the trial in the IDegAsp, IDegAsp 45 and BIAsp 30 groups, respectively.		
Statistical methods	Change from baseline in HbA_{1c}, FPG, 9-point SMPG mean postprandial increments, mean IG after 16 weeks, and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, OAD treatment at screening, sex and country as fixed factors, and age, baseline $HbA_{1c,}$ baseline FPG in FPG analysis and baseline body weight in body weight analysis as covariates. Fluctuations of the IG profiles after 16 weeks of treatment were log transformed and analysed separately using ANOVA method with the addition of the profile mean as a covariate. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, OAD treatment at screening, sex and country as fixed factors, and age and baseline HbA_{1c} as covariates. All analyses in this trial were pre-specified in the protocol.		
Descriptive statistics and estimate (SD)	**Treatment group**	**IDegAsp 30 (B)**	**BIAsp 30**
	Number of subjects (FAS)	61	62
	Change from baseline in HbA_{1c} after 16 weeks of treatment mean %(SD)	-1.79 (1.11)	-1.84 (0.93)
	HbA_{1c} at baseline, mean % (SD)	8.5 (1.2)	8.6 (1.0)
	HbA_{1c} at Week 16, mean % (SD)	6.7 (1.0)	6.7 (0.7)
	HbA_{1c} < 7.0% at end of trial, N (%)	45 (73.8)	48 (77.4)
	Change from baseline in FPG after 16 weeks of treatment, mean mmol/L (SD)	-5.07 (2.89)	-4.28 (3.01)
	Prandial PG increment, mean mmol/L (SD)	0.84 (1.72)	1.11 (1.53)
	Observed rate of confirmed hypoglycaemic episodes per 100 PYE	287	730
	Observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE	39	108
	Change from baseline in body weight after 16 weeks of treatment, mean kg (SD)	1.1 (2.8)	1.4 (3.2)
	Total daily insulin dose after 16 weeks of treatment, mean units (SD)	52 (27)	61 (29)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) – BIAsp 30
		Treatment contrast	-0.02
		95% CI	[-0.27; 0.24]
	Additional primary endpoint: HbA_{1c} <7.0% at end of trial	No statistical analysis was performed	
	Secondary endpoint: Change from baseline in FPG after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) – BIAsp 30
		Treatment contrast	-0.99
		95% CI	[-1.68;-0.29]

	Secondary endpoint: Prandial PG increment after 16 weeks of treatment	Comparison groups	IDegAsp 30 (B) - BIAsp 30
		Treatment contrast	-0.23
		95% CI	[-0.84; 0.38]
	Secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDegAsp 30 (B) / BIAsp 30
		Rate ratio	0.42
		95% CI	[0.23; 0.75]
	Secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDegAsp 30 (B) / BIAsp 30
		Rate ratio	0.33
		95% CI	[0.09; 1.14]
	Secondary endpoint: Change from baseline in body weight after 16 weeks of treatment, mean kg, (SD)	Comparison groups	IDegAsp 30 (B) - BIAsp 30
		Treatment contrast	-0.14
		95% CI	[-1.14; 0.87]
	Secondary endpoint: Total daily insulin dose (U)	Comparison groups	IDegAsp 30 (B) / BIAsp 30
		Treatment ratio	0.85
Notes	[a]Confirmed hypoglycaemic episodes are the same as minor hypoglycaemic episodes in this trial as there were no major or severe episodes reported in this trial (i.e., minor = confirmed).		

BIAsp: biphasic insulin aspart; BMI: body mass index; 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 A_{1c}; HbA_{1c} <7% : Endpoint was only defined for subjects exposed for at least 12 treatment weeks; IDegAsp: insulin degludec/insulin aspart; IG: interstitial glucose; met: metformin; NN5401: the name previously used for insulin degludec/insulin aspart (IDeg/IAsp); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; PG: plasma glucose; SAS: safety analysis set; SD: standard deviation; SIAC - soluble insulin analogue combination was a name formerly used for insulin degludec/insulin aspart (IDegAsp); SMPG: self-measured plasma glucose

IDeg – Therapeutic Confirmatory Trials

Summary of Efficacy for Trial 3583

Title: A 52-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin in subjects with type 1 diabetes			
Study identifier	Protocol number: NN1250-3583; EudraCT number: 2008-005774-13; Study identifier: NCT00982228.		
Design	This trial was a 52-week, multicentre, multinational, open-labelled, randomised (3:1), two arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg OD with IGlar OD, all in combination with IAsp. During the 1-week follow-up period, the subjects were treated with insulin NPH + IAsp. Subjects eligible for the trial were subjects with type 1 diabetes mellitus treated with any basal-bolus regimen. The trial has been extended with a 52-week extension trial.		
	Duration of main phase: Duration of extension phase:		52 weeks + 1 week follow-up 52 weeks + 1 week follow-up (Trial 3644, ongoing)
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). The trial also aimed at showing superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Number of nocturnal confirmed hypoglycaemic episodes; 2) Number of confirmed hypoglycaemic episodes; 3) Change from baseline in FPG; 4) Within-subject variation in SMPG.		
Treatments groups	Insulin degludec (IDeg) + insulin aspart (IAsp)		A total of 472 subjects were randomised to IDeg dosed OD with the main evening meal + IAsp at main meals. The total treatment duration was 52 weeks.
	Insulin glargine (IGlar) + insulin aspart (IAsp)		A total of 157 subjects were randomised to IGlar dosed OD according to approved labelling + IAsp at main meals. The total treatment duration was 52 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	See Hypothesis.
	1) Confirmatorysecondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	2) Confirmatorysecondary endpoint	Number of confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	3) Confirmatorysecondary endpoint	Change from baseline in FPG (central lab-measured) after 52 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDeg minus IGlar) was entirely below zero.
	4) Confirmatorysecondary endpoint	Within-subject variability in SMPG after 52 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated treatment ratio (IDeg/IGlar) (CV%) was entirely below one.
	Supportive secondary endpoint	Change from baseline in body weight after 52 weeks of treatment	Body weight change from baseline to 52 weeks was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 52 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	08-Dec-2010		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of efficacy endpoints including analyses of confirmatory analyses on confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia, were based on the FAS (n=629), while the safety endpoints were summarised using the SAS (n=626). The population consisted of male and female subjects with type 1 diabetes mellitus with a mean age of 43.0 years (ranging from 18.4 to 78.2 years), mean duration of diabetes of 18.9 years (ranging from 1.0 to 63.2 years), mean HbA_{1c} of 7.7 % and mean BMI of 26.1 kg/m^2. The time point duration for all analyses was 52 weeks. A total of 99% of the subjects in both treatment groups were treated with a basal-bolus insulin regimen pre-trial. Of these 70.6% of the subjects were treated with IGlar pre-trial. A total of 85.6% of subjects in the IDeg group and 87.3% of subjects in the IGlar group completed the trial.		
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariates. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed pre-breakfast SMPG values as repeated measures. The model included treatment, antidiabetic treatment at screening, sex, and region as factors, age as covariate, subject as random factor and assumed independent within- and between-subject errors with variance depending on treatment. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IGlar**
	Number of subjects (FAS)	472	157
	Change from baseline in HbA_{1c} after 52 weeks of treatment, mean % (SD)	-0.40 (0.7)	-0.39 (0.8)
	HbA_{1c} at baseline, mean % (SD)	7.69 (0.9)	7.72 (1.0)
	HbA_{1c} at Week 52, mean % (SD)	7.29 (1.0)	7.33 (1.1)
	Change from baseline in FPG after 52 weeks of treatment, mean mmol/L (SD)	-1.27 (5.0)	-1.39 (5.3)
	Within-subject variability in SMPG after 52 weeks of treatment, CV%	Not Applicable	Not Applicable
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	4253.6	4017.7
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	440.7	585.7
	Change from baseline in body weight after 52 weeks of treatment, mean kg (SD)	1.79 (4.0)	1.59 (4.2)
	Total daily insulin dose after 52 weeks of treatment mean units (SD)	61 (34)	66 (34)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.01
		95% CI	[-0.14; 0.11][†]
	1) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.75
		95% CI	[0.59; 0.96]*
	2) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	1.07
		95% CI	[0.89; 1.28]
	3) Confirmatory secondary endpoint: Change from baseline in FPG after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.33
		95% CI	[-1.03; 0.36]
	4) Confirmatory secondary endpoint: Within-subject variability (CV%) in SMPG after 52 weeks of treatment	Comparison groups	IDeg/IGlar
		Treatment ratio	0.96
		95% CI	[0.86; 1.05]
	Supportive secondary endpoint: Change from baseline in body weight after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	0.18
		95% CI	[-0.54; 0.91]

	Supportive secondary endpoint: Total daily insulin dose after 52 weeks of treatment	No statistical analysis was performed.

BMI: body mass index; 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 A_{1c}; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OD: once daily; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast); [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Summary of Efficacy for Trial 3585

Title: A 26-week confirmatory, randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of NN1250 and insulin detemir in a basal-bolus regimen with insulin aspart as mealtime insulin in subjects with type 1 diabetes mellitus.			
Study identifier	Protocol number: NN1250-3585; EudraCT number: 2009-011672-29; Study identifier: NCT01074268.		
Design	This trial was a 26-week, multicentre, multinational, open-labelled, randomised (2:1), two arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg OD with IDet OD or BID, all in combination with IAsp. During the 1-week follow-up period, the subjects were treated with insulin NPH + IAsp. Subjects eligible for the trial were subjects with type 1 diabetes mellitus treated with any basal-bolus regimen. The trial has been extended with a 26-week extension trial.		
	Duration of main phase: Duration of extension trial:		26 weeks + 1 week follow-up 26 weeks + 1 week follow-up (Trial 3725, ongoing)
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – IDet) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). If non-inferiority was confirmed for the primary endpoint then superiority of a number of confirmatory secondary endpoints was tested using a hierarchical testing procedure to control the overall type I error rate: 1) Number of nocturnal confirmed hypoglycaemic episodes; 2) Number of confirmed hypoglycaemic episodes; 3) Change from baseline in FPG; 4) Within-subject variability in SMPG.		
Treatments groups	Insulin degludec (IDeg) + insulin aspart (IAsp)		A total of 303 subjects were randomised to IDeg dosed OD in the evening (from start of main evening meal to bedtime) + IAsp at main meals. The total treatment duration was 26 weeks.
	Insulin detemir (IDet) + insulin aspart (IAsp)		A total of 153 subjects randomised to IDet dosed OD according to approved labelling + IAsp at main meals. A second dose of IDet could be added after 8 weeks of treatment, in case of inadequate glycaemic control. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	1) Confirmatorysecondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IDet) was entirely below one.
	2) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IDet) was entirely below one.
	3) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDeg minus IDet) was entirely below zero.
	4) Confirmatory secondary endpoint	Within-subject variability in SMPG after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated treatment ratio (IDeg/IDet) (CV%) was entirely below one.
	Supportive secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	10-Jan -2011		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of efficacy endpoints, including analyses of body weight and hypoglycaemia, were based on FAS (n=455), while the safety endpoints were summarised using the SAS (n=453). The population consisted of male and female subjects with type 1 diabetes mellitus with a mean age of 41.3 years (ranging from 18.1 to 80.9 yrs), mean duration of diabetes of 13.9 years (ranging from 1.0 to 51.7 years), mean HbA_{1c} of 8.0 % and mean BMI of 23.6 kg/m^2. The time point duration for all analyses was 26 weeks. Overall, 48.6% of the subjects were treated with IGlar and 36.3% of the subjects were treated with IDet pre-trial. A total of 93.4% of subjects in the IDeg group and 90.2% of subjects in the IDet group completed the trial.		
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed pre-breakfast SMPG values as repeated measures. The model included treatment, antidiabetic treatment at screening, sex, and region as factors, age as covariate, subject as random factor and assumed independent within- and between-subject errors with variance depending on treatment. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IDet**
	Number of subjects (FAS)	302	153
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-0.73 (0.9)	-0.65 (0.9)
	HbA_{1c} at baseline, mean % (SD)	7.98 (1.0)	7.99 (0.9)
	HbA_{1c} at Week 26, mean % (SD)	7.25 (1.0)	7.35 (0.9)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-2.60 (4.9)	-0.62 (4.5)
	Within-subject variability in SMPG after 26 weeks of treatment, CV%	Not applicable	Not applicable
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	4583.1	4568.9
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	414.1	593.5
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	1.50 (2.7)	0.42 (2.4)
	Total daily insulin dose after 26 weeks of treatment, mean units (SD)	61 (36)	69 (38)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-0.09
		95% CI	[-0.23; 0.05]†
	1) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/IDet
		Rate ratio	0.66
		95% CI	[0.49; 0.88]*
	2) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg/IDet
		Rate ratio	0.98
		95% CI	[0.80; 1.20]
	3) Confirmatory secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-1.66
		95% CI	[-2.37; -0.95]*
	4) Confirmatory secondary endpoint: Within-subject variability (CV%) in SMPG after 26 weeks of treatment	Comparison groups	IDeg/IDet
		Treatment ratio	1.02
		95% CI	[0.91; 1.12]
	Supportive secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	1.08
		95% CI	[0.58; 1.57]*
	Supportive secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.	

BID: twice daily; BMI: body mass index; 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 A_{1c}; IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; IGlar: insulin glargine; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OD: once daily; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast); [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Table 12 Summary of Efficacy for Trial 3770

Title: A 26-week, randomised, controlled, open label, multicentre, multinational, three-arm, parallel, treat-to-target trial comparing efficacy and safety of two different dosing regimens of NN1250 insulin degludec and one dosing regimen of insulin glargine, both in combination with meal-time insulin aspart in subjects with type 1 diabetes mellitus with a 26-week extension period investigating the long term safety of NN1250.			
Study identifier	Protocol number: NN1250-3770; EudraCT number: 2009-012923-27; Study identifier: NCT01079234.		
Design	This trial was a 26-week, multicentre, multinational, open-labelled, randomised (1:1:1), three arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg in a flexible OD dosing schedule (IDeg FF) versus IGlar OD and versus IDeg OD, all in combination with IAsp. During the 1-week follow-up period, subjects were treated with insulin NPH + IAsp. Subjects eligible for the trial were subjects with type 1 diabetes mellitus treated with injected-based therapies in a basal-bolus regimen consisting of either 1 or 2 basal injections and at least 3 bolus injections. The trial has been amended with a 26-week extension period.		
	Duration of main phase: Duration of extension phase:		26 weeks + 1 week follow-up 26 weeks + 1 week follow-up (Trial 3770 amended, ongoing)
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg FF – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). None of the secondary endpoints were analysed as confirmatory endpoints.		
Treatments groups	Insulin degludec flexible (IDeg FF) + insulin aspart (IAsp)		A total of 164 subjects were randomised to IDeg administered OD according to a flexible dosing schedule with 8-40 h intervals between doses + IAsp at main meals. The total treatment duration of the main trial was 26 weeks.
	Insulin degludec (IDeg OD) + insulin aspart (IAsp)		A total of 165 subjects were randomised to IDeg dosed OD with the main evening meal + IAsp at main meals. The total treatment duration was 26 weeks.
	Insulin glargine (IGlar) + insulin aspart (IAsp)		A total of 164 subjects were randomised to IGlar dosed OD according to approved labelling + IAsp at main meals. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	Secondary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDeg FF and IDeg OD.
	Secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	Comparing the change in FPG from baseline after 26 weeks of treatment between IDeg FF and IGlar, and between IDeg FF and IDeg OD.
	Secondary endpoint	Number of confirmed hypoglycaemic episodes	The number of confirmed hypoglycaemic episodes was compared between IDeg FF and IGlar, and between IDeg FF and IDeg OD, and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	The number of nocturnal confirmed hypoglycaemic episodes was compared between IDeg FF and IGlar, and between IDeg FF and IDeg OD, and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks 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 was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	14-Dec-2011		
Results and Analysis			
Analysis description	**Primary Analysis and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. All statistical analyses, including analyses of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were based on the FAS (n=493), while the safety endpoints were summarised using the SAS (n=490). The population consisted of male and female subjects with type 1 diabetes mellitus with a mean age of 43.7 years (ranging from 19.3 to 82.4 years), mean duration of diabetes of 18.5 years (ranging from 1.1 to 52.7 years), mean HbA_{1c} of 7.7 % and mean BMI of 26.5 kg/m^2. The time point duration for all analyses was 26 weeks. All subjects (except one subject in the IDeg FF group) were treated on a basal bolus insulin regimen pre-trial. Of these, 63.7% and 27.4% of the subjects were treated pre-trial with IGlar and IDet , respectively. A total of 84.1% of subjects in the IDeg FF group, 84.2% of subjects in the IDeg OD group and 92.7% of subjects in the IGlar group completed the trial.				
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariates. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.				
Descriptive statistics and estimate variability	**Treatment group**	**IDeg FF**	**IDeg OD**	**IGlar**	
	Number of subjects (FAS)	164	165	164	
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-0.40 (0.6)	-0.41 (0.7)	-0.58 (0.7)	
	HbA_{1c} at baseline, mean % (SD)	7.69 (1.0)	7.70 (0.9)	7.73 (0.9)	
	HbA_{1c} at Week 26, mean % (SD)	7.29 (0.9)	7.29 (0.9)	7.15 (0.8)	
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-1.28 (5.0)	-2.54 (5.1)	-1.33 (5.2)	
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	8237.7	8825.1	7973.4	
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	623.2	960.7	995.6	
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	1.16 (3.5)	0.79 (2.5)	1.61 (3.7)	
	Total daily insulin dose after 26 weeks of treatment, mean units (SD)	65 (36)	59 (41)	70 (51)	
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups		IDeg FF – IGlar	
		Treatment contrast		0.17	
		95% CI		[0.04; 0.30]†	
	Secondary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups		IDeg FF – IDeg OD	
		Treatment contrast		0.01	
		95% CI		[-0.13; 0.14]	
	Secondary endpoint: Change from baseline in FPG after 26 weeks of treatment, mmol/L	Comparison groups		IDeg FF – IGlar	IDeg FF – IDeg OD
		Treatment contrast		-0.05	0.95
		95% CI		[-0.85; 0.76]	[0.15; 1.75]
	Secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups		IDeg FF/ IGlar	IDeg FF/ IDeg OD
		Rate ratio		1.03	0.92
		95% CI		[0.85; 1.26]	[0.76; 1.12]
	Secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups		IDeg FF/ IGlar	IDeg FF/ IDeg OD
		Rate ratio		0.60	0.63
		95% CI		[0.44; 0.82]*	[0.46; 0.86]*
	Secondary endpoint: Change from baseline in body weight after 26 weeks of	Comparison groups		IDeg FF – IGlar	IDeg FF – IDeg OD
		Treatment contrast		-0.44	0.33

	treatment	95% CI	[-1.14; 0.27]*	[-0.38; 1.03]
	Secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.		

BMI: body mass index; 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; FF: fixed flexible, subjects treated with a rotation dosing schedule; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A_{1c}; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; NN1250: the name previously used for insulin degludec (IDeg); IDet: insulin detemir; Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OD: once daily; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Summary of Efficacy for Trial 3582

Title: A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin ± treatment with metformin, ± pioglitazone in subjects with type 2 diabetes currently treated with insulin qualifying for intensified treatment			
Study identifier	Protocol number: NN1250-3582; EudraCT number: 2008-005777-35; Study identifier: NCT00972283		
Design	This trial was a 52-week, multicentre, multinational, open-labelled, randomised (3:1), two arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg OD with IGlar OD, all in combination with IAsp ± met ± pio. Subjects eligible for the trial were subjects with type 2 diabetes mellitus treated with any insulin regimen (premix, self-mix, basal only, basal-bolus [one or more boluses], bolus only, pump) ± OAD(s). At randomisation, the subject's current antidiabetic treatment was discontinued except for metformin and pioglitazone, if applicable. The trial was stratified according to previous insulin regimen with the categories basal-bolus regimen, basal insulin only, or other insulin regimen. The trial has been extended with a 26-week extension trial.		
	Duration of main phase: Duration of extension phase:		52 weeks + 1 week follow-up 26 weeks + 1 week follow-up (Trial 3667, ongoing)
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). The trial also aimed at showing superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Number of confirmed hypoglycaemic episodes; 2) Change from baseline in FPG; 3) Within-subject variability in SMPG; 4) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec (IDeg) + insulin aspart (IAsp)		A total of 755 subjects were randomised to IDeg dosed OD with the main evening meal + IAsp at main meals ± metformin (met) ± pioglitazone (pio) dosed as pre-trial. The total treatment duration was 52 weeks.
	Insulin Glargine (IGlar) + insulin aspart (IAsp)		A total of 251 subjects randomised to IGlar dosed OD according to approved labelling + IAsp at main meals ± metformin (met) ± pioglitazone (pio) dosed as pre-trial. The total treatment duration was 52 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	2) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 52 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed if the 95% CI for the treatment difference (IDeg minus IGlar) was entirely below zero.
	3) Confirmatory secondary endpoint	Within-subject variability in SMPG after 52 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated treatment ratio (IDeg/IGlar) (CV%) was entirely below one.
	4) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDeg/IGlar) was entirely above one.
	Supportive secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	The number of nocturnal confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in body weight after 52 weeks of treatment	Body weight change from baseline to 52 weeks was a safety endpoint compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 52 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	26-Nov-2010		
Results and Analysis			

Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		
Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of efficacy endpoints, including analyses of hypoglycaemia and body weight, were based on the FAS (n=992). The safety endpoints were summarised using the SAS (n=1004). The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 58.9 years (ranging from 23.1 to 86.3 years), mean duration of diabetes of 13.5 years (ranging from 0.6 to 57.2 years), mean HbA_{1c} of 8.3 % and mean BMI of 32.2 kg/m^2. The time point duration for all analyses was 52 weeks. Pre-trial, the majority of subjects (49.0%) were treated on a basal-bolus insulin regimen with or without OADs, 24.4% were on a premix regimen with or without OADs and 21.2% were on a basal insulin regimen with or without OADs. The most commonly used basal insulin pre-trial was IGlar (43.0%). A total of 81.9% of subjects in the IDeg group and 84.1% of subjects in the IGlar group completed the trial.		
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of the number of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All of the analyses included in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IGlar**
	Number of subject	744	248
	Change from baseline in HbA_{1c} after 52 weeks of treatment, mean % (SD)	-1.17 (1.0)	-1.29 (1.0)
	HbA_{1c} at baseline, mean % (SD)	8.27 (0.8)	8.36 (0.9)
	HbA_{1c} at Week 52, mean % (SD)	7.10 (1.0)	7.07 (1.0)
	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia, N (%)	171 (24.4)	55 (23.2)
	Change from baseline in FPG after 52 weeks of treatment, mean mmol/L (SD)	-2.44 (3.5)	-2.14 (3.6)
	Within-subject variability in SMPG after 52 weeks of treatment, CV%	Not applicable	Not applicable
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	1108.9	1363.4
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	138.7	184.4
	Change from baseline in body weight after 52 weeks of treatment, mean kg (SD)	3.61 (4.9)	3.97 (4.6)
	Total daily insulin dose after 52 weeks of treatment, mean units (SD)	143.1 (94.7)	139.0 (98.1)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	0.08
		95% CI	[-0.05; 0.21]†
	1) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.82
		95% CI	[0.69; 0.99]*
	2) Confirmatory secondary endpoint: Change from baseline in FPG after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.29
		95% CI	[-0.65; 0.06]
	3) Confirmatory secondary endpoint: Within-subject variability in SMPG (CV%)	Comparison groups	IDeg/IGlar
		Treatment ratio	0.94
		95% CI	[0.87; 1.01]
	4) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Odds ratio	1.02
		95% CI	[0.72; 147]
	Supportive secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.75
		95% CI	[0.58; 0.99]*
	Supportive secondary endpoint: Change from baseline in body weight after 52	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.31

	weeks of treatment	95% CI	[-0.98; 0.37]
	Supportive secondary endpoint: Total daily insulin dose after 52 weeks of treatment	No statistical analysis was performed.	

BMI: body mass index; 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} <7.0%: endpoint was only defined for subjects exposed for at least 12 weeks; HbA_{1c}: glycosylated haemoglobin A_{1c}; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; met: metformin; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; pio: pioglitazone; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast); [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Summary of Efficacy for Trial 3579

Title: A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of NN1250 and insulin glargine, both injected daily in combination with oral anti-diabetic drugs (OADs), in subjects with type 2 diabetes mellitus currently treated with OADs and qualifying more intensified treatment (BEGIN™: Once Long)			
Study identifier	Protocol number: NN1250-3579; EudraCT number: 2008-005776-27; Study identifier: NCT00982644.		
Design	This trial was a 52-week, multicentre, multinational, open-labelled, randomised (3:1), two arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg OD with IGlar OD, all + met ± DPP-4I. During the 1-week follow-up period, subjects were treated with insulin NPH and continued OAD treatment. Subjects eligible for the trial were insulin-naïve subjects with type 2 diabetes mellitus currently treated with OAD(s) qualifying for intensified treatment. At randomisation, the subject's current antidiabetic treatment was discontinued except for metformin and DPP-4 inhibitor (if applicable according to approved labelling). The trial has been extended with a 52-week extension trial.		
	Duration of main phase: Duration of extension phase:		52 weeks + 1 week follow-up 52 weeks + 1 week follow-up (Trial 3643, ongoing)
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). The trial also aimed at showing superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Number of confirmed hypoglycaemic episodes; 2) Change from baseline in FPG; 3) Within-subject variation in SMPG; 4) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec (IDeg)		A total of 773 subjects were randomised to IDeg dosed OD with the main evening meal + metformin (met) ± dipeptidyl-peptidase 4-inhibitor (DPP-4I) dosed as pre-trial. The total treatment duration was 52 weeks.
	Insulin glargine (IGlar)		A total of 257 subjects randomised to IGlar dosed OD according to approved labelling + metformin (met) ± dipeptidyl-peptidase 4-inhibitor (DPP-4I) dosed as pre-trial. The total treatment duration was 52 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	2) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 52 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDeg minus IGlar) was entirely below zero.
	3) Confirmatory secondary endpoint	Within subject variability in SMPG after 52 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated treatment ratio (IDeg/IGlar) (CV%) was entirely below one.
	4) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was to be considered confirmed for this endpoint if the 95% CI for the odds ratio (IDeg/IGlar) was entirely above one.
	Supportive secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	Comparing the number of nocturnal confirmed hypoglycaemic episodes between the treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in body weight after 52 weeks of treatment	Body weight change from baseline to 52 weeks was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 52 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	17-Jan-2011		
Results and Analysis			

Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		
Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The safety endpoints were summarised using the SAS (n=1023). The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of efficacy endpoints, including analyses of body weight and hypoglycaemia, were based on the FAS (n=1030). The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 59.1 years (ranging from 21.9 to 87.0 years), mean duration of diabetes of 9.2 years (ranging from 0.5 to 44.4 years), mean HbA_{1c} of 8.2 % and mean BMI of 31.1 kg/m^2. The time point duration for all analyses was 52 weeks. The majority of subjects in both treatment groups were insulin-naïve at screening, with 60.1% of subjects on two OADs and 29.2% on one OAD pre-trial. A total of 78.5% of subjects in the IDeg group and 76.7% of subjects in the IGlar group completed the trial.		
Statistical methods	Change from baseline in HbA_{1c}, FPG, and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of subjects achieving HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed prebreakfast SMPG values as repeated measures. The model included treatment, antidiabetic treatment at screening, sex, and region as factors, age as covariate, subject as random factor and assumed independent within- and between-subject errors with variance depending on treatment.The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses described in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IGlar**
	Number of subjects (FAS)	773	257
	Change from baseline in HbA_{1c} after 52 weeks of treatment, mean % (SD)	-1.06 (1.0)	-1.19 (1.0)
	HbA_{1c} at baseline, mean % (SD)	8.16 (0.8)	8.21 (0.8)
	HbA_{1c} at Week 52, mean % (SD)	7.10 (1.0)	7.03 (1.0)
	HbA_{1c} <7.0% without confirmed hypoglycaemia, N (%)	296 (42.1)	106 (45.7)
	Change from baseline in FPG after 52 weeks of treatment, mean mmol/L (SD)	-3.76 (3.0)	-3.30 (2.9)
	Within-subject variability in SMPG after 52 weeks of treatment, CV%	Not applicable	Not applicable
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	152.0	184.9
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	25.3	38.5
	Change from baseline in body weight after 52 weeks of treatment, mean kg (SD)	2.33 (4.3)	2.12 (4.1)
	Total daily insulin dose after 52 weeks of treatment, mean units (SD)	56.0 (38.7)	57.8 (34.1)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	0.09
		95% CI	[-0.04; 0.22][†]
	1) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.82
		95% CI	[0.64; 1.04]
	2) Confirmatory secondary endpoint: Change from baseline in FPG after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.43
		95% CI	[-0.74; -0.13]*
	3) Confirmatory secondary endpoint: Within-subject variability	Comparison groups	IDeg/IGlar
		Treatment ratio	0.99

	in SMPG (CV%) after 52 weeks of treatment	95% CI	[0.92; 1.06]
	4) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia	Comparison groups	IDeg/IGlar
		Odds ratio	0.86
		95% CI	[0.63; 1.17]
	Supportive secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.64
		95% CI	[0.42; 0.98]*
	Supportive secondary endpoint: Change from baseline in body weight after 52 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	0.28
		95% CI	[-0.32; 0.88]
	Supportive secondary endpoint: Total daily insulin dose after 52 weeks of treatment	No statistical analysis was performed.	

BMI: body mass index; CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; DDP-4I: dipeptidyl-peptidase 4-inhibitor; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c} <7.0%: endpoint was only defined for subjects exposed for at least 12 weeks; HbA_{1c}: glycosylated haemoglobin A_{1c}; IDeg: insulin degludec; IGlar: insulin glargine; met: metformin; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic drug; OD: once daily; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast); [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Summary of Efficacy for Trial 3672

Title: BEGIN™: LOW VOLUME. A trial comparing efficacy and safety of NN1250 and insulin glargine in subjects with type 2 diabetes			
Study identifier	Protocol number: NN1250-3672; EudraCT number: 2009-010662-28; Study identifier: NCT01068665.		
Design	This trial was a 26-week multicentre, multinational, open-labelled, randomised (1:1), two arm parallel-group, treat-to-target trial comparing efficacy and safety of IDeg 200 U/mL OD with IGlar OD, all + met ±DPP-4I. During the 1-week follow-up period, the subjects were treated with insulin NPH and continued OAD treatment. Subjects eligible for the trial were insulin-naïve subjects with type 2 diabetes mellitus currently treated with OADs who qualified for intensified treatment. At randomisation, the subject's current antidiabetic treatment was discontinued except for metformin and DPP-4 inhibitor (if applicable according to approved labelling).		
	Duration of main phase		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). The trial also aimed at showing superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Number of confirmed hypoglycaemic episodes; 2) Change from baseline in FPG; 3) Within-subject variability in SMPG; 4) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec (IDeg)		A total of 230 subjects were randomised to IDeg dosed OD with the main evening meal + metformin (met) ± dipeptidyl-peptidase 4-inhibitor (DPP-4I) dosed as pre-trial. The total treatment duration was 26 weeks.
	Insulin glargine (IGlar)		A total of 230 subjects were randomised to IGlar dosed OD according to approved labelling + metformin (met) ± dipeptidyl-peptidase 4-inhibitor (DPP-4I) dosed as pre-trial. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	2) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDeg minus IGlar) was entirely below zero.
	3) Confirmatory secondary endpoint	Within-subject variability in SMPG after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated treatment ratio (IDeg/IGlar) (CV%) was entirely below one.
	4) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDeg/IGlar) was entirely above one.
	Supportive secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	The number of nocturnal confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks was a safety endpoint compared between treatment groups and evaluated by statistical analysis.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	21-Dec-2010		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of all efficacy endpoints were based on the FAS (n=457) as were analyses of hypoglycaemia and body weight. All other endpoints related to safety were based on the SAS (n=456). The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 57.5 years (ranging from 31.0 to 78.0 years), mean duration of diabetes of 8.2 years (ranging from 0.5 to 59.7 years), mean HbA_{1c} of 8.3 % and mean BMI of 32.4 kg/m^2. The time point duration for all analyses was 26 weeks. The majority of subjects (60.0%) were on two OADs at screening and 28.9% were on one OAD at screening. A total of 87.0% of subjects in the IDeg group and 87.4% of subjects in the IGlar group completed the trial.			
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of the number of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed prebreakfast SMPG values as repeated measures. The model included treatment, antidiabetic treatment at screening, sex, and region as factors, age as covariate, subject as random factor and assumed independent within- and between-subject errors with variance depending on treatment.The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses described in this table were pre-specified in the protocol.			
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IGlar**	
	Number of subjects (FAS)	228	229	
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-1.30 (1.0)	-1.32 (1.0)	
	HbA_{1c} at baseline, mean % (SD)	8.29 (1.0)	8.24 (0.9)	
	HbA_{1c} at Week 26, mean % (SD)	6.99 (0.9)	6.93 (1.0)	
	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia, N (%)	95 (45.2)	96 (44.7)	
	Change from baseline in FPG after 26 weeks of treatment, mean,(SD), mmol/L	-3.70 (3.1)	-3.38 (3.0)	
	Within-subject variability in SMPG after 26 weeks of treatment, CV%	Not applicable	Not applicable	
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	122.1	142.1	
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	18.0	28.1	
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	1.87 (3.5)	1.47 (3.5)	
	Total daily insulin dose after 26 weeks of treatment, mean units (SD)	59.5 (35.2)	62.7 (31.7)	
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDeg – IGlar	
		Treatment contrast	0.04	
		95% CI	[-0.11; 0.19]†	
	1) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar	
		Rate ratio	0.86	
		95% CI	[0.58; 1.28]	
	2) Confirmatory secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDeg – IGlar	
		Treatment contrast	-0.42	
		95% CI	[-0.78; -0.06]*	
	3)Confirmatory secondary endpoint: Within-subject variability in SMPG (CV%) after 26 weeks of treatment	Comparison groups	IDeg/IGlar	
		Treatment ratio	0.92	
		95% CI	[0.84; 1.01]	
	4) Confirmatory secondary	Comparison groups	IDeg/IGlar	

	endpoint: HbA_{1c} < 7.0% at end of trial without confirmed hypoglycaemia	Odds ratio	1.05
		95% CI	[0.69;1.61]
	Supportive secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.64
		95% CI	[0.30; 1.37]
	Supportive secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	0.44
		95% CI	[-0.20; 1.08]
	Supportive secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.	

BMI: body mass index; CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; DDP-4I: dipeptidyl-peptidase 4-inhibitor; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c} <7.0%: endpoint was only defined for subjects exposed for at least 12 weeks; HbA_{1c}: glycosylated haemoglobin A_{1c}; IDeg: insulin degludec; IGlar: insulin glargine; met: metformin; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic drug; OD: once daily; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast); [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Summary of Efficacy for Trial 3586

Title: A 26-week randomised, confirmatory, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of NN1250 and insulin glargine, both injected once daily as add on to current OAD treatment in insulin naïve subjects with type 2 diabetes mellitus qualifying for more intensified treatment			
Study identifier	Protocol number: NN1250-3586; EudraCT number: not applicable; Study identifier: NCT01059799.		
Design	This was a 26-week, multicentre, multinational, open-labelled, randomised (2:1), two arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg OD with IGlar OD, all ± met ± SU/glin ± α-GI. During the 1-week follow-up period, the subjects were treated with insulin NPH and continued OAD treatment. Subjects eligible for the trial were insulin-naïve subjects with type 2 diabetes mellitus currently treated with OAD(s) qualifying for intensified treatment. At randomisation, the subject's current antidiabetic treatment was continued except for DPP-4 inhibitor.		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). The trial also aimed at showing superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Number of confirmed hypoglycaemic episodes; 2) Number of nocturnal confirmed hypoglycaemic episodes; 3) Change from baseline in FPG; 4) Within-subject variability in SMPG; 5) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec (IDeg)		A total of 289 subjects were randomised to IDeg dosed OD in the evening (from start of main evening meal to bedtime) ± metformin (met) ± sulphonylurea (SU)/glinides (glin) ± alpha-glucosidase inhibitor (α-GI) dosed as pre-trial. The total treatment duration was 26 weeks.
	Insulin glargine (IGlar)		A total of 146 subjects randomised to IGlar dosed OD according to approved labelling ± metformin (met) ± sulphonylurea (SU)/glinides (glin) ± alpha-glucosidase inhibitor (α-GI) dosed as pre-trial. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Number of confirmed hypoglycaemic episodes	If non-inferiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	2) Confirmatory secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated rate ratio (IDeg/IGlar) was entirely below one.
	3) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDeg minus IGlar) was entirely below zero.
	4) Confirmatory secondary endpoint	Within-subject variability in SMPG after 26 weeks of treatment	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the estimated treatment ratio (IDeg/IGlar) (CV%) was entirely below one.
	5) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDeg/IGlar) was entirely above one.
	Supportive secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	17-Jan-2011		
Results and Analysis			

Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		
Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of all efficacy endpoints were based on the FAS (n=435), including the analyses of hypoglycaemia and body weight. All other endpoints related to safety were based on the SAS (n=430). The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 58.6 years (ranging from 20.0 to 83.1 years), mean duration of diabetes of 11.6 years (ranging from 0.5 to 38.7 years), mean HbA_{1c} of 8.5% and mean BMI of 25.0 kg/m^2. The majority of subjects (65.5%) were on two OADs at screening and 22.3% were on more than two OADs. A total of 89.3% of subjects in the IDeg group and 93.2% of subjects in the IGlar completed the trial.		
Statistical Methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of the number of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed prebreakfast SMPG values as repeated measures. The model included treatment, antidiabetic treatment at screening, sex, and region as factors, age as covariate, subject as random factor and assumed independent within- and between-subject errors with variance depending on treatment.The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IGlar**
	Number of subjects (FAS)	289	146
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-1.24 (0.9)	-1.35 (0.9)
	HbA_{1c} at baseline, mean % (SD)	8.45 (0.8)	8.46 (0.8)
	HbA_{1c} at Week 26, mean % (SD)	7.21 (0.7)	7.10 (0.8)
	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia, N (%)	78 (29.1)	45 (31.5)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-2.88 (2.5)	-2.97 (2.3)
	Within-subject variability in SMPG after 52 weeks of treatment, CV%	Not applicable	Not applicable
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	297.6	369.9
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	78.0	123.8
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	1.29 (2.2)	1.41 (2.2)
	Total daily insulin dose after 26 weeks of treatment mean units (SD)	19.0 (13.3)	24.2 (16.8)
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	0.11
		95% CI	[-0.03; 0.24][†]
	1) Confirmatory secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.82
		95% CI	[0.60; 1.11]
	2) Confirmatory secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Rate ratio	0.62
		95% CI	[0.38; 1.04]
	3) Confirmatory secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.09
		95% CI	[-0.41; 0.23]
	4) Confirmatory secondary	Comparison groups	IDeg/IGlar

	endpoint: Within-subject variability in SMPG (CV%) after 26 weeks of treatment	Treatment ratio	0.89
		95% CI	[0.80; 0.99]
	5) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes	Comparison groups	IDeg/IGlar
		Odds ratio	0.89
		95% CI	[0.56; 1.42]
	Supportive secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.17
		95% CI	[-0.59; 0.26]
	Supportive secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.	

α-GI: alpha-glucosidase inhibitor; BMI: body mass index; CI: confidence interval; Confirmed hypoglycaemic episodes: the subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L; DDP-4: dipeptidyl-peptidase 4; FAS: full analysis set; FPG: fasting plasma glucose; glin: glinides; HbA_{1c} <7.0%: endpoint was only defined for subjects exposed for at least 12 weeks; HbA_{1c}: glycosylated haemoglobin A_{1c}; IDeg: insulin degludec; IGlar: insulin glargine; met: metformin; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic drug; OD: once daily; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose (pre-breakfast); SU: sulphonylurea; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Summary of Efficacy for Trial 3580

Title: A 26-week randomised, controlled, open label, multicentre, multinational trial comparing efficacy and safety of NN1250 with sitagliptin as add on to current oral antidiabetic treatment in insulin-naïve subjects with type 2 diabetes mellitus inadequately controlled with 1-2 oral antidiabetic drugs (metformin, sulphonylurea, glinides or pioglitazone)			
Study identifier	Protocol number: NN1250-3580; EudraCT number: 2008-005770-12; Study identifier: NCT01046110.		
Design	This trial was a 26-week, multicentre, multinational, open-labelled, randomised (1:1), two arm parallel-group, treat-to-target trial comparing the efficacy and safety of IDeg OD with sitagliptin, all ± met ± SU/glin ± pio. Subjects eligible for the trial were insulin-naïve subjects with type 2 diabetes mellitus currently treated with 1-2 OAD(s) qualifying for intensified treatment. The trial was stratified according to the use of pioglitazone at screening.		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg – sitagliptin) for the mean change in HbA_{1c} was below 0% (superiority). The trial also aimed at showing superiority of a number of confirmatory secondary endpoints using a hierarchical testing procedure to control the overall type I error rate: 1) Change from baseline in FPG; 2) HbA_{1c} <7.0% at end of trial; 3) HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes.		
Treatments groups	Insulin degludec (IDeg)		A total of 229 subjects were randomised to IDeg dosed OD ± metformin (met) ± sulphonylurea (SU)/glinides (glin) ± pioglitazone (pio) (pre-trial regimen and dose). IDeg could be administed at any time of day with the option to change injection time from day-to-day. The total treatment duration was 26 weeks.
	Sitagliptin		A total of 229 subjects randomised to sitagliptin dosed OD orally ± metformin (met) ± sulphonylurea (SU)/glinides (glin) ± pioglitazone (pio) (pre-trial regimen and dose). The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	1) Confirmatory secondary endpoint	Change from baseline in FPG (central lab-measured) after 26 weeks of treatment	If superiority was confirmed for the primary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the treatment difference (IDeg minus sitagliptin) was entirely below zero.
	2) Confirmatory secondary endpoint	HbA_{1c}<7.0% at end of trial	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDeg/sitagliptin) was entirely above one.
	3) Confirmatory secondary endpoint	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia	If superiority was confirmed for the previous confirmatory secondary endpoint, then superiority was confirmed for this endpoint if the 95% CI for the odds ratio (IDeg/sitagliptin) was entirely above one.
	Supportive secondary endpoint	Number of confirmed hypoglycaemic episodes	The number of confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	The number of nocturnal confirmed hypoglycaemic episodes was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Total daily insulin dose after 26 weeks of treatment	The total daily insulin dose was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	01-Dec-2010		
Results and Analysis			
Analysis description	**Primary Analysis, Confirmatory Secondary Analyses and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of efficacy endpoints including analyses of hypoglycaemia and body weight, were based on the FAS (n=447), while the safety endpoints were summarised using the SAS (n=454). The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 55.7 years (ranging from 22.0 to 84.4 years), mean duration of diabetes of 7.7 years (ranging from 0.5 to 34.0 years), mean HbA_{1c} of 8.9 % and mean BMI of 30.4 kg/m^2. The time point duration for all analyses was 26 weeks. The majority of subjects (67.6%) were on two OADs pre-trial and 32.0% were on one OAD. A total of 76.0% of subjects completed the trial in both the treatment groups.		
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} (FPG in FPG analysis and body weight in body weight analysis) as covariates. The analysis of subjects reaching HbA_{1c} <7.0% was based on a logistic regression model using the same factors and covariates as for the analysis of the primary endpoint. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**Sitagliptin**
	Number of subjects (FAS)	225	222
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-1.56 (1.1)	-1.22 (1.2)
	HbA_{1c} at baseline, mean % (SD)	8.77 (1.0)	8.97 (1.0)
	HbA_{1c} at Week 26, mean % (SD)	7.21 (1.0)	7.74 (1.2)
	HbA_{1c} <7.0% at end of trial, N (%)	92 (40.9)	62 (27.9)
	HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia, N (%)	49 (24.9)	43 (22.9)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-3.22 (3.2)	-1.39 (3.1)
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	307.0	126.1
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	52.3	29.7
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	2.28 (4.4)	-0.35 (3.9)
	Total daily insulin dose after 26 weeks of treatment, mean units (SD)	42.7 (27.7)	NA
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDeg – Sitagliptin
		Treatment contrast	-0.43
		95% CI	[-0.61; -0.24]†
	1) Confirmatory secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups	IDeg – Sitagliptin
		Treatment contrast	-2.17
		95% CI	[-2.59; -1.74]*
	2) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial	Comparison groups	IDeg/Sitagliptin
		Odds ratio	1.60
		95% CI	[1.04; 2.47]*
	3) Confirmatory secondary endpoint: HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemia	Comparison groups	IDeg/Sitagliptin
		Odds ratio	0.92
		95% CI	[0.55; 1.53]
	Supportive secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups	IDeg /Sitagliptin
		Rate ratio	3.81
		95% CI	[2.40; 6.05]*
	Supportive secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups	IDeg/Sitagliptin
		Rate ratio	1.93
		95% CI	[0.90; 4.10]
	Supportive secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups	IDeg – Sitagliptin
		Treatment contrast	2.75
		95% CI	[1.97; 3.54]*
	Supportive secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.	

BMI: body mass index; 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; glin: glinides; HbA_{1c} <7.0%: endpoint was only defined for subjects exposed for at least 12 weeks; HbA_{1c}: glycosylated haemoglobin A_{1c}; IDeg: insulin degludec; met: metformin; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; OAD: oral antidiabetic drug; OD: once daily; pio: pioglitazone; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SU: sulphonylurea; [†]Superiority criterion: Upper confidence limit of difference less than or equal to 0.0 (%); *= statistically significant

Summary of Efficacy for Trial 3668

Title: A 26-week randomised, controlled, open-label, multicentre, multinational, three-arm, treat-to-target trial comparing efficacy and safety of three different dosing regimens of either NN1250 or insulin glargine with or without combination with OAD treatment, in subjects with type 2 diabetes mellitus			
Study identifier	Protocol number: NN1250-3668; EudraCT number: 2008-005771-10; Study identifier: NCT01006291		
Design	This was a 26-week, multicentre, multinational, open-labelled, randomised (1:1:1), three arm parallel-group, treat-to-target trial comparing the efficacy and safety of insulin IDeg in a flexible OD dosing schedule versus IGlar OD and versus IDeg OD, all ± met ± SU/glin ± pio. During the 1-week follow-up period, the subjects were treated with insulin NPH and continued OAD treatment. Subjects eligible for the trial were subjects with type 2 diabetes mellitus treated with OADs alone, OADs in combination with basal insulin or with basal insulin alone, but qualifying for intensified treatment. The trial was stratified according to treatment prior to randomisation.		
	Duration of main phase:		26 weeks + 1 week follow-up
Hypothesis	Efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference (IDeg FF – IGlar) for the mean change in HbA_{1c} was below or equal to 0.4% (non-inferiority). None of the secondary endpoints were analysed as confirmatory endpoints.		
Treatments groups	Insulin degludec flexible (IDeg FF)		A total of 229 subjects were randomised to IDeg administered OD according to a flexible dosing schedule with 8-40 h intervals between doses + pre-trial (if any) OAD treatment regimen and dose (± metformin (met) ± sulphonylureas (SU)/ glinides (glin) ± pioglitazone (pio)). The total treatment duration was 26 weeks.
	Insulin degludec (IDeg OD)		A total of 228 subjects were randomised to IDeg dosed OD with the evening meal + pre-trial (if any) OAD treatment regimen and dose (± metformin (met) ± sulphonylureas (SU)/ glinides (glin) ± pioglitazone (pio)). The total treatment duration was 26 weeks.
	Insulin glargine (IGlar)		A total of 230 subjects were randomised to IGlar dosed OD according to approved labelling + pre-trial (if any) OAD treatment regimen and dose (± metformin (met) ± sulphonylureas (SU)/ glinides (glin) ± pioglitazone (pio)). The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	Secondary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDeg FF and IDeg OD.
	Secondary endpoint	Change in FPG (central lab-measured) after 26 weeks of treatment	Comparing the change in FPG from baseline to end of treatment between IDeg FF and IGlar, and between IDeg FF and IDeg OD.
	Secondary endpoint	Number of confirmed hypoglycaemic episodes	The number of confirmed hypoglycaemic episodes was compared between IDeg FF and IGlar, and between IDeg FF and IDeg OD, and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Number of nocturnal confirmed hypoglycaemic episodes	The number of nocturnal confirmed hypoglycaemic episodes was compared between IDeg FF and IGlar, and between IDeg FF and IDeg OD, and assessed by statistical analysis as part of the efficacy evaluation.
	Secondary endpoint	Change from baseline in body weight after 26 weeks of treatment	Body weight change from baseline to 26 weeks 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 was a safety endpoint summarised descriptively and compared between treatment groups as part of the efficacy evaluation.
Database lock	07-Oct-2010		
Results and Analysis			
Analysis description	**Primary Analysis and Key Supportive Secondary Endpoints**		

Analysis population and time point description	The FAS included all randomised subjects. The PP analysis set included subjects without any major protocol violations that may have affected the primary endpoint. The SAS included all subjects receiving at least one dose of the investigational product or its comparator. All statistical analyses, including analyses of hypoglycaemia and bodyweight, were based on the FAS (n=687), while the safety endpoints were summarised using the SAS (n=685). The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 56.4 years (ranging from 22.9 to 80.9 years), mean duration of diabetes of 10.6 years (ranging from 0.5 to 40.6 years), mean HbA_{1c} of 8.4 % and mean BMI of 29.6 kg/m^2. The time point duration for all analyses was 26 weeks. Approximately 58% of subjects in each treatment group were only treated with OADs pre-trial and 39% of subjects in each treatment group were treated with basal insulin plus OADs. A total of 88.6% of subjects in the IDeg FF group, 89.5% of subjects in the IDeg OD group and 88.3% of subjects in the IGlar group completed the trial.				
Statistical methods	Change from baseline in HbA_{1c}, FPG and body weight at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariates. The number of 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, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All analyses in this table were pre-specified in the protocol.				
Descriptive statistics and estimate variability	**Treatment group**	**IDeg FF**	**IDeg OD**	**IGlar**	
	Number of subjects	229	228	230	
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-1.28 (1.0)	-1.07 (1.0)	-1.26 (1.1)	
	HbA_{1c} at baseline, mean % (SD)	8.50 (1.0)	8.38 (0.9)	8.41 (0.9)	
	HbA_{1c} at Week 26, mean % (SD)	7.22 (0.9)	7.31 (1.0)	7.15 (0.9)	
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-3.15 (2.9)	-2.91 (3.0)	-2.78 (3.1)	
	Observed rate of confirmed hypoglycaemic episodes, per 100 PYE	364.3	362.6	348.4	
	Observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE	62.9	55.6	74.8	
	Change from baseline in body weight after 26 weeks of treatment, mean kg (SD)	1.51 (3.0)	1.56 (2.8)	1.27 (2.8)	
	Total daily insulin dose after 26 weeks of treatment, mean units (SD)	46.4 (32.3)	44.6 (30.6)	44.5 (25.9)	
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups		IDeg FF – IGlar	
		Treatment contrast		0.04	
		95% CI		[-0.12; 0.20]†	
	Secondary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups		IDeg FF – IDeg OD	
		Treatment contrast		-0.13	
		95% CI		[-0.29; 0.03]	
	Secondary endpoint: Change from baseline in FPG after 26 weeks of treatment	Comparison groups		IDeg FF – IGlar	IDeg FF – IDeg OD
		Treatment contrast		-0.42	-0.05
		95% CI		[-0.82; -0.02]*	[-0.45; 0.35]
	Secondary endpoint: Number of confirmed hypoglycaemic episodes	Comparison groups		IDeg FF/ IGlar	IDeg FF/ IDeg OD
		Rate ratio		1.03	1.10
		95% CI		[0.75; 1.40]	0.79; 1.52]
	Secondary endpoint: Number of nocturnal confirmed hypoglycaemic episodes	Comparison groups		IDeg FF/ IGlar	IDeg FF/ IDeg OD
		Rate ratio		0.77	1.18
		95% CI		[0.44; 1.35]	[0.66; 2.12]
	Secondary endpoint: Change from baseline in body weight after 26 weeks of treatment	Comparison groups		IDeg FF – IGlar	IDeg FF – IDeg OD
		Treatment contrast		0.27	0.00
		95% CI		[-0.25; 0.79]	[-0.53; 0.52]
	Secondary endpoint: Total daily insulin dose after 26 weeks of treatment	No statistical analysis was performed.			

BMI: body mass index; 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; FF: fixed flexible, subjects treated with a rotation dosing schedule; FPG: fasting plasma glucose; glin: glinides; HbA_{1c}: glycosylated haemoglobin A_{1c}; IDeg: insulin degludec; IGlar: insulin glargine; met: metformin; NN1250: the name previously used for insulin degludec (IDeg); Nocturnal: 00:01-05:59; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic drug; OD: once daily; pio: pioglitazone; PP: per protocol; PYE: patient years of exposure; SAS: safety analysis set; SD: standard deviation; SU: sulphonylurea; [†]Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); *: statistically significant

Supportive studies

Two exploratory trials were submitted with this application, NN5401–1791 and NN5401-1792. Both were 16-week randomised, open-labelled, 3-armed, parallel group, treat-to-target trials. Trial 1791 compared once daily injection of IDegAsp, IDegAsp 45 and insulin glargine, all in combination with metformin in subjects with type 2 diabetes failing on OAD treatment, whereas trial 1792 compared IDegAsp, IDegAsp 45 and NovoMix30 (BIAsp 30) taken twice daily. Both trials included insulin-naïve patients with T2DM.

Since the development of IDegAsp 45 has been discontinued, the data concerning this formulation will not be further discussed.

OD treatment with IDegAsp or IGlar, combined with metformin (trial 1791), lead to similar glycaemic control, as determined by HbA1c, after 16 weeks of treatment in subjects with T2DM. FPG decrease to a similar level in both treatment groups. Subjects treated with IDegAsp experienced fewer nocturnal hypoglycaemic episodes compared to IGlar. No unexpected safety issues were identified with IDegAsp OD.

Trial 1792 showed that twice daily treatment with IDegAsp and BIAsp 30, both combined with metformin, lead to similar glycaemic control, as determined by HbA1c, after 16 weeks of treatment in subjects with T2DM, inadequately controlled on OADs. FPG was approximately 1.0 mmol/L (18 mg/dL) lower in IDegAsp group than in BIAsp 30 group after 16 weeks of treatment. Subjects treated with IDegAsp experienced a lower rate of nocturnal hypoglycaemic episodes as well as hypoglycaemic episodes compared to subjects treated with BIAsp 30.

Thus, the data from the exploratory trials were in line with the outcome of the confirmatory trials.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of IDegAsp has been investigated in five confirmatory studies, one in T1DM patients and four in T2DM patients. The T1DM trial included 548 subjects and 1866 subjects were included in the T2DM trials. All trials were of 26 weeks duration and the T1DM trial had a 26 week extension. Data on flexible dosing based on clinical studies with the basal component IDeg has also been provided. In addition two supportive exploratory trials have been submitted.

The inclusion and exclusion criteria were considered adequate and ensured enrolling a representative population of T1DM and T2DM subjects. Exclusion criteria included among others treatment with GLP-1 analogues, cardiovascular disease within the last 6 months (e.g. stroke, HF NYHA III-IV, MI) uncontrolled severe hypertension, impaired renal and hepatic function, cancer, and recurrent severe hypoglycaemia. The T2DM trials allowed all OAD background therapies with the exception of insulin secretagogues, α-glucosidase inhibitors or GLP-1 agonists. It is a weakness that metformin was not a requirement in all T2DM trial, being the cornerstone in antidiabetic treatment of T2DM patients. As insulin secretagogues were to be discontinued, there is no data on the combination of metformin and

insulin secretagogues. However, since the combination of prandial insulin and insulin secretagogues is not recommended by the recognized clinical treatment guidelines, this is acceptable.

In the T2DM trials, OADs not allowed were discontinued. The trials did not have a run-in phase and an adequate baseline evaluation is thus not ensured after discontinuation of OADs. However, since the duration of action of 18 to 72 hours of sulfonylureas is short relative to the 26-week duration of the therapeutic confirmatory trials, the absence of a washout period is not considered to impact the overall evaluation of the trials. Approximately 45% of subjects were treated with sulphonylureas (SU)/glinides pre-trial, overall but percentages were as high as 90.5% in trial 3590 for SU.

All trials were performed with active comparator and the choice of comparators (IDet in the T1DM trial, IGlar in the T2DM OD trials and BIAsp in the T2DM BID trials) was adequate and in line with the advice given in T2DM trials.

All trials were designed as non-inferiority, treat-to-target trials and insulin doses were titrated according to predefined titration algorithms. During the Scientific Advice procedure it was recommended to reconsider and strengthen the FPG criterion with respect to withdrawal. An adequate justification for the criterion applied has been provided.

The chosen primary and secondary outcomes are acceptable and in line with the given advice. The occurrence of hypoglycaemia was included as an efficacy endpoint. In the program, hypoglycaemia was clearly defined applying a cut-off of 3.1 mmol/l glucose which is in line with the adopted CHMP guideline. However, data was also collected applying the more conservative cut-off of 3.9 mmol/l glucose. The occurrence of insulin antibodies was also studied and is discussed in the safety section of this report.

The choice of the confirmatory endpoints and the choice of their hierarchy was elaborated on by the applicant. In the T1DM trial the 1st confirmatory endpoint is change in FPG, the second is HBA1c<7% without severe hypoglycaemic episodes and the 3rd is number of nocturnal hypoglycaemic episodes. Although regarding the 2nd confirmatory endpoint it would have to be expected that severe hypoglycaemia is a very rare event which is not suitable to discriminate two treatments from each other, this was the only possibility to discriminate treatments, as confirmed hypoglycaemia occurs in almost all patients.

In studies 3590 and 3593 "prandial PG increment at main evening meal" was chosen as 1st confirmatory endpoint. The CHMP considered that the relevance of this endpoint was debatable. In these two trials the choice of the treatment groups was not fully appropriate as the IDegAsp treatment arm had a bolus insulin component in their treatment in contrast to the IGlar treatment arm which had basal insulin only; therefore it is clear that the IDegAsp group must be expected to be favoured for this endpoint (IDegAsp was administered once daily with dinner (evening meal) or the largest meal).

The studies were generally well conducted. Due to the difference in appearance of IDegAsp, IDet, BIAsp 30 and IGlar and the fact that a double-dummy design was considered neither safe not feasible, an open design was chosen. This justification is acceptable. During the study period, it turned out that a defective lot of glucose strips had been used. Due to the low risk of experiencing too low readings, the data outcome and quality of the trials was not affected. Further to this, one site participating in the study program in support of the basal component IDeg was closed due to data quality issues. Adequate actions were taken with regards to handling of data from this site.

Thus, the clinical study program is considered adequate both with regards to study size, duration and design.

Efficacy data and additional analyses

Across the study program, the treatment groups were generally well balanced with regards to demographic and diabetes characteristics with only minor differences in age as well as sex distribution observed in the T1DM population. European patient were well represented (about 30 % of patients) both in the T1DM trial and the T2DM trials. Thus the populations recruited are considered representative for the target population. The pre-trial treatments with regards to insulin reflect the current treatment practice and were well balanced between groups. T2DM groups were well balanced with regards to OAD treatment and patients were treated with adequate doses of metformin, DPP-4 inhibitors and glimepiride pre-trial to ensure that these patients were true treatment failures. Withdrawal rates were rather low and balanced between study groups.

The primary endpoint was met in all trials. In the T1DM trial, the improvement of HbA1c was similar for IDegAsp and the comparator over time and the effect was maintained over the 52 week study period. Non-inferiority criteria were met and although the predefined delta was somewhat high (0.4 %) and not in accordance with advice given, the outcome was acceptable both in the ITT and the PP populations with an upper 95 % CI in the range of 0.1 %. Although numerically higher in the IDegAsp treated group, the proportion of patients achieving the HbA1c target 7.0 % was not statistically different between groups. However, due to the hierarchical testing applied none of the secondary endpoints were formally met in the T1DM trial although a significant difference in nocturnal hypoglycaemia was observed. Lower postprandial PG levels were observed with IDegAsp at end of trial compared to IDet. An improvement in the 9-point profiles was observed in both groups.

In the T2DM trials, the improvement of HbA1c was similar for IDegAsp and the comparators over time. Non-inferiority criteria were met in all trials and the outcome was acceptable both in the ITT and the PP populations with an upper 95 % CI in the range of 0.2 %. As in the T1DM population, numerically higher proportions of patients achieved the HbA1c target of 7.0%, but in none of the trials was any statistically significant differences observed. FPG at end of trial was higher for IDegAsp when compared to IGlar; this may be due to the fact that less long-acting insulin was given in the IDegAsp treated patients. When compared to BIAsp BID, statistically significant lower FPG was observed in the IDegAsp treated groups. Although some differences were observed between treatment groups, the 9-point profiles were generally similar between the groups. Consistent findings were observed with regards to the secondary endpoints "prandial PG" (OD treatment) and "FPG" (BID treatment). Findings with regards to different aspects of hypoglycaemia were not entirely consistent across trials.

Except for the T2DM OD trials where IDegAsp was compared to IGlar, titration targets were achieved faster with IDegAsp compared to IDet or BIAsp.

The findings regarding within subject variability were not consistent over the study program. Although the data on mean fluctuations give some indication of a lower fluctuation with IDegAsp compared to IGlar, no statistically significant differences were observed. Apart from a lower prandial increment after breakfast with IDegAsp, no significant differences were observed nocturnal or overall IG profiles. The clinical data thus are unable to confirm that the lower PD variability transforms into a more stable glucose profile in clinical practice.

No clinically relevant changes or differences between groups were observed in the patient related outcomes.

Since the studies were of treat-to-target design with the aim of showing non-inferiority against comparators, focus was to show a difference in hypoglycaemia pattern. The lower cut-off of 3.1 mmol/l glucose for identifying hypoglycaemia was applied throughout the studies, which is in line with the currently adopted guideline. Analyses according to the 3.9 mmol/l limit (documented symptomatic and asymptomatic) largely confirm the analyses in the lower cut-off limit, although the statistically

significantly higher rate of hypoglycaemias of IDegAsp in the T2DM trial with OD dosing could no longer be confirmed. Thus, the finding of a lower rate of nocturnal confirmed hypoglycaemias was consistent over the study program.

Across the study program, severe hypoglycaemias were low and generally numerically lower in the IDegAsp groups. Few patients withdrew due to hypoglycaemia and the withdrawals were balanced between groups in the T1DM trial whereas in the T2DM trials, more withdrawals occurred in the IDegAsp groups. Due to the low numbers, this is not considered too seriously affect the results.

In the T1DM trial, there was a trend towards fewer confirmed hypoglycaemias over time in the IDegAsp treated group. In patients with T2DM, treatment with insulin degludec/insulin aspart once daily (trials 3590, 3593) entailed significantly more confirmed hypoglycaemic episodes compared to treatment with IGlar (estimated treatment ratio 2.17 [1.59; 2.94]95%CI and 1.43 [1.07; 1.92]95%CI in Trials 3590 and 3593, respectively). Lower rates of confirmed hypoglycaemias were observed in T2DM patients treated with a BID regimen.

The rates of nocturnal hypoglycaemia were lower with IDegAsp in all trials and the difference was statistically significant in the T1DM population as well as in study 3590 (T2DM, OD treatment) and study 3592 (T2DM, BID treatment).

Considering that metformin was not mandatory in all T2DM trials, subgroup analyses of the main efficacy/safety results for those patients actually being treated with metformin in trials 3592 and 3597 were provided in the responses to the Day 120 LoQ. The presented analyses did not suggest a relevant difference in HbA1c and confirmed hypoglycaemic /nocturnal confirmed hypoglycaemic episodes for the subgroups of patients with/without metformin.

Despite positive effects on nocturnal hypoglycaemia with IDegAsp, in both T2DM trials it was observed that comparable glycaemic control was achieved with a higher rate of overall confirmed hypoglycaemia when IDegAsp was dosed once daily and compared to IGlar. The highest rate of hypoglycaemia compared to IGlar was observed in trial 3590 where dosing of IDegAsp was done with the morning meal. The Applicant was requested to explain this high level of hypoglycaemias as part of a major objection in the Day 120 LoQ. In the Day 121 responses the Applicant explained that the majority of confirmed hypoglycaemic events occurred in the hours after dosing, as can be expected due to the IAsp component. In contrast, in trial 3593, where dosing was performed with the largest meal, the hypoglycaemic events are more smoothly distributed through the day. Thus, it was shown show that the higher rates of hypoglycaemias with IDegAsp in studies 3590 and 3593 was temporally related to the rapid-acting component of IDegAsp. The data support the recommendation given in the SmPC to take IDegAsp with the largest meal of the day.

Both in the T1DM trial 3594 and in the T2DM trials 3590 and 3593, IDegAsp was compared to long-acting insulin without short-acting component (IDet and IGlar, respectively). In study 3594 the majority of patients (119) injected IDet in the evening whereas a large proportion of the remaining patients (75 % out of 61 patients) shifted their dosing from OD to BID during the course of the study. Thus no meaningful comparisons between different dosing times can be made.

Data on the dosing time for IGlar is only available for study 3593. Additional data is available from a Japanese study, 3896. In these studies, IGlar was dosed according to label, thus IGlar was used in a way which represents the clinical situation. Dosing with the evening meal/before bedtime was most common. The rate of confirmed hypoglycaemias was highest with breakfast dosing in both studies whereas findings were not consistent with regards to nocturnal hypoglycaemias. In study 3593, the rate of nocturnal hypoglycaemias was highest with breakfast dosing compared to evening meal/bedtime dosing whereas the opposite was observed in study 3896. Since in both these studies IGlar was compared to IDegAsp, no direct comparison of hypoglycaemia rates by dosing time can be

made between IDeg and IGlar. The inconsistent finding regarding the rate of nocturnal hypoglycaemias related to pre-breakfast dosing cannot be fully analysed based on the presented data. The higher incidence of hypoglycaemias observed with IGlar compared to IDeg cannot be explained by a choice of time of dosing disfavouring IGlar.

A weight increase is to be expected when HbA1c is lowered by intensified insulin treatment. In the T1DM population, weight increase was higher with IDegAsp; it should be taken into consideration that IDet has been associated with less weight increase than other insulins. Compared to IGlar OD (T2DM) the weight gain was more pronounced with IDegAsp, whereas the opposite was observed when compared to BIAsp BID.

No clinically relevant differences between IDegAsp and the comparators were observed in the subpopulations studied. Subgroup analyses for elderly ≥65-<74 years and ≥75-<84, ≥85 years were provided for the primary endpoint and the main safety endpoints in the responses to the Day 120 LoQ. A slightly larger decrease in HbA1c was observed for the youngest age group <65 years, however, these patients had also the highest baseline HbA1c in T2DM. Similar results were seen in T1DM. As regards confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia no clear pattern was evident for the different age groups. There was no relevant difference between treatment groups either. Overall it has to be considered that the number of patients ≥75 was very low (4 with T1DM and 32 with T2DM treated with IDegAsp), for this reason the results of the eldest age groups should be interpreted cautiously.

Insulin dose is determined by individual need and the dose therefore has to individually titrated. In the clinical trials IDegAsp treatment was initiated at a starting dose of 10 U in insulin naïve patients, and data support that this can be safely done. Furthermore, transfer from previous insulin treatments to IDegAsp was performed on a unit-to-unit basis without increase in hypoglycaemic event or deterioration of glycaemic control. It has also been shown that IDegAsp may be dosed with any main meal of the day. Data from trials 3770 and 3668 with the basal component IDeg supports that flexible dosing is feasible. The data regarding insulin doses during the trials does not indicate any loss of efficacy over time.

The outcomes of the two exploratory trials were in all essential aspects comparable to the outcomes of the confirmatory trials.

2.5.4. Conclusions on the clinical efficacy

Efficacy in terms of HbA1c lowering has been adequately shown. In this aspect IDegAsp has been shown to be non-inferior to three different comparators and dosing regimens. The data provided support the proposed dosing recommendations. In addition, a lower risk of nocturnal hypoglycaemia has been shown for IDegAsp.

2.6. Clinical safety

The safety and tolerability of IDegAsp as monotherapy or in combination with other antidiabetic agents (metformin, pioglitazone and DDP-4 inhibitors) in subjects with T1DM and T2DM is described. A formulation of IDeg, was developed in parallel with IDegAsp in a separate clinical development programme. In these clinical trials there was a considerable exposure to IDeg, and for the purpose of this application the IDeg safety data will be considered supportive.

The main safety parameters assessed in the trials were adverse events, vital signs, physical examinations, clinical laboratory values and ECG measurements. For practical and ethical reasons an open-label design was chosen for all the therapeutic confirmatory and therapeutic exploratory trials.

Two analysis sets were defined. The safety analysis set consisted of all subjects who took at least one dose of IMP or its comparator, whereas the full analysis set included all randomised subjects. Descriptive safety data were based on the safety analysis set. Statistical analysis of body weight, lipids and QTc (Ideg only) were based on pre-specified analyses for each individual trial and the full analysis set.

Patient exposure

The clinical development programme for IDegAsp consisted of a total of 21 completed trials. In these trials 2031 subjects were exposed to IDegAsp. The assessment of safety in subjects with T1DM and T2DM was mainly based on the 5 completed therapeutic confirmatory trials, representing the major part of the exposure. In these trials 1360 subjects were exposed to IDegAsp, 1181 subjects for at least 6 months and 235 subjects for at least 12 months. T2DM accounted for 73 % of the IDegAsp exposure and within the exposed T2DM population approximately 27% were insulin-naïve. The exposure of patients with T1DM and T2DM to IDegAsp at dose levels intended for clinical use has been sufficient to assess the safety of the product.

Table 21 Exposure Time (Months) – All Therapeutic Confirmatory Trials – All Subjects – IDegAsp vs. Comparator – Safety Analysis Set

	Any exposure		>= 6 months		>= 9 months		>= 12 months		Total Exposure in Subject Years
	N	%	N	%	N	%	N	%	
Therapeutic Confirmatory Trials									
All Subjects									
IDegAsp	1360	(100.0)	1181	(86.8)	245	(18.0)	235	(17.3)	750.2
Comparator	1037	(100.0)	910	(87.8)	119	(11.5)	114	(11.0)	538.8
Subjects with T1DM									
IDegAsp	362	(100.0)	322	(89.0)	245	(67.7)	235	(64.9)	296.9
Comparator	180	(100.0)	157	(87.2)	119	(66.1)	114	(63.3)	145.5
Subjects with T2DM									
IDegAsp	998	(100.0)	859	(86.1)	0		0		453.4
Comparator	857	(100.0)	753	(87.9)	0		0		393.4
Insulin-naïve Subjects with T2DM									
IDegAsp	265	(100.0)	220	(83.0)	0		0		118.3
Comparator	261	(100.0)	232	(88.9)	0		0		122.0
Insulin-treated Subjects with T2DM									
IDegAsp	733	(100.0)	639	(87.2)	0		0		335.1
Comparator	596	(100.0)	521	(87.4)	0		0		271.4

N = Number of subjects, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus, A month is defined as 30 days
Completers in 26 weeks and 52 weeks trials counts as having 6 months and 12 months exposure respectively

OAD use at end of trial in the pooled IDeg + IDegAsp trials is presented below:

10: OADs at the End of Treatment - All Therapeutic Confirmatory Trials - Subjects with T2DM - IDeg + IDegAsp vs. Comparator - Summary - Safety Analysis Set

	Number of Subject	Treatment	Mono therapy N	%	In Combination with other OAD N	%	Total N	%
Biguanide	4171	IDeg + IDegAsp	2721	(65.2)	853	(20.5)	3574	(85.7)
	2659	Comparator	1827	(68.7)	558	(21.0)	2385	(89.7)
Sulphonylurea	4171	IDeg + IDegAsp	60	(1.4)	668	(16.0)	728	(17.5)
	2659	Comparator	34	(1.3)	433	(16.3)	467	(17.6)
Thiazolidinedione	4171	IDeg + IDegAsp	16	(0.4)	112	(2.7)	128	(3.1)
	2659	Comparator	7	(0.3)	73	(2.7)	80	(3.0)
DPP-4 inhibitor	4171	IDeg + IDegAsp	0	(0.0)	85	(2.0)	85	(2.0)
	2659	Comparator	0	(0.0)	78	(2.9)	78	(2.9)
Alpha-glucosidase inhibitor	4171	IDeg + IDegAsp	0	(0.0)	66	(1.6)	66	(1.6)
	2659	Comparator	0	(0.0)	31	(1.2)	31	(1.2)
Glinide	4171	IDeg + IDegAsp	3	(0.1)	37	(0.9)	40	(1.0)
	2659	Comparator	2	(0.1)	11	(0.4)	13	(0.5)

For patients concomitantly treated with biguanides, sulphonylureas, DDP-4 inhibitors and alpha-glucosidase inhibitors, the AEs rate was either lower in the IDeg+IDegAsp group or similar in both treatment groups. Concomitant treatment with glinides and thiazolidinediones was associated with a higher AE rate in the IDeg+IDegAsp group than in the comparator group, however this was based on a low number of subjects, and the differences identified in the reporting pattern of different Preferred Terms were small and not considered clinically relevant. Thus, although the data on concomitant treatment with agents other biguanides and sulphonylurea is somewhat limited, overall the data do not indicate any major differences in the AE rate between treatment groups.

Co-administration of insulin degludec with GLP-1-analogues has not been investigated in clinical trials, and is included as missing information in the EU-RMP.

Adverse events

Safety data from the 5 completed therapeutic trials were pooled for the following subgroups: All subjects; subjects with T1DM and subjects with T2DM.

The proportion of subjects experiencing at least one AE was numerically higher in the IDegAsp group (65.1%) than in the comparators (61.9%). However, the rates of AEs per 100 PYE were similar between groups (IDegAsp 387.3 vs. comparators 392.7). More AEs were reported in subjects with T1DM than T2DM, but the pattern was similar to that seen in all subjects (T1DM-IDegAsp vs., comparator: 73.8 % and 407.6 events per 100 PYE vs. 70.6% and 442.1 events per 100 PYE, T2DM-IDegAsp vs. comparator: 62.0% and 374.4 events per 100 PYE vs. 60.1% and 374.1 events per 100 PYE).

The majority of AEs were mild or moderate in severity. Hypoglycaemic episodes were only recorded as AEs if they fulfilled the definition of a SAE or severe hypoglycaemia.

Table 22 Adverse Events – Treatment-emergent – All Therapeutic Confirmatory Trials – All Subjects – IDegAsp vs. Comparator – Summary – Safety Analysis Set

	IDegAsp				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	1360				1037			
All Adverse Events	886	(65.1)	2906	387.3	642	(61.9)	2116	392.7
Serious Adverse Events	115	(8.5)	149	19.9	80	(7.7)	101	18.7
Adverse Events leading to Death	4	(0.3)	4	0.5	1	(0.1)	1	0.2
Adverse Events Possibly or Probably Related to IMP	171	(12.6)	247	32.9	133	(12.8)	235	43.6
Severity								
Mild	761	(56.0)	2140	285.2	555	(53.5)	1532	284.3
Moderate	347	(25.5)	619	82.5	249	(24.0)	447	83.0
Severe	108	(7.9)	147	19.6	81	(7.8)	137	25.4
Adverse Events withdrawals	25	(1.8)	28	3.7	16	(1.5)	24	4.5

N = Number of Subjects with adverse events
% = Proportion of subjects in analysis set having adverse events
E = Number of adverse events
R = Number of events divided by Subject years of exposure multiplied by 100
IMP = Investigational Medicinal Product

The most frequently reported AEs (frequency ≥2%) in the therapeutic confirmatory trials are shown in the table below.

Table 23 Adverse Event in >= 2% of Subjects by System Organ Class and Preferred Term – Treatment-emergent – All Therapeutic Confirmatory Trials – All Subjects – IDegAsp vs. Comparator – Summary – Safety Analysis Set

	IDegAsp				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	1360				1037			
Total Exposure (yrs)	750.2				538.8			
All Adverse Events	886	(65.1)	2906	387.3	642	(61.9)	2116	392.7
Infections and infestations								
Nasopharyngitis	200	(14.7)	266	35.5	119	(11.5)	164	30.4
Upper respiratory tract infection	90	(6.6)	112	14.9	69	(6.7)	89	16.5
Gastroenteritis	31	(2.3)	32	4.3	24	(2.3)	25	4.6
Influenza	32	(2.4)	32	4.3	21	(2.0)	25	4.6
Gastrointestinal disorders								
Diarrhoea	53	(3.9)	65	8.7	46	(4.4)	52	9.7
Nausea	24	(1.8)	35	4.7	29	(2.8)	33	6.1
Vomiting	27	(2.0)	28	3.7	22	(2.1)	23	4.3
Dyspepsia	13	(1.0)	14	1.9	22	(2.1)	29	5.4
Musculoskeletal and connective tissue disorders								
Back pain	47	(3.5)	52	6.9	35	(3.4)	41	7.6
Arthralgia	37	(2.7)	41	5.5	31	(3.0)	32	5.9
Pain in extremity	37	(2.7)	42	5.6	21	(2.0)	23	4.3
Nervous system disorders								
Headache	91	(6.7)	169	22.5	66	(6.4)	91	16.9
Dizziness	30	(2.2)	33	4.4	12	(1.2)	12	2.2
General disorders and administration site conditions								
Pyrexia	37	(2.7)	42	5.6	23	(2.2)	24	4.5
Oedema peripheral	26	(1.9)	35	4.7	23	(2.2)	23	4.3
Metabolism and nutrition disorders								
Hypoglycaemia	50	(3.7)	77	10.3	47	(4.5)	81	15.0
Eye disorders								
Diabetic retinopathy	48	(3.5)	49	6.5	32	(3.1)	32	5.9
Respiratory, thoracic and mediastinal disorders								
Cough	32	(2.4)	35	4.7	19	(1.8)	20	3.7
Oropharyngeal pain	30	(2.2)	33	4.4	19	(1.8)	21	3.9
Vascular disorders								
Hypertension	44	(3.2)	48	6.4	21	(2.0)	22	4.1

N= Number of Subjects with adverse events, %= Proportion of subjects in analysis set having adverse events, E= Number of adverse events, R= Number of events divided by Subject years of exposure multiplied by 100.
Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

Nasopharyngitis, upper respiratory infections, headache and diarrhoea were the most frequently occurring adverse events in both treatment groups.

In all subjects there were no pronounced differences in reporting rates between treatment groups. However, smaller differences were seen mainly for the PTs nasopharyngitis, dizziness, pain in extremity, and dyspnoea, where AEs were reported at a slightly higher rate in the IDegAsp group than

in the comparators. The distribution of AEs was generally similar in subjects with T1DM and T2DM, although, sinusitis, headache, hyperglycaemia, oropharyngeal pain, weight increased and peripheral oedema were slightly more common in the IDegAsp group than in comparators in subjects with T1DM, but not in subjects with T2DM.

In the pooled data from all IDeg + IDegAsp therapeutic confirmatory trials (all subjects) the rate of AEs was similar between treatment groups. Also, the distribution of adverse events was similar to that seen in the IDegAsp trials, with slight between-group differences in reporting rates for nasopharyngitis, headache, wrong drug administered and weight increased, favouring the comparators.

These slight differences in rates of certain AEs are not considered clinically significant. Furthermore, they could likely be explained by the open label trial design (many subjects in the comparator group continued on their usual treatment) and by random variation as for many of the PTs the number of subjects reporting AEs was low.

Adverse Events of Special Interest

Injection site reactions were reported at a lower rate in the IDegAsp group than in the comparator group (5.1 events per 100 PYE and 10.0 events per 100 PYE, respectively). This was a reflection of the significantly lower rate seen in subjects with T1DM (IDegAsp 3.4 vs. IDet 28.2 events per 100 PYE), and was mainly due to one subject in the IDet group reporting many events. In contrast, the rate of injection site reactions in subjects with T2DM was numerically higher in the IDegAsp group than in the comparators (IDegAsp 6.2 vs. comparators 3.3 events per 100 PYE). The majority of injection site reactions were mild. No injection site reactions were assessed as serious. No differences were seen in time of onset or duration of the injection site reactions between IDegAsp and the comparators, with most reactions resolving spontaneously in a few days.

The rates of *lipodystrophy* in the therapeutic confirmatory trials were low for both IDegAsp (0.3 events per 100 PYE) and comparators (2.2 events per 100 PYE).

Injections site reactions and lipodystrophy are included in section 4.8 of the SmPC.

Peripheral oedema was reported at a similar rate for IDegAsp and comparators for all subjects (IDegAsp 4.7 vs. comparator 4.3 events per 100 PYE) and for subjects with T2DM (IDegAsp 5.1 vs. comparator 5.8 events per 100 PYE). In subjects with T1DM, 8 subjects in the IDegAsp groups (4.0 events per 100 PYE) and no subjects in the IDet group reported peripheral oedema. The majority of events were mild in severity. None of the events were severe or serious.

Four events were assessed as possibly or probably related to IDegAsp (0.5 events per 100 PYE) and two events as related to the comparators (0.4 events per 100 PYE). In the four subjects treated with IDegAsp, the time to onset of the events was at least one month after start of treatment and all subjects were diagnosed with one or more confounding medical history.

Peripheral oedema has been included in section 4.8 of the SmPC.

Cardiovascular safety was assessed based on a meta-analysis of independently confirmed and blindly adjudicated major adverse cardiovascular events (MACE). Initially, a MACE analysis based on data from all 16 therapeutic confirmatory IDeg + IDegAsp trials, including one completed extension trial (Trial 3645) was submitted. The observed population included 8941 subjects (safety analysis set), 5635 exposed to IDeg/IDegAsp and 3306 subjects exposed to comparators, and included a wide range of patients from early to more advanced stages of disease.

Overall, the rates of cardiovascular events were similar between IDeg + IDegAsp and comparators (Cardiac Disorders: IDeg/IDegAsp 6.4 events per 100 PYE and comparators 6.9 events per 100 PYE and Vascular Disorders: IDeg/IDegAsp 8.2 events per 100 PYE and comparators 7.1 events per 100

PYE). In the Vascular SOC, hypertension was the most frequently reported event, and was numerically higher in the IDeg group (IDeg: 5.9 events per 100 PYE, comparators: 4.5 events per 100 PYE). No specific pattern was observed for the cardiac events.

The incidence rate of MACE was 1.48 events per 100 PYE in the IDeg + IDegAsp group and 1.44 events per 100 PYE in the comparator group. The estimated hazard ratio for IDeg + IDegAsp versus comparators was 1.10 (95% confidence interval [CI]: [0.68; 1.77]).

In response to the second D180 LoQ an updated MACE analysis with May 1, 2012 as a cut-off was submitted including 9 additional completed trials: 6 extension trials (5 IDeg and 1 IDegAsp), 1 new IDegAsp phase 3a trial in Japanese patients (Trial 3896), and 2 new IDeg phase 3b trials (Trials 3846 and 3923). The nine trials included an additional 742 patients treated with IDeg+IDegAsp and 149 patients treated with comparator products and added 1837.8 PYE for IDeg+IDegAsp and 688.9 PYE for comparator to the MACE analyses. More than 80% of the additional exposure originated from trials with extension periods.

Updated analyses of MACE events were conducted based on all completed randomized phase 3 trials. In addition, post-hoc analyses were presented for 1) all completed phase 3 trials (including the extension trials) and including MACE events occurring up-to 30 days post treatment, 2) MACE events occurring up to 7 days post-treatment excluding unstable angina pectoris and 3) MACE events occurring up to 30 days post-treatment and excluding unstable angina pectoris.

MACE Analysis	Type of Analysis	Patients with MACE /All Patients	Estimated Hazard Ratio IDeg+IDegAsp/Comparator Point Estimate [95% CI]
Prespecified MACE definition within 7 days, MAA/NDA	Primary prespecified analysis	80/8918	1.097 [0.681; 1.768]
MACE definition excluding UAP, within 7 days, MAA/NDA	FDA-requested *post-hoc* sensitivity analysis	54/8918	1.393 [0.757; 2.565]
Prespecified MACE definition within 7 days, all randomised trials, May 1, 2012 (i.e., excluding 7 extensions)	*Post-hoc* sensitivity analysis	85/9806	1.125 [0.705; 1.797]
Prespecified MACE definition, within 30 days, May 1, 2012	FDA-requested *post-hoc* sensitivity analysis	141/9806	1.290 [0.881; 1.888]
MACE definition excluding UAP, within 30 days, May 1, 2012	FDA-requested *post-hoc* sensitivity analysis	99/9806	1.614 [0.999; 2.609]

Full analysis set.

When all randomized trials up to May 1, 2012 were included (excluding the extension phases), the estimated hazard ratio was in line with that of the prespecified primary analysis; 1.125 vs 1.097.

In the post-hoc analysis, hazard ratios increased in favor of the comparator when the MACE analysis included data from the extension phase of the clinical studies and the definition was extended to include cases up to 30 days after treatment discontinuation or limited to exclude cases of unstable angina pectoris (UAP). The highest hazard ratio (1.614; [0.999;2.609]) was observed for the MACE definition combining these two (i.e. excluding cases of UAP and extending the time period to 30 days post treatment).

The applicant argued that the analyses including the extension data are not as robust, as these were based on low patient numbers (a total of 49 MACE events, 40 with IDeg/IDegAsp and 9 with comparator), as the original randomization of the trials was compromised (patients had to elect whether or not to continue participating in the extension trials) and as the switch to NPH insulin could

result in a transient reduction of glycaemic control in between the main and the extension trials. These arguments are acknowledged.

The increase in estimated hazard ratio observed when excluding cases of UAP has not been explained. However, there is no indication from pre-clinical data that IDeg/IDegAsp was associated with any increased cardiovascular risk. Furthermore, the underlying pathomechanism for unstable angina is expected to be the same as that involved in the other cardiovascular events included in the MACE analysis (acute coronary syndrome/MI). Thus, this finding could likely be due to chance.

Overall, the estimated hazard ratios based on data from the randomized trials are close to one. The somewhat large confidence intervals are a reflection of the limited number of cases. A number of post-hoc sensitivity analyses of the MACE data all supported the result of the primary analysis. Thus, the current data does not reveal an increased CV risk for IDeg/IDegAsp treated patients. Based on this, the applicant did not include cardiovascular events in the RMP, and no pharmacovigilance activities are proposed. This is considered acceptable by the CHMP.

Neoplasms were analysed based on the therapeutic confirmatory trials for IDeg and IDegAsp.

A total of 211 events of neoplasm reported with IDeg, IDegAsp or comparators were identified. These were sent in a blinded manner to an external independent consultant for classification into malignant (n=45), benign (n=128) or unclassifiable (n=25) events. The proportion of subjects being diagnosed with malignant neoplasm was the same (0.5%) in both treatment groups, and the overall numbers of malignant neoplasms reported with IDeg+IDegAsp in the therapeutic confirmatory trials were low and similar to comparators (IDeg+IDegAsp: 0.9 events per 100 PYE; comparator: 0.8 events per 100 PYE).

The five most frequently reported malignancies were skin (n=13), gastro-intestinal (n=11), breast (n=5), thyroid (n=4) and bladder neoplasms (n=3). The first 3 are further discussed below. Skin and gastro-intestinal malignant neoplasms were more common in IDeg + IDegAsp group, whereas breast, thyroid and bladder malignant neoplasms were more common in the comparator group.

Of the 13 malignant skin neoplasms, 11 events were reported with IDeg + IDegAsp (0.31 events per 100 PYE). Two events were reported with comparators (0.12 events per 100 PYE). Except for one event of malignant melanoma reported with IDeg, all events were either basal cell carcinomas or squamous cell carcinomas; none of the events were related to injection sites. The majority of the events (n=9, 73%) in the IDeg+IDegAsp group were diagnosed within 3 months of start of trial. Furthermore, in five events in the IDeg+IDegAsp group (45%) the skin lesion was present at baseline and/or the subject had a medical history of skin cancer. When excluding these events, the rates of basal cell carcinoma and squamous cell carcinoma in the IDeg + IDegAsp group were 0.05 events per 100 PYE for both carcinoma types. These rates are comparable to the incidence rates of basal cell carcinoma and squamous cell carcinoma in the non-diabetic background population, which range between 0.05 to 0.12 cases per 100 PYE (average incidence rate 0.078 cases per 100 PYE [CI: 0.077; 0.079]) and 0.01 to 0.04 cases per 100 PYE (average incidence rate 0.020 cases per 100 PYE [CI: 0.020; 0.021]), respectively.

Of the 11 malignant gastro-intestinal neoplasms 8 events were reported with IDeg + IDegAsp (0.22 events per 100 PYE) and 3 events with comparator (0.16 events per 100 PYE). Of the eight malignant gastrointestinal neoplasms reported with IDeg + IDegAsp, seven of the events were related to colon cancer and one event was a gastric cancer. The three events reported in the comparator group were: one event of colon cancer, one event of pancreatic cancer and one event metastatic gastric cancer. All of the events of colon neoplasms were reported in subjects with T2DM, and the majority of the subjects were obese. One event of colon cancer was diagnosed shortly after trial start. The remaining events were diagnosed within 6-7 months after trial start. The reporting rate for the colon neoplasms in the IDeg + IDegAsp group (0.20 events per 100 PYE) is comparable to the incidence rate observed

in the background diabetic population. According to studies in the literature, the incidence rate of colo-rectal cancer in subjects with diabetes, irrespective of treatment, range from 0.17-0.31 cases per 100 PYE, and the average incidence rate is calculated to 0.21 cases (CI: 0.20;0.22) per 100 PYE.

Thus, overall the number of neoplastic events in the clinical setting was low and balanced between treatment groups. Colon cancer and skin cancer were reported more frequently in the IDeg+IDegAsp group than in the comparators; however, the rate was similar to that seen in the general diabetic population. Furthermore, the non-clinical data did not indicate any increased neoplastic potential associated with IDeg. Thus, the disparities observed within the individual PTs for both malignant and benign neoplasms are considered attributable to random variation. Based on this, the applicant has not included neoplastic events in the RMP, and no additional pharmacovigilance activities are proposed. This is endorsed. The Applicant has committed to closely monitoring events of colon cancer in future PSURs.

Medication errors were reported at a rate of 2.4 % (5.2 events per 100 PYE) and 2.2 % (3.2 events per 100 PYE) in the IDegAsp group and the comparator group, respectively.

Most medication errors were reported as wrong drug administered due to mix-ups between insulins, or incorrect dose administered. The remaining medication errors were due to dispensing errors, missed dose, administration of insulin from patients' own supply, inappropriate schedule and wrong injection technique.

The rate of medication mix-ups was slightly higher in the IDegAsp group than in the comparators (IDegAsp 1%, 2.1 events per 100 PYE vs. comparators 0.6%, 1.1 events per 100 PYR), as was the rate of incorrect dosing (IDegAsp 1%, 2.0 events per 100 PYE vs. comparator 0.6%, 1.1 events per 100 PYE). Approximately 60% of mix-ups were reported within the first two months of treatment and in half of the cases a hypoglycaemic episode was reported in relation to the mix-up. Except for one case (requiring assistance of a family member), the subjects were able to treat themselves.

The applicant provides several explanations for the higher rate of medication errors in the IDegAsp group. Particularly, it could be due to more focus on medication errors with a new insulin and that many of the patients randomised to the comparator insulin might have been familiar with the device prior to trial treatment. Furthermore, the device used during trials for which the medication errors were reported, differed from the planned marketed product, for which the final packaging and labelling has been developed and optimized to minimize the potential risk for product mix-ups. These explanations are accepted. The risk of mix-ups may be increased in subjects with visual impairment. To mitigate this risk, the Applicant has revised the SmPC, the PIL and the IFU, stating that patients with visual impairment should get assistance from a person with good vision who is trained in using the device. This is endorsed. With regards to patients with inherent colour blindness, normally affecting the red and green colour spectra, this is unlikely to be a concern with Ryzodeg which has a blue colour code.

Diabetic retinopathy related events occurred at a similar rate with IDegAsp and comparators (8.3 events per 100 PYE and 8.2 events per 100 PYE, respectively). The median time to onset of retinopathy events in all subjects was similar between IDegAsp (183 days) and comparator (181 days) groups.

A higher rate of diabetic retinopathy was reported in both treatment groups in the Pan-Asian population (16 events and 14 events per 100 PYE for IDegAsp and comparator, respectively). The higher reporting rate in the Japanese subjects may be partly explained by the widespread use of the Fukuda-criteria in Japan for classifying and grading severity of retinopathy. These criteria allow a more detailed and specific grading of the stage of retinopathy.

Abrupt improvement in glycaemic control may be associated with a temporary worsening of diabetic retinopathy. This is a class effect of insulins and a statement regarding this has been included in the SmPC section 4.4. This is accepted.

Peripheral neuropathy was reported at a lower rate in the IDegAsp group (5.1 events per 100 PYE) than comparators (7.1 events per 100 PYE). The majority of the events were mild or moderate in severity. The rates of peripheral neuropathy were higher in the subjects with T2DM than in the subjects with T1DM for both treatment groups. In the subjects with T2DM the rate of peripheral neuropathy was lower for IDegAsp (6.8 events per 100 PYE) than comparators (8.9 events per 100 PYE).

Hyperglycaemia was reported at a similar rate with IDegAsp and comparators (1.6 events per 100 PYE and 2.0 events per 100 PYE, respectively). As expected, due to the nature of the disease, the rates of hyperglycaemia were higher in the subjects with T1DM than in the subjects with T2DM for both IDegAsp and comparators.

Six SAEs of hyperglycaemia (all cases of diabetic ketoacidosis) were reported, three with IDegAsp and three with comparators.

Hypoglycaemic events have been reported and analysed in the efficacy section. Hypoglycaemic episodes were only recorded as AEs (and reported in the safety section) if they fulfilled the definition of a SAE or severe hypoglycaemia. Serious hypoglycaemic events are discussed in the section on SAEs. Events of severe hypoglycaemia, defined according to the CHMP draft guideline on the clinical investigation of medicinal products in the treatment of diabetes mellitus (CHMP/EWP/1080/00 Rev. 1), were reported as events of special interest and are discussed below.

The rate of severe hypoglycaemia (and nocturnal severe hypoglycaemia) was lower in the IDegAsp group than in the comparator group, both in subjects with T1DM ((27 and 45 episodes per 100 PYE and 5 and 19 nocturnal episodes per 100 PYE, respectively) and T2DM ((3.5 and 8.1 episodes per 100 PYE and 0.4 and 2.3 nocturnal episodes per 100 PYE, respectively). In subjects with T2DM, most events were reported in previously insulin treated individuals with BID dosing. In the IDegAsp group, more events occurred within the first 3-4 months of the trials and the occurrence over the time of day was constant (T1DM) or lower during the afternoon and early night than during the day (T2DM). The duration of hypoglycaemic episodes did not differ between treatment groups.

In the subgroup of subjects experiencing severe hypoglycaemia, the rates of confirmed hypoglycaemic episodes and nocturnal confirmed hypoglycaemic episodes were similar between groups in T1DM and higher in the IDegAsp group than in the comparators for subjects with T2DM. However, this observation was based on a low number of subjects (34 in total).

Episodes of severe hypoglycaemia was also analysed as a pre-specified secondary analysis in the prospectively planned meta-analysis including all therapeutic confirmatory trials with IDeg OD and IGlar as comparators. This meta-analysis showed no statistically significant treatment difference between treatment groups (IDeg-IGlar); estimated rate ratio 0.98 [0.66; 1.45]95%CI.

Counter-regulation to controlled hypoglycaemia was studied in one trial (3538) with IDeg. In this trial, the clinical response and counter-regulatory mechanisms to hypoglycaemia was similar with IDeg and IGlar. Furthermore, a review of the patient reported hypoglycaemia questionnaires and the case narratives of episodes of hypoglycaemia, fatal cases and overdoses, did not indicate any difference in the duration or recurrence of hypoglycaemic episodes between treatment groups.

In addition, recurrent hypoglycaemic episodes in patients with a confirmed episode of hypoglycaemia in the basal only trials were analyzed. Overall, the event rate in both treatment groups was similar (or lower) in the IDeg group compared to the IGlar group.

Serious adverse events and deaths

In all subjects in the therapeutic confirmatory trials, the rates of SAEs were similar for IDegAsp and comparators (IDegAsp: 8.5% and 19.9 events per 100 PYE vs. comparators: 7.7% and 18.7 events per 100 PYE) but higher than that observed in the IDeg trials (IDeg: 7.9%, 15.1 events per 100 PYE). In subjects with T1DM the rate of the SAEs was higher for IDegAsp (12.7%, 24.3 events per 100 PYE) than IDet (11.1%, 19.2 events per 100 PYE) whereas in subjects with T2DM the rates of SAEs were similar between treatment groups (IDegAsp: 6.9%, 17 events and comparators: 7.0%, 18.6 events per 100 PYE).

In T1DM most SAEs (≥1% subjects in one or both treatment groups) were reported in the following SOCs: Metabolism and nutrition disorders, Musculoskeletal disorder and connective tissue disorders, and Gastrointestinal disorders (both IDegAsp and comparators), and Infections and infestations and Injury, Poisoning and procedural complications (IDegAsp). The most frequently reported SAEs in both groups were hypoglycaemia. Other than that, SAEs for individual PTs were only reported once or twice.

The combined rate of hypoglycaemia reported as SAEs was higher in the IDegAsp group than in the IDet group (IDegAsp: 12.5 episodes per 100 PYE, comparator: 9.6 episodes per 100 PYE). This difference was driven by one subject in the IDegAsp group having 8 (of a total of 38) hypoglycaemic events reported as SAEs, and the proportion of patients with serious hypoglycaemic events was similar in both treatment groups (IDegAsp 6.9% vs. comparator 7.7%).

In T2DM most SAEs (≥1% of subjects in one or both treatment groups) for both IDegAsp and comparators were reported in the following SOCs: Cardiac disorders, Infections and Infestations, and Metabolism and nutrition disorders. The most frequently reported SAEs in both groups were hypoglycaemia. Other than that there was no specific pattern or clustering of SAEs.

The combined rate of hypoglycaemic episodes reported as SAEs was lower for IDegAsp than comparators (0.6% and 1.8 events per 100 PYE vs. 1.6% and 3.6 episodes per 100 PYE, respectively).

In total, six deaths were reported in the completed clinical trials conducted with IDegAsp (IDegAsp: 4 subjects, BIAsp 30: 2 subjects). AEs with the outcome of death were balanced between treatment groups.

In the pooled populations of IDeg + IDegAsp therapeutic confirmatory trials the rates of SAEs were similar for IDeg + IDegAsp (16.1 events per 100 PYE), and comparators (15.0 events per 100 PYE), and somewhat lower than that reported for IDegAsp alone (19.9 events per 100 PYE). The distribution of SAEs was similar in all treatment groups (IDeg, IDegAsp and comparators).

Laboratory findings

Few subjects had clinically significant changes in laboratory values, clinical examination results (including funduscopy/fundusphotography) or ECG recordings and there was no difference between treatment groups for any of these parameters.

A "thorough QT study" was not conducted. However, QTc measurements were collected in one clinical trial including 766 subjects treated with IDeg and 257 subjects treated with comparator. No significant differences between treatment groups were detected (ANOVA statistical analysis). Thus, the lack of a thorough QT study is considered acceptable.

Safety in special populations

Detailed analyses of the impact of age, sex, race, body mass index and renal and hepatic function on the frequency of adverse events in the Pivotal Safety Population were performed.

In the group of subjects aged >65, a higher rate of hypertension and haematoma was seen with IDegAsp than with comparators. This pattern was also seen in the IDeg trials. However, the between group differences were based on few cases and are likely due to chance. Furthermore, in many cases confounding factors were reported. In subjects >75 years, higher rates of AEs and SAEs were observed for IDegAsp than for comparators. However, this was based on a low number of subjects and should be interpreted with caution.

In the controlled therapeutic exploratory and confirmatory trials, 1303 (20.4%) subjects < 65 years were exposed to IDeg or IDegAsp including 153 subjects ≥ 75 years. This is in accordance with the ICH E7 guideline. Exposure to IDeg + IDeg/Asp in the subgroup of subjects with T1DM >75 years was low (n=13, PYE = 9) and may not have been sufficient to adequately address the safety of the product in subjects with T1DM. Thus, "use in subject >75 years with T1DM" has been addressed as Missing Information in the RMP. The SmPC recommends intensified glucose monitoring in the elderly. This is considered sufficient.

Renal impairment was evaluated in a pharmacokinetic study. The study did not show any differences in the pharmacokinetic properties of IDeg in subjects with different degrees of renal impairment; however, the study was very small, including only 30 patients.

In the pivotal clinical trials the number of IDeg + IDegAsp treated patients with moderate renal impairment was limited (n=65), and it is difficult to draw conclusions regarding any between treatment group differences in this small subgroup of patients. Therefore, moderate renal impairment has been included as missing information in the RMP.

The most informative data are derived from the IDeg + IDegAsp treated patients with mild renal impairment (n = 824), where data on adverse events, severe hypoglycaemia and confirmed hypoglycaemic episodes, were evaluated using two different analysis (renal impairment defined based on estimated creatinine clearance (mild, moderate) and based on baseline serum creatinine (at or above 75 percentile)). Overall, the results of these two analyses were consistent.

In subjects with T1DM and mild renal impairment the rate of adverse events including severe hypoglycaemic episodes was numerically lower with IDegAsp that with comparator. For confirmed hypoglycaemic episodes the results were conflicting, with numerically higher rates with IDegAsp vs. comparator when based on estimated creatinine clearance, and numerically lower for IDegAsp when based on baseline creatinine.

In subjects with T2DM and mild renal impairment the rate of AEs was numerically higher with IDegAsp than comparator, whereas for severe hypoglycaemia and confirmed hypoglycaemic episodes, there were no consistent differences between treatment groups.

Hepatic impairment was evaluated in a pharmacokinetic study (Trial 1989) including 24 subjects with different degrees of hepatic impairment. Exposure to IDeg as measured by AUCIDeg,0-120h,SD was not affected by degree of hepatic impairment.

In the clinical development program, the number of subjects with hepatic impairment (based on bilirubin and albumin as adapted from the Child-Pugh criteria) was: 15 subjects with T1DM (IDeg+IDegAsp: 13 and comparator: 2) and 25 subjects with T2DM (IDeg: 13 and comparator: 12). Although there were more SAEs (by rate and exposure) in the IDeg/IDegAsp group compared to comparator (IDeg+IDegAsp 49.5 events/100 PYE, comparator 11.6 events/100 PYE), the overall

number of SAEs was low and there was no clustering of SAE in the IDeg/IDegAsp group. The proposed labelling concerning hepatic impairment is in line with other basal insulin analogues and is acceptable.

Other than that, there was no consistent pattern of TEAEs to suggest an association between intrinsic factors and an increased risk of experiencing a TEAE.

Immunological events

Immunogenicity related AEs are included as an important identified risk in the RMP.

Allergic reactions were assessed based on events reported in IDeg and IDegAsp trials. In the therapeutic confirmatory trials, the reporting rate was similar for IDeg + IDegAsp and comparators (1.3 events per 100 PYE (0.8%) and 0.9 events per 100 PYE (0.5%), respectively) and similar between subjects with T1DM and T2DM.

In all IDeg/IDegAsp trials, a total of 65 immunogenicity related AEs were identified. All cases were assessed for a potential causal association. Ten (10) events were assessed as potentially related to IMP (IDeg or IDegAsp n=7 and comparator n=3). The 7 events in the IDeg/IDegAsp group were hypersensitivity (3) and urticaria (4). Three cases reported with IDeg were assessed as serious and according to narratives in one of these cases the sponsor assessed the event as possibly related to IDeg.

Furthermore, there was one case of periorbital oedema in the therapeutic exploratory trials and one event of suspected anaphylactic reaction in a clinical pharmacology trial, assessed as possibly related to IDeg by the investigator, but not included among the events with a causal association after medical evaluation by the applicant. The event of periorbital oedema does not seem to be related to treatment with IDeg, as the subject continued in the trial and recovered from the event without additional treatment or changes in IDeg treatment. In contrast, the second case is suggestive of an allergic reaction to IDeg, reporting generalised pruritus, redness and swelling of lips and eyelids following one dose of IDeg. No events consistent with an anaphylactic reaction were reported. Overall, the frequencies of immunogenicity related AEs was low and not unexpected and are appropriately reflected in the proposed labelling in section 4.8 of the SmPC.

The number of subjects that had an increase of 10%B/T or more in antibodies cross-reacting with human insulin or an increase in specific insulin analogue antibodies of 5% B/T or more was low in both the IDegAsp and the comparator group (IDegAsp n= 86, comparator n=139. When pooling the three IDegAsp trials where antibodies were measured, the change from baseline to the end of the trial in mean and median level of cross-reacting antibodies in the IDegAsp group was lower than in the comparator groups. There was no change from baseline to the end of the trial in mean or median level of IDeg specific antibodies in the IDegAsp group.

No immunogenicity-related events were reported in the IDegAsp groups for these subjects (two events were reported in the comparator group).

The lower rate of cross reacting antibodies observed in the IDegAsp group compared to the comparator groups is considered reassuring. However, all insulin products carry a risk of antibody development. From what is known about other insulin products, a subgroup of antibody positive patients will develop antibodies with a neutralising capacity. As neutralizing antibodies are infrequent, it is not possible to entirely exclude this risk based on data from the clinical trials with IDeg+IDegAsp. Thus, "Immunological Events – formation of insulin antibodies", has been included as an Important Potential Risk in the RMP, and relevant information has been included in SmPC section 4.4.

Based on the fact that a relatively large number of subjects were included in the IDeg (and IDegAsp) trials and that there is no evidence to indicate that IDeg is more immunogenic that the comparators, routine pharmacovigilance activities are considered sufficient.

Safety related to drug-drug interactions and other interactions

There was no evidence of a clinically significant interaction between IDeg and concomitant glucose increasing, glucose lowering or protein binding drugs. Medicinal products known to interact with glucose metabolism have been included in section 4.5 of the SmPC.

Discontinuation due to adverse events

The percentages of subjects who withdrew from the trial due to an AE were low for both IDegAsp (1.8% and 3.7 events per 100 PYE) and comparators (1.5% and 4.5 events per 100 PYE) and similar in subjects with T1DM and T2DM. The majority of the AEs leading to withdrawal were SAEs in both IDegAsp and comparators group. The percentages of subjects who withdrew from the trial due to a SAE was similar between treatment groups for all subjects (IDegAsp: 1.4% and 2.8 events per 100 PYE and comparators: 1.1% and 2.4 events per 100 PYE) and for subjects with T2DM. In subjects with T1DM, the majority of AEs leading to withdrawal in the IDegAsp group were SAEs while only one of the AEs leading to withdrawal in the IDet group was a SAE. Therefore, the rate of SAEs leading to withdrawal was numerically higher for IDegAsp (1.7% and 2.7 events per 100 PYE) than comparators (0.6% and 0.7 events per 100 PYE).

In T1DM, four out of the six AEs leading to withdrawal in the IDegAsp group were related to hypoglycaemia. In the comparator group only one SAE was reported (diabetic ketoacidosis).

In T2DM, all the events leading to withdrawal in the IDegAsp group were reported only once, except for headache (2 events), wrong drug administered (2 events) and interstitial lung disease (2 events). None of the events in the comparators group were reported more than once.

Discontinuation due to hypoglycaemia was similar in both treatment groups in subjects with T1DM (IDeg 3%, comparator 2.2%) and T2DM (IDeg 0.8%, comparator 0.6%).

2.6.1. Discussion on clinical safety

In the 21 completed clinical trials constituting the clinical development program for IDegAsp, a total of 2031 subjects were exposed to IDegAsp. The assessment of safety in subjects with T1DM and T2DM was mainly based on the 5 completed therapeutic confirmatory trials, where 1360 subjects were exposed to IDegAsp, 1181 subjects for at least 6 months and 235 subjects for at least 12 months. The exposure of patients with T1DM and T2DM to IDegAsp at dose levels intended for clinical use is considered sufficient to assess the safety of the product.

Overall, AEs were reported in a somewhat lower frequency than that seen in the IDeg trials (IDegAsp 65.1%, 387.3 events per 100 PYE, IDeg 70.6%, 428.1 events per 100 PYE). The rate and distribution of AEs was similar in the IDegAsp group and in the comparators, and the vast majority of AEs were mild or moderate in severity. Nasopharyngitis, upper respiratory infections, headache and diarrhoea were the most frequently occurring adverse events in both treatment groups.

No major differences in reporting rates between treatment groups were observed. However, for certain PTs, AEs were reported with a slightly higher frequency in the IDegAsp group than in the comparators. These differences were most pronounced for the PTs nasopharyngitis, dizziness, pain in extremity, dyspnoea, sinusitis (T1DM), headache (T1DM), hyperglycaemia (T1DM), oropharyngeal pain (T1DM),

weight increased (T1DM) and peripheral oedema (T1DM). However, these slight differences in rates of certain AEs are not considered clinically significant. Furthermore, they could likely be explained by the open label trial design (many subjects in the comparator group continued on their usual treatment) and by random variation (for many of the PTs the number of subjects reporting AEs was low).

AEs with the outcome of death were balanced between treatment groups. Relatively few SAEs were reported. The most frequently reported SAEs in all subjects were events related to hypoglycaemia. Hypoglycaemic episodes were only recorded as AEs if they fulfilled the definition of a SAE or severe hypoglycaemia (according to the CHMP guideline, CHMP/EWP/1080/00 Rev. 1). The combined rate of hypoglycaemic episodes reported as SAEs was higher for IDegAsp than the comparator in subjects with T1DM, however, this was driven by one subject reporting several events, and the proportion of subjects reporting serious hypoglycaemic events were similar in both treatment groups. The rate of severe hypoglycaemia and nocturnal severe hypoglycaemia was lower in the IDegAsp group than in the comparator group, both in subjects with T1DM and T2DM. The number of subjects withdrawing from the clinical trials due to hypoglycaemia was low and generally similar between treatment groups.

The duration of severe hypoglycaemic episodes was similar between treatment groups, when assessed based on case narratives, patient reported hypoglycaemia questionnaires and on an analysis of recurrent hypoglycaemia in patients with confirmed hypoglycaemic episodes. Furthermore, the clinical response and counter-regulatory mechanisms to hypoglycaemia was investigated in a clinical pharmacology IDeg trial, and found to be similar to that seen with IGlar.

Medication errors, mainly due to administration of the wrong drug (mix-ups between bolus and basal insulin) or dose, were observed at a slightly higher frequency in the IDegAsp group than in the comparator group. This was also seen in the IDeg trials. This could be due to more focus on medication errors with a new insulin and that many of the patients randomised to the comparator insulin might have been familiar with the device prior to trial treatment. Furthermore, the device used during trials for which the medication errors were reported, differed from the planned marketed product, for which the final packaging and labelling has been developed and optimized to minimize the potential risk for product mix-ups. These explanations were considered acceptable by the CHMP. The risk of medication errors in subjects with visual impairment is considered mitigated by the differentiation features introduced to the insulin pen (including tactile features) and the information included in the SmPC and PIL, stating that one of the requirements for patients to self-inject is that they can read the dose counter of the pen. “Medication Errors Due to Mix-up between Ryzodeg and Bolus Insulin” has been included as an important potential risk in the RMP which is accepted.

Overall the incidence of malignant neoplasms was low and there was no difference between treatment groups in the proportion of patients developing a malignancy. There was a slight imbalance between treatment groups (skin malignancies and gastrointestinal malignancies were more common in the IDeg/IDegAsp group, whereas breast, thyroid and bladder malignant neoplasms were more common in the comparator group). Approximately half of all malignant events in the IDeg/IDegAsp groups occurred within 3 months of treatment. With regards to skin cancer, all events but one were squamous or basal cell carcinoma of which several were present at baseline or occurred within the first three months of treatment. When excluding these cases, the reporting rate of skin cancer was similar to that seen in epidemiological studies. Colon cancer was numerically more frequent in the IDeg+IDegAsp group than in the comparators, however, the number of events was low and the rate was similar to that seen in the general diabetic population. Furthermore, in non-clinical studies IDeg has been demonstrated to have a relatively low IGF-1 receptor binding affinity compared to insulin receptor binding, and the balance between the metabolic and proliferative actions of IDeg is similar to that of human insulin. Also, IDeg was not associated with any treatment related changes in the occurrence of hyperplastic or neoplastic lesions in the pre-clinical studies. Thus, the CHMP concluded that the

disparities observed within the individual PTs for both malignant and benign neoplasms are considered attributable to random variation. In view of this, the Applicant has not included neoplastic events in the RMP, and no additional pharmacovigilance activities are proposed. This is endorsed by the CHMP. The Applicant will closely monitor events of colon cancer in future PSURs.

Injection site reactions were reported with a similar frequency in both treatment groups. The incidence of lipodystrophy was low and similar in both groups.

The rates of immunogenicity related AEs, including AEs assessed as related to IMP, were generally low and similar between groups. The most frequently reported AE in both treatment groups were urticaria, however, there were reports of swelling of the face, eyes, lips and tongue consistent with events of angioedema. There were 7 immunogenicity related events where a potential causal relationship to IDeg or IDegAsp could not be excluded. Three cases reported with IDeg were assessed as serious and according to narratives in one of these cases the sponsor assessed the event as possible related to IDeg. There were no reports of anaphylactic reactions. The risk of hypersensitivity reactions is adequately reflected in the SmPC.

The mean change from baseline to end of treatment in antibodies cross-reacting with human insulin and in specific insulin analogue antibodies was low, and there was no difference between treatment groups. No increase in AEs or differences in treatment effect was seen in these subjects. However, all insulin products carry a risk of antibody development. From what is known about other insulin products, a subgroup of antibody positive patients will develop antibodies with a neutralising capacity. As neutralizing antibodies are infrequent, it is not possible to entirely exclude this risk based on data from the clinical trials with IDeg+IDegAsp. Thus, "Immunological Events – formation of insulin antibodies", has been included as an Important Potential Risk in the RMP. Reports of positive neutralising antibody cases will be reported in future PSURs, and the potential risk of 'Immunological Events – formation of neutralizing insulin antibodies' will be reevaluated in each PSUR based on the case reports. The potential risk has also been reflected in section 4.4 of the SmPC.

Cardiovascular safety was assessed, initially based on meta-analysis of independently confirmed, blindly adjudicated MACE events among the 16 therapeutic confirmatory IDeg + IDegAsp trials (HR 1.10, 95% CI: [0.68; 1.77). In addition, an updated MACE analyses was submitted icluding a further three phase 3 trials (cut-off May 1, 2012); HR 1.13, 95% CI: [0.705; 1.797. The wide confidence interval reflects the low number of events. However, there were no differences in the distribution of cardiovascular events between treatment groups. Furthermore, there is no indication from non-clinical data or from what is known about other basal insulin analogues that IDeg/IDegAsp is associated with an increased risk of cardiovascular events. Also, a number of post-hoc sensitivity analyses of the MACE data all supported the result of the primary analysis.

Few subjects had clinically significant changes in laboratory values, clinical examinations or ECG recordings (including QTc measurements) and there was no difference between treatment groups for any of these parameters.

There were no major differences between treatment groups regarding the interaction between intrinsic factors and distribution of AEs and SAEs. Overall, subjects >65 years experienced a similar rate of AEs to those aged 18-65, and there were no clinically relevant differences between treatment groups. The number of patients >65 years (n=1303) and >75 years (n=153) is in accordance with the ICH E7 guideline. Exposure to IDeg + IDeg/Asp in the subgroup of subjects with T1DM >75 years was low (n=13, PYE = 9) and may not have been adequate to address the safety of the product in these subjects. Therefore, "use in subjects with T1DM >75 years" has been addressed as Missing Information in the RMP. The recommendations for use in the elderly in the SmPC are considered adequate.

The number of subjects with moderate renal impairment included in the clinical trials was limited precluding any firm conclusions regarding the safety profile of IDeg+IDegAsp in this population. Treatment in moderate renal impairment has therefore been included in the RMP as missing information. There were no consistent and/or clinically meaningful differences between treatment groups in the AE rate or rate of confirmed hypoglycaemic episodes in subjects with T1DM and T2DM with mild renal impairment. The current wording in the SmPC recommends intensified glucose-monitoring and adjustment of dosing when required in this patient population and at present this is considered adequate and appropriate. In the IDeg trials, the AE rate and the rate of confirmed hypoglycaemic episodes was consistently higher in the IDeg group than in the comparator group for patients with T1DM and mild renal impairment. Hypoglycaemia is included as an identified risk in the RMP.

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

Overall, the results of the clinical studies demonstrate that the use of IDegAsp in patients with T1DM and T2DM as monotherapy or in combination with oral antidiabetic agents is generally safe and in line with the safety profile of other insulin analogues.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk Management Plan

The applicant submitted a risk management plan.

Table 1. Summary of the risk management plan

Safety issue	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Important identified risks		
Hypoglycaemia	Routine pharmacovigilance	SmPC, Product Label and Patient Information • Section 4.4 'Special warnings and precautions for use' • Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. • Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. • Patients, whose blood glucose control is greatly improved (e.g., by intensified insulin therapy), may experience a change in their usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		symptoms may be altered in patients with longstanding diabetes. • Concomitant illness, especially infections and fever, usually increase the patient's insulin requirement. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose. • As with all basal insulins or insulins with a basal component, their prolonged effect may delay recovery from hypoglycaemia. • Section 4.5 'Interaction with other medicinal products and other forms of interaction' • A number of medicinal products are known to interact with the glucose metabolism. • The following substances may reduce the insulin requirement: Oral anti-diabetic medicinal products, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides. • The following substances may increase the insulin requirement: Oral contraceptive, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormones and danazol. • Beta-blocking agents may mask the symptoms of hypoglycaemia. • Octreotide/lanreotide may either increase or decrease the insulin requirement. • Alcohol may intensify or reduce the hypoglycaemic effect of insulin. • Section 4.8 'Undesirable effects' • The most frequently reported adverse reaction during treatment is hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue,

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. • Section 4.9 'Overdose' • A specific overdose for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required. • Mild hypoglycaemic episodes can be treated by oral administration of glucose. It is therefore recommended that the patient always carries glucose containing products. • Severe hypoglycaemic episodes, where the patient is not able to treat himself, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a health care professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.
Immunogenicity-related events (allergic reactions)	Routine pharmacovigilance	SmPC, Product Label and Patient Information • Section 4.3 'Contra-indications' • Hypersensitivity to the active substances or to any of the excipients. • Section 4.8 'Undesirable effects' • With insulin preparations allergic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening. • With Ryzodeg hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.
Important potential risks		

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Medication errors due to mix-up between Ryzodeg and bolus insulin	Routine pharmacovigilance (including structured follow-up questionnaire)	Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder, as well as tactile features. SmPC • Section 4.4 'Special warnings and precautions for use' • Avoidance of accidental mix-ups: Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients, who are blind or have poor vision, must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device. • Section 6.6 'Special precautions for disposal and other handling' • The pre-filled pen (FlexTouch) is designed to be used with NovoFine/NovoTwist injection needles up to a length of 8 mm. It delivers 1–80 units in steps of 1 unit. Detailed instructions accompanying the pre-filled pen must be followed. • Ryzodeg pre-filled pen (FlexTouch) is for use by one person only. The pre-filled pen must not be refilled. Patient Information • Start by checking your pen to make sure that it contains Ryzodeg 100 units/ml, then look at the illustrations to get to know the different parts of your pen and needle. • Do not use your pen without proper training from your doctor or nurse. • If you are blind or have poor eyesight, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Ryzodeg FlexTouch pen.
Immunological events – formation of neutralising insulin antibodies	Routine pharmacovigilance	SmPC • Section 4.4 'Special warnings and precautions for use' • Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important missing information		
Pregnant and lactating women	Routine pharmacovigilance	SmPC, Product Label and Patient Information • Section 4.6 'Fertility, Pregnancy and Lactation': • There is no clinical experience from the use of Ryzodeg in pregnant women. Animal reproduction studies have not revealed any differences between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimester. After delivery, insulin requirements usually return rapidly to pre-pregnancy values. • There is no clinical experience with Ryzodeg during breast-feeding. In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma. It is unknown whether insulin degludec/insulin aspart is excreted in human milk. No metabolic effects are anticipated in the breast-fed newborn/infant. • Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility.
Children and adolescents <18 years	Routine pharmacovigilance and clinical trial	SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • The safety and efficacy of Ryzodeg in children and adolescents below 18 years of age have not been established. Currently available data are described in Section 5.2 but no recommendation on posology can be made. • Section 4.8 'Undesirable effects' • Ryzodeg has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (See Section 5.2). Safety and efficacy have not been investigated in children and adolescents. • Section 5.2 'Pharmacokinetic properties'

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		• The pharmacokinetic properties of Ryzodeg in type 1 diabetes mellitus were investigated in children (6–11 years) and adolescents (12–17 years) and compared to adults after single dose administration. Total exposure and peak concentration of insulin aspart are higher in children than in adults and are similar for adolescents and adults. The properties of Tresiba seen in adults are preserved in children and adolescents. Total exposure of Tresiba after single dose administration is higher in children and adolescents than in adults with type 1 diabetes mellitus.
Patients with hepatic impairment	Routine pharmacovigilance	SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • Ryzodeg can be used in renal and hepatic impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see Section 5.2). • Section 4.8 'Undesirable effects' • Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population. • Section 5.2 'Pharmacokinetic properties' • There are no clinical relevant differences in the pharmacokinetics of Ryzodeg between elderly and younger patients, between races or between healthy subjects and patients with renal or hepatic impairment.
Moderate and severe renal impairment	Routine pharmacovigilance	
Elderly patients (>75 years) with T1DM	Routine pharmacovigilance and clinical trial	SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • Ryzodeg can be used in elderly patients. As with all insulin products, glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2). • Section 4.8 'Undesirable effects' • Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population. • Section 5.1 'Pharmacodynamic properties' • There is no clinically relevant difference in the pharmacodynamics of Ryzodeg between elderly and younger subjects.
Co-administration with GLP-1	Routine pharmacovigilance Additional pharmacovigilance activities: NN1250-3948: A trial comparing the efficacy and safety of adding liraglutide versus addition of insulin aspart with the largest meal to insulin degludec, both in combination with metformin, in subjects with type 2 diabetes qualifying for treatment intensification	SmPC, Product Label and Patient Information • Section 4.5 'Interaction with other medicinal products and other forms of interaction' • The following substances may reduce insulin requirement: oral anti-diabetic medicinal products, glucagon-like peptide-1 (GLP-1) receptor agonists, monoamino oxidase inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, salicylates, anabolic steroids and sulphonamides.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. 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

The IDegAsp consists of 30% IAsp and 70% IDeg, IDeg being a new long-acting insulin analogue. At the target tissues, IDeg and IAsp monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake as confirmed by the non-clinical data. The mechanism of action of IDeg is similar to that of other insulins, only with a slightly lower activity and prolonged duration of action.

Benefits

Beneficial effects

The pharmacodynamic properties of IDegAsp has been adequately characterised in a well-designed program. IDegAsp has been shown to have a clear distinction between the short-acting component and the long-acting component, which has a flatter profile than currently available long-acting insulins.

Furthermore, the duration of action of the long-acting component extends well over 24 hours at doses of 0.4 U/kg thereby allowing once daily dosing. The potency of the basal component IDeg has been shown to be similar to that of IGlar, thus one unit of IDeg corresponds to one unit of IGlar. This may be extrapolated to other insulin analogues and human insulin.

In a dedicated PD study, it was shown that the response to hypoglycaemia with IDeg is not significantly altered when compared to IGlar. This is reassuring considering the long duration of action with a potential risk for protracted hypoglycaemia. Less glucose was needed to reverse the hypoglycaemia induced by IDeg, the clinical relevance of this finding is unknown.

There are indications that the long-acting component has less intra-individual variability than IGlar, the clinical benefit of this finding, however, remains to be seen.

The efficacy of IDegAsp has been investigated in five confirmatory studies, one in T1DM patients and four in T2DM patients. The T1DM trial included 548 subjects and 1866 subjects were included in the T2DM trials. All trials were of 26 weeks duration and the T1DM trial had a 26 week extension. Data on flexible dosing based on clinical studies with the basal component IDeg has also been provided. In these studies IDeg was administered with alternating narrow (8–12 hours) and wide (36–40 hours) dosing intervals. The clinical study program is considered adequate both with regards to study size, duration and design and was generally well conducted.

The populations recruited are considered representative for the target population. European patients were well represented (about 30 % of patients) both in the T1DM trial and the T2DM trials. The pretrial treatments with regards to insulin reflect the current treatment practice. T2DM groups were well balanced with regards to OAD treatment and patients were treated with adequate doses pretrial to ensure that these patients were true treatment failures. Co-administration of all OADs with the exception of insulin secretagogues, α-glucosidase inhibitors and GLP-1 agonists were allowed in the T2DM studies. The lack of data regarding the latter should be reflected in the SPC.

The HbA1c lowering effect of IDegAsp has been adequately shown across trials, well fulfilling the non-inferiority criteria. Adequate lowering of HbA1c (0.7-1.7 %) was achieved in all trials, taking the baseline HbA1c into account. In the T1DM trial, effect was maintained over the 52 week study period. Secondary endpoints generally supported the findings. The low intra-individual variability observed in the PD studies did not transform into less fluctuation in the interstitial glucose profiles. No clinically relevant changes or differences between groups were observed in the patient related outcomes.

Since the studies were of treat-to-target design with the aim of showing non-inferiority against comparators, focus was to show a difference in hypoglycaemia pattern. The lower cut-off of 3.1 mmol/l glucose for identifying hypoglycaemia was applied throughout the studies, which is in line with the currently adopted guideline. Hypoglycaemias were also recorded applying the stricter cut-off of 3.9 mmol/l, in line with the scientific advice given; these data were in line with the data using the lower cut-off.

In the T1DM trial, there was a trend towards fewer confirmed hypoglycaemias over time in the IDegAsp treated group. In patients with T2DM, treatment with insulin degludec/insulin aspart once daily (trials 3590, 3593) initial data entailed significantly more confirmed hypoglycaemic episodes compared to treatment with IGlar (estimated treatment ratio 2.17 [1.59; 2.94]95%CI and 1.43 [1.07; 1.92]95%CI in Trials 3590 and 3593, respectively) without improved glycaemic control. It could, however be shown that the higher rates of hypoglycaemias with IDegAsp in studies 3590 and 3593 was temporally related to the rapid-acting component of IDegAsp. New data provided from trial 3896, where IDegAsp was administered once daily showed no difference in overall hypoglycaemia rates between IDegAsp and the comparator IGlar. The data underscores the importance of taking IDegAsp together with the largest meal of the day. Lower rates of confirmed hypoglycaemias were observed in

T2DM patients treated with a BID regimen. The finding of a lower rate of nocturnal confirmed hypoglycaemias was consistent over the study program. However, due to the differences observed between the T1DM and T2DM populations no claims on an overall reduction of the risk of hypoglycaemia can be made.

A weight increase is to be expected when HbA1c is lowered by intensified insulin treatment. Compared to BIAsp weight increase was lower with IDegAsp. Compared to both IDet and IGlar, weight increase was higher with IDegAsp. In the case of IDet this may be explained by the fact that IDet has been shown to result in lower weight increase than other insulins. When compared to IGlar, the study design of trial 3590 resulted in higher doses with IDegAsp than IGlar which explains the observed difference in body weight. No difference in body weight gain was observed in trials where doses were similar for IDegAsp and IGlar at end of trial.

Uncertainty in the knowledge about the beneficial effects.

The Applicant proposed that the reduced variability observed with the basal component IDeg compared to IGlar in the PD studies would transform into less hypo- and hyperglycaemia. The data indicate a lower risk of hypoglycaemia, especially nocturnal hypoglycaemia, with IDeg; however, the fluctuations in interstitial glucose levels were not different with IDegAsp compared to IGlar. The clinical relevance of the lower variability is therefore debatable, since the lower occurrence of nocturnal hypoglycaemias may well be due to the flatter PD profile observed with IDeg. Although the data on the reduced variability is included in the SmPC, no claims can currently be made on the significance of this characteristic.

Risks

Unfavourable effects

In the therapeutic confirmatory trials with IDegAsp the most commonly reported AEs in both treatment groups were nasopharyngitis (IDegAsp: 14.7 % vs. comparator 11.5%), headache (IDegAsp: 6.7% vs. comparator 6.4%), upper respiratory tract infection (IDegAsp: 6.6% vs. comparator 6.7%) and diarrhoea (IDegAsp 3.9% vs. comparator 4.4%).

Hypoglycaemic episodes were only recorded as AEs if they fulfilled the definition of a SAE or severe hypoglycaemia (according to the CHMP guideline for the Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, CHMP/EWP/1080/00 Rev. 1). Overall, the rate of serious and severe hypoglycaemic episodes was somewhat lower in subjects treated with IDegAsp than in the comparators. The combined rate of serious and severe hypoglycaemic episodes in subjects with T1DM was 14.6% and 26.6 events per 100 PYE with IDegAsp vs. 21.7% and 46.0 events per 100 PYE with comparators. In subjects with T2DM the corresponding figures were 1.2% and 3.5 events per 100 PYE vs. 2.8 % and 7.6 events per 100 PYE, respectively. This was true also for episodes of severe hypoglycaemia and nocturnal severe hypoglycaemia and for serious hypoglycaemic events (IDegAsp 6.9% vs. comparator 7.7%). The duration of severe hypoglycaemic episodes did not differ between treatment groups.

Despite positive effects on nocturnal hypoglycaemia with IDegAsp, in both T2DM trials it was observed that comparable glycaemic control was achieved with a higher rate of overall confirmed hypoglycaemia when IDegAsp was dosed once daily and compared to IGlar. It could, however, be shown that the higher rate of hypoglycaemia was due to the short-acting component (IAsp) and that the hypoglycaemia rates were comparable to those observed for IGlar when IDegAsp was administered with the main meal. Hypoglycaemic events are listed in the RMP as an important identified risk.

The incidence of allergic reactions was low and similar in both treatment groups (IDeg+IDegAsp: 0.8% vs. comparators: 0.5%). The most common allergic reaction was urticaria (IDeg+IDegAsp 0.4% vs. comparator: 0.2%).

Allergic reactions are listed in the RMP as an important identified risk.

Injection site reactions and lipodystrophy were of mild or moderate severity and the rate was lower in the IDegAsp group than in the comparators (IDegAsp: 5.1 events per 100 PYE vs. comparator 10 events per 100 PYE, respectively).

The incidence of peripheral oedema was comparable in both IDegAsp and comparators arms (1.9% vs. 2.2%, respectively). The majority of events of peripheral oedema were mild in severity.

Cardiovascular safety was assessed, initially based on meta-analysis of independently confirmed, blindly adjudicated MACE events among the 16 therapeutic confirmatory IDeg + IDegAsp trials (HR 1.10, 95% CI: [0.68; 1.77]). In addition, an updated MACE analyses was submitted in response to the second D180 LoQ including a further three phase 3 trials (cut-off May 1, 2012); HR 1.13, 95% CI: 0.705; 1.797.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Uncertainty in the knowledge about the unfavourable effects

The development of specific IDeg antibodies or insulin cross reacting antibodies was generally low in both treatment groups (IDegAsp n=86, comparator n=139). No influence of antibodies on glycosylated haemoglobin (HbA1c) and dose at the end of trial was detected. However, based on the low number of subjects, it is not possible to draw any firm conclusions regarding the potential influence of insulin antibodies on the product efficacy and safety. Therefore, this potential risk has been included in the RMP.

Few very elderly subjects with T1DM were included in the clinical trial programme, making it difficult to draw any firm conclusions regarding the safety profile in this population. However, the overall number of subjects >75 years was adequate, and no major differences in the safety profile between subjects with T1DM and T2DM are expected. Based on this, treatment in very elderly subjects (>75 years) with T1DM has been included as missing information in the RMP. Dosing and monitoring in the elderly population is addressed in the proposed SmPC and this is considered adequate.

Also, very few subjects with moderate and severe renal impairment were included in the clinical trials (IDeg+IDegAsp n=65), therefore, there is an uncertainty regarding the safety in these patients, and moderate and severe renal impairment has been included as missing information in the RMP. Recommendations for use in subjects with renal impairment are included in the SmPC and are considered adequate.

There has been an on-going debate regarding the potential relationship between insulin analogues and an increased risk of cancer, possibly mediated by increased IGF-1 receptor activation or by sustained signalling by the insulin receptor. In non-clinical studies IDeg has been demonstrated to have a relatively low IGF-1 receptor binding affinity compared to insulin receptor binding, and the balance between the metabolic and proliferative actions of IDeg is similar to that of human insulin. Also, IDeg was not associated with any treatment related changes in the occurrence of hyperplastic or neoplastic lesions in the pre-clinical studies. During IDeg and IDegAsp clinical development the overall incidence of malignant neoplasms was low and there was no difference between treatment groups in the proportion of patients developing a malignancy. However, colon cancer was numerically more frequent

in the IDeg+IDegAsp group than in the comparators, even if the number of events was low and the rate was similar to that seen in the general diabetic population. Thus, events of colon cancer will be monitored in future PSURs.

Benefit-risk balance

Importance of favourable and unfavourable effects

The pharmacodynamic profile has been adequately characterised. IDegAsp provides a distinctive peak through the short-acting component and a basal component with a flatter profile compared to currently available long-acting insulins. The HbA1c lowering effect has been sufficiently demonstrated throughout the clinical program. In this respect, IDegAsp is comparable to other available insulins. The data from the clinical program indicate that the risk of especially nocturnal hypoglycaemias is lower with IDegAsp treatment in patients with type 1 diabetes. Since hypoglycaemia is a major obstacle when trying to obtain good glycaemic control, this is a finding of importance. Due to the long duration of action, IDegAsp also allows once daily dosing and a more flexible dosing, which is an advantage from the patient's perspective. In patients with T2DM, treatment with insulin degludec/insulin aspart once daily (trials 3590, 3593) initial data entailed significantly more confirmed hypoglycaemic episodes compared to treatment with IGlar (estimated treatment ratio 2.17 [1.59; 2.94]95%CI and 1.43 [1.07; 1.92]95%CI in Trials 3590 and 3593, respectively) without improved glycaemic control. It could, however, be shown that this increase was associated with the short-acting component (IAsp) and that the hypoglycaemia rates were comparable to those observed for IGlar when IDegAsp was administered with the main meal, as currently recommended in the SmPC. Lower rates of confirmed and nocturnal hypoglycaemias were observed in T2DM patients treated with a BID regimen.

Overall, the results of the clinical studies demonstrate that the use of IDegAsp in patients with T1DM and T2DM as monotherapy or in combination with oral antidiabetic agents is generally safe and in line with the safety profile of other insulin analogues. No unexpected AEs were identified, and the reporting rate was generally similar between treatment groups.

Data on very elderly subjects (>75 years) and subjects with moderate renal impairment are limited and should be followed post-marketing. These populations have been addressed adequately in the SmPC. Furthermore, the potential effect that insulin antibodies may have on the product efficacy and safety remains to be fully established. Therefore, antibody positive cases will be closely monitored post-marketing and reported in PSURs.

Regarding CV safety, the wide confidence interval in the MACE analysis, reflects the low number of events. However, there were no differences in the distribution of cardiovascular events between treatment groups. Furthermore, there is no indication from non-clinical data or from what is known about other basal insulin analogues that IDeg/IDegAsp is associated with an increased risk of cardiovascular events. Also, a number of post-hoc sensitivity analyses of the MACE data all supported the result of the primary analysis. It is therefore agreed that there are no indications of increased CV risk.

Discussion on the benefit-risk balance

In view of all the above considerations the CHMP concluded that the benefit risk balance in patients with type 1 and type 2diabetes is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ryzodeg in the treatment diabetes mellitus in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in Edition 3 (version 5) of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

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

Not applicable.

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that insulin degludec, as part of insulin degludec/insulin aspart, is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/96/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).