EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/CHMP/557821/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Tresiba

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

Procedure No. **EMEA/H/C/002498**

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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

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 Tresiba, 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.

Information on Paediatric requirements

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

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

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 substance insulin degludec 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 IDeg (EMEA/CHMP/SAWP/257964/2007, EMEA/CHMP/SAWP/311991/2008 and EMEA/CHMP/SAWP/80644/2009). 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 requirements for approval of the 200 units/mL strength, the definitions of responders and hypoglycaemia, the strategy for statistical testing and the safety evaluation (meta analysis for hypoglycaemia, antibodies, CV risk profile).

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 first Healthcare Professional and Patient Organisation consultation was launched on the 10 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 05 June 2012.
- The overview of comments of the first Healthcare Professional and Patient Organisation consultation was finalized on the 11 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
- The second Healthcare Professional and Patient Organisation consultation was launched on the 10 September 2012.
- The overview of comments of the second Healthcare Professional and Patient Organisation consultation was finalized on the 20 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 a meeting of SAG Diabetes/Endocrinology on 10 October 2012, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting in September 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 Tresiba on 18 October 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Despite advances in diabetes management, the majority of subjects with diabetes fail to meet the recommended levels of glycaemic control required to reduce long-term vascular complications. Hypoglycaemia and the fear of hypoglycaemia act as barriers for timely initiation of insulin and remain the major limiting factors for achieving target levels of glucose control in insulin-treated patients with diabetes. Strict treatment regimens have an impact on a patient's lifestyle contributing to lack of adherence and hence suboptimal glycaemic control. One particular limitation is that current injection devices only allow administration of a maximum of 80 units (U) per injection and that administration of large volumes (>1 mL) are associated with pain or discomfort.

About the product

Insulin degludec (IDeg) 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 glutamic acid spacer. This structure allows IDeg to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the subcutaneous injection site into the circulation, leading to the observed long pharmacokinetic and pharmacodynamic profiles. As a result of the changed pharmacokinetics with continuous release of IDeg monomers from the soluble multihexamer subcutaneous depot, IDeg has a longer duration of action than currently available basal insulin analogues such as insulin glargine (IGlar) and insulin detemir (IDet).

In patients with type 2 diabetes mellitus, insulin degludec can 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 must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements. Insulin degludec is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose. As with all insulin products adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Insulin degludec has been developed in two strengths as insulin degludec 100 U/ml and insulin degludec 200 U/ml, both being clear and colourless solutions containing the drug substance insulin degludec in a concentration of 600 nmol/ml and 1200 nmol/ml.

Insulin degludec 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.

Insulin degludec 200 U/ml is intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialled in 2 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. Insulin degludec is a long-acting basal insulin for once-daily subcutaneous administration at any time of the day. The potency of insulin analogues, including insulin degludec, is expressed in units (U). 1 unit (U) insulin degludec corresponds to 1 international unit (IU) of insulin human and to one unit of all other insulin analogues.

A paediatric investigation plan (PIP) for insulin degludec has been agreed with the EMA (EMA/190278/2010). The EMA has waived the obligation to submit the results of trials with insulin degludec in:

- neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and
- 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.

The EMA has deferred the obligation to submit the results of trials with insulin degludec in one or more subsets of the paediatric population in:

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

2.2. Quality aspects

2.2.1. Introduction

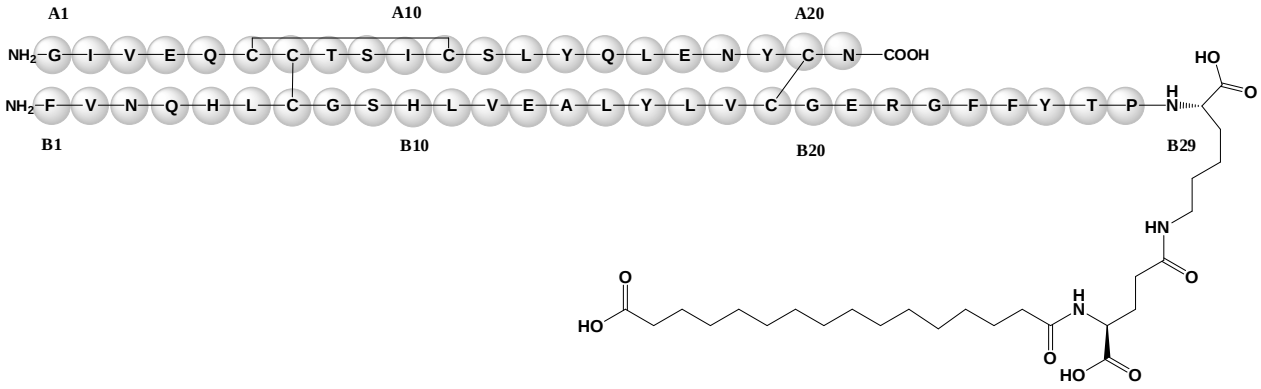
The drug products intended for the market, insulin degludec 100 U/ml and insulin degludec 200 U/ml, are clear and colourless solutions containing the drug substance insulin degludec in a concentration of 600 nmol/ml and 1200 nmol/ml respectively. Insulin degludec 100 U/ml drug product is intended for the market in two presentations, as a Penfill 3ml cartridge and as a pre-filled disposable PDS290 pen-injector. Insulin degludec 200 U/ml drug product is intended for the market in a pre-filled disposable PDS290 pen-injector. The drug products are intended for subcutaneous injection.

2.2.2. Active Substance

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

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The drug product is a clear solution of insulin degludec, preservatives, glycerol as isotonic agent, and zinc as a stabilising agent. There are two strengths: 100 U/mL and 200 U/mL.

The drug product is filled in 3 mL glass cartridges assembled into pre-filled disposable pens. The product is also provided in the glass cartridges, which are fitted by the patient into a Novo Nordisk delivery system.

The proposed commercial formulation has been used in some phase 2 and all phase 3 clinical trials. No comparability issues have been identified. The use of overages has been described and justified.

Adventitious agents

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

Manufacture of the product

Overall, the manfacturing process for insulin degludec has been sufficiently decsribed and validated. Critical steps in the production have been adequately identified and are monitored by in-process controls.

Product specification

The analytical methods used for release testing of insulin degludec drug product have been adequately described and validated.

In general, appropriate drug product specifications have been set and justified. The release specification for insulin degludec 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 100 U/ml and insulin degludec 200 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 56 days at up to 30°C, is proposed for insulin degludec 100 U/ml and 200 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 contained in the medicinal product Tresiba 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 Tresiba 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 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 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.

The focus of the pharmacology program has been on *in vitro* studies comparing the biological activity of insulin degludec to human insulin.

2.3.2. Pharmacology

Primary and secondary pharmacodynamic studies

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.

Safety pharmacology programme

In vivo safety pharmacology studies were performed 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 67-fold (rat) and 5.3-fold (dog) the mean clinical dose of 0.75 U/kg (~ 4.5 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

Insulin degludec was quantified by a specific sandwich enzyme-linked immuno sorbent assay (ELISA) used in all non-clinical regulatory safety studies and clinical trials where exposure was assessed. Results showed that the assay was valid for analysing insulin degludec in serum and plasma samples in terms of recovery, linearity, accuracy, precision and sensitivity.

Antibody development against insulin degludec in non-clinical studies was measured by a validated radio-immunoassay (RIA) using radiolabelled (^{125}I) insulin degludec. The amount of precipitated radioactivity was measured and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. The %B/T value is proportional to the amount of insulin degludec antibody present in the sample.

The methods of analysis were considered appropriate by the CHMP.

The pharmacokinetic studies confirmed that insulin degludec has the desired prolonged pharmacokinetic profile after subcutaneous (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 intravenous (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.

2.3.4. Toxicology

Overview of pivotal toxicity studies

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

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.

Single- dose toxicity

Subcutaneous toxicity after a single dose of insulin degludec was assessed in rats in a standard design single dose study and in dogs as an integrated part of a maximum tolerated dose (MTD) study. In rats, single subcutaneous administration of 24000 nmol/kg body weight was well-tolerated without mortality. In the dog, single subcutaneous administration of 30 nmol/kg body weight was well-tolerated without mortality.

Repeat-dose toxicity

The main design and main findings of the repeat-dose toxicity studies can be seen in the following tables:

Repeat-dose toxicity studies in rats

Study No.	205239	206315	206539
Species/strain	Wistar rats	Wistar rats	Sprague-Dawley rats
Test article	Insulin degludec	Insulin degludec	Insulin degludec
Duration (weeks)	4	26	52
Comparator	None	NPH insulin	NPH insulin
Route of administration	s.c	s.c	s.c
Animals/sex/ group	Main study: 4 groups: 10 males and 10 females Satellite study: 4 groups: 9 males and 9 females	Main study: 4 groups: 20 males and 20 females Satellite study: 4 groups: 12 males and 12 females Recovery study: 2 groups: 10 males and 10 females Comparator group: 20 males and 20 females Comparator satellite group: 12 males and 12 females	Main study: 3 groups: 40 males and 40 females and one group of 50 males and 50 females (high-dose) Comparator group: 50 males and 50 females
Dose levels (nmol/kg/day)	0, 25, 150, 250	0, 20, 50, 125 and 80/50[a] NPH insulin	0, 20, 65/50/40[b], 100/80/60[b] and 65/50/40[b] NPH insulin
Major findings	Clinical signs of hypoglycaemia, hypoglycaemia-related mortality, changes in clinical pathology parameters and decreased liver weight and liver glycogen depletion. The effects were considered related to the pharmacological action or exaggerated pharmacology of insulin degludec and not considered unexpected toxic effects.	Clinical signs of hypoglycaemia, hypoglycaemia-related mortality, changes in clinical pathology parameters and decreased liver weight and depletion of liver glycogen. The effects were comparable to those seen in animals dosed with NPH insulin, showed recovery and were considered related to the pharmacological action or exaggerated pharmacology of insulin and not considered unexpected toxic effects.	Clinical signs of hypoglycaemia, hypoglycaemia-related mortality, changes in clinical pathology parameters and decreased liver weight and depletion of liver glycogen. The effects were comparable to those seen in animals dosed with NPH insulin, showed recovery and were considered related to the pharmacological action or exaggerated pharmacology of insulin and not considered unexpected toxic effects.
Conclusion	NOEL: <25 nmol/kg/day	NOEL: <20 nmol/kg/day	NOEL: <20 nmol/kg/day

	NOAEL: 250 nmol/kg/day	NOAEL: 125 nmol/kg/day	NOAEL: 60 nmol/kg/day

a - Dose-level reduced study day 130 due to hypoglycaemia and hypoglycaemia-related mortality

b - Dose-levels reduced study day 76 and again study day 225 due to hypoglycaemia and hypoglycaemia-related mortality

Repeat-dose toxicity studies in dogs

Study No.	205238	206314
Species/strain	Beagle dog	Beagle dog
Test article	Insulin degludec	Insulin degludec
Duration	4 weeks	26 weeks
Comparator	None	NPH insulin
Route of administration	s.c	s.c
Animals/sex/group	4 groups: 3 males and 3 females	Main study: 4 groups: 4 males and 4 females Recovery study: one group: 2 males and 2 females[a] Comparator group: 3 males and 3 females dosed with NPH insulin
Dose levels (nmol/kg/day)	0, 4, 8 and 12	0, 4, 8, 12/10/8[b] and 8 NPH insulin
Major findings	No signs of toxicity	Marked hypoglycaemia and hypoglycaemia-related mortality necessitating dose-reduction in 12 nmol/kg/day group to 10 nmol/kg/day and subsequently to 8 nmol/kg/day. The effects were comparable to those seen in animals dosed with NPH insulin, showed recovery and were considered related to the pharmacological effect or exaggerated pharmacology of insulin and not toxic effects.
Conclusion	NOEL: <8 nmol/kg/day NOAEL: 12 nmol/kg/day	NOEL: <4 nmol/kg/day NOAEL: 8 nmol/kg/day

a - To preserve integrity of the recovery group one male and one female from the high dose group was reallocated to this group

b - Dose-level reduced day 48 and again day 108 due to hypoglycaemia and hypoglycaemia-related mortality

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.

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

The potential reproductive and developmental toxicity of insulin degludec was investigated according to ICH S5(R2) comprising studies covering fertility, embryonic and foetal development and pre-and postnatal development in rats and rabbits using NPH insulin as a reference substance. In rats, a combined study on fertility and embryo-foetal toxicity was performed. The toxicokinetic parameters are presented below.

Toxicokinetics in reproductive and developmental toxicity studies

Non-clinical study	**AUC $_{(0\text{-}24h)}$ (h×nmol/L)**	**C_{max} (nmol/L)**
Rat: fertility and embryo-foetal development		
NOAEL male fertility: 125 nmol/kg/day[a]	2814	358
Exposure level ratio: rat/human	17	38

NOAEL female fertility and embryo-toxicity: 125 nmol/kg/day[b] Exposure level ratio: rat/human	866 5.1	146 15
Rabbit: embryo-foetal development NOAEL maternal toxicity and reproductive performance: 20 nmol/kg[c] Exposure level ratio: rabbit/human NOAEL embryo-foetal toxicity: 20 nmol/kg/day[c] Exposure level ratio: rabbit/human	 1658 9.7 1658 9.7	 125 13 125 13
Rat: pre-and post-natal study NOAEL reproductive performance F_0: 125 nmol/kg/day[b] Exposure level ratio: rat/human NOAEL F_1: 125 nmol/kg/day[b] Exposure level ratio: rat/human	 866 5.1 866 5.1	 146 15 146 15
Human clinical exposure		
NN1250-1993 (exposure in steady-state) × NN1250-3582 (dose: 0.75 U/kg)	170	9.48

a – Exposure extrapolated from repeated dose study in rats (206315)

b – Exposure extrapolated from preliminary study in pregnant rats (206075)

c – Exposure extrapolated from preliminary study in pregnant rabbits (206073)

In the 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, peri-parturient 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.

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 was 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. 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.

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.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme for IDeg comprises a total of 41 completed clinical trials; 25 clinical pharmacology trials (7 of which include both IDeg and IDegAsp), 3 therapeutic exploratory trials, 11 therapeutic confirmatory trials, and 2 trials in the category 'other therapeutic trials' (see Figure "Overview of Clinical Trials in the IDeg Development Programme"). The formulation of the IDeg drug products used in the phase 2 and 3a development programmes is identical to the proposed commercial formulation. The therapeutic confirmatory programme investigated the efficacy and safety of IDeg in subjects with T1DM and T2DM in combination with bolus insulin, and in both insulin-naïve and previously insulin–treated subjects with T2DM in combination with OADs (see Table "All Therapeutic Confirmatory Trials with IDeg").

IDeg was investigated as once-daily (OD) treatment and as a three-times-weekly (3TW) dosing regimen. Whereas clinically relevant improvement in glycosylated haemoglobin (HbA1c) was demonstrated with IDeg 3TW, non-inferiority versus IGlar OD could not be confirmed for the primary endpoint. Therefore, the Applicant did not pursue the 3TW dosing regimen for IDeg. The IDeg 3TW trials are included in the overall assessment of safety, and key results related to efficacy and dosing are presented for completeness.

A total of 5624 subjects were exposed to IDeg and 4404 subjects were exposed to comparator products as part of the entire completed clinical development programme up until the clinical cut-off date (31 January 2011). In addition, safety information recorded in the period 1 February 2011 – 31 March 2011 is included from six ongoing clinical trials, five of which are extensions to completed therapeutic confirmatory trials.

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 requirements for approval of the 200U/ml strength, 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.

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 must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements. This was accepted by the CHMP.

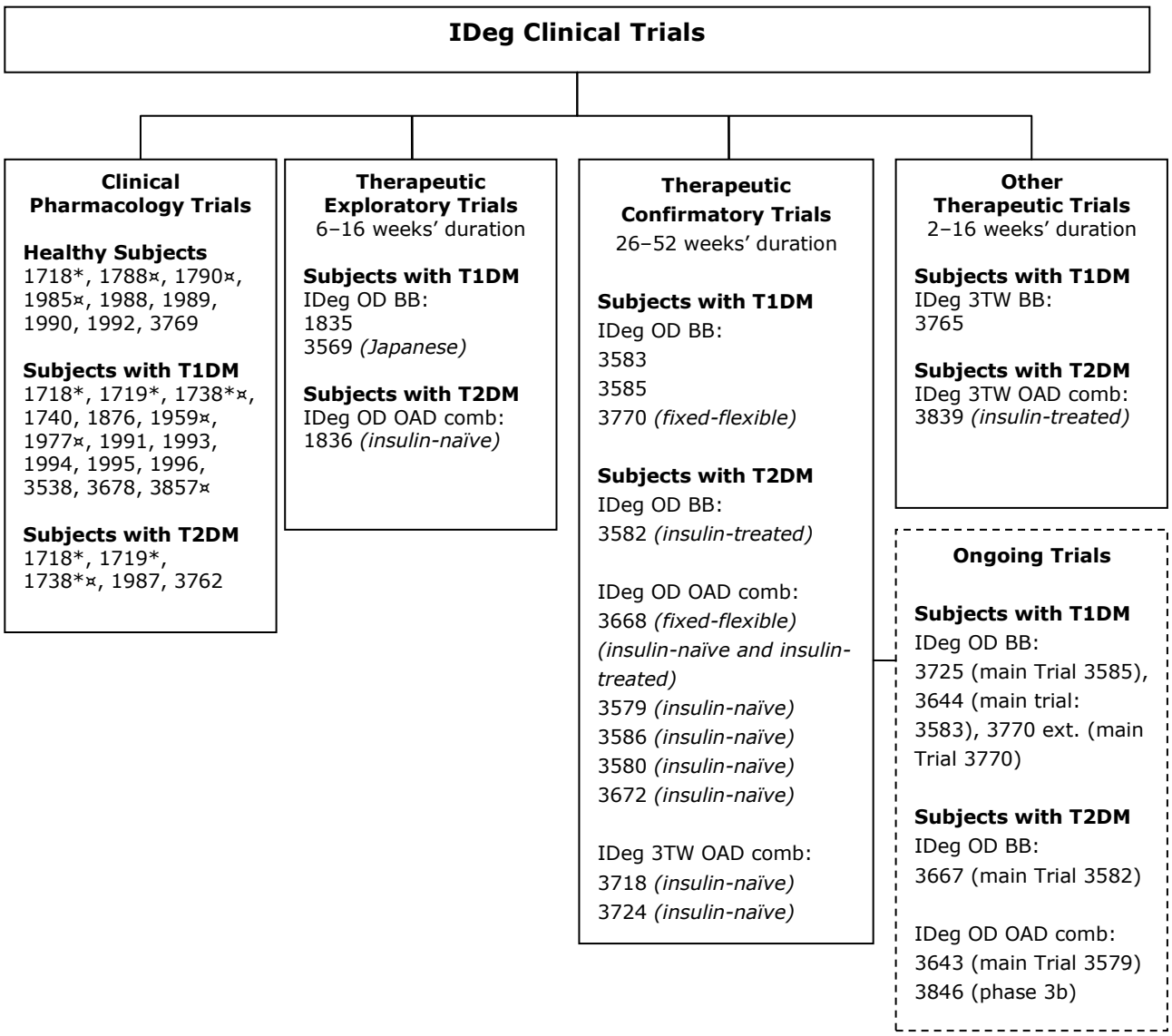
GCP

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 IDeg Development Programme



Trials marked with * included both subjects with T1DM and subjects with T2DM. Trial 1718 also included healthy subjects. Trials marked with ¤ included both IDeg and IDegAsp. 3TW: three times weekly, BB: basal–bolus, IDeg: insulin degludec, IDegAsp: insulin degludec/insulin aspart, OAD: oral antidiabetic drug, OD: once daily, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus.

The clinical development program for IDeg included a total of 11 therapeutic confirmatory trials conducted to evaluate the efficacy and safety of IDeg OD (100 U/mL and 200 U/mL) in subjects with T1DM and T2DM from early onset to more advanced stages of disease using various dosing schedules; please see the table below for details on trial design.

Table: All Therapeutic Confirmatory Trials with IDeg

Trial	Trial Description and Treatment	Subjects Population	Antidiabetic Therapy at Screening	Duration (Weeks)	IDeg: Comp.	No. Subjects (FAS)
T1DM IDeg OD[§] Basal–bolus Therapy						
3583	IDeg OD versus IGlar OD *(+ IAsp TID)*	T1DM Insulin-treated	Any basal–bolus regimen	52	3:1	IDeg: 472 IGlar: 157
3585	IDeg OD versus IDet OD)[#] *(+ IAsp TID)*	T1DM Insulin-treated	Any basal–bolus regimen	26	2:1	IDeg: 302 IDet: 153
3770	IDeg Flex versus IGlar OD and IDeg Flex versus IDeg OD *(all arms + IAsp TID)*	T1DM Insulin-treated	Any basal insulin (OD or BID) + any bolus insulin (≥3 daily injections)	26	1:1:1	IDeg FF: 164 IDeg: 165 IGlar: 164
T2DM IDeg OD[§] Basal–Bolus Therapy						
3582	IDeg OD versus IGlar OD *(+ IAsp TID ± met ± PIO)*	T2DM Insulin-treated	Any insulin regimen (with or without OADs)	52	3:1	IDeg: 744 IGlar: 248
T2DM IDeg OD[§] OAD–Insulin Combination Therapy						
3579	IDeg OD versus IGlar OD *(+ met ± DPP-4 Inhib.)*	T2DM Insulin-naïve	met monotherapy met + [SU ± α-GI ± DPP-4 inhib.] in any combination	52	3:1	IDeg: 773 IGlar: 257
3672	IDeg 200 U/mL OD versus IGlar OD *(+ met ± DPP-4 inhib.)*	T2DM Insulin-naïve	met monotherapy met + [SU/Glin ± DPP-4 inhib. ± α-GI] in any combination	26	1:1	IDeg: 228 IGlar: 229
3586	IDeg OD versus IGlar OD *(+OAD except DPP-4 inhib.)*	T2DM Insulin-naïve	monotherapy (met or SU); met + [SU ± α -GI ± DPP-4 inhib.]; SU + [α -GI ± DPP-4 inhib.]; met + SU + [α -GI or DPP-4 inhib.]	26	2:1	IDeg: 289 IGlar: 146
3580	IDeg OD versus sitagliptin *(± met ± SU/Glin ± pio)*	T2DM Insulin-naïve	1–2 OADs, any combination of: met ± SU/Glin ± pio	26	1:1	IDeg: 225 Sita: 222
3668	IDeg Flex versus IGlar OD and IDeg Flex versus IDeg OD *(all arms ± OADs acc. to label)*	T2DM Insulin-naïve/ basal insulin–treated	OAD(s) only (any combination of met ± SU/Glin ± pio) basal insulin only basal insulin + OAD(s)	26	1:1:1	IDeg FF: 229 IDeg: 228 IGlar: 230
T2DM IDeg 3TW OAD–Insulin Combination Therapy						
3718	IDeg 200 U/mL 3TW (evening) versus IGlar OD *(+ met ± DPP-4 inhib.)*	T2DM Insulin-naïve	met monotherapy met + [SU/Glin ± DPP 4 inhib. ± α -GI] in any combination	26	1:1	IDeg: 233 IGlar: 234
3724	IDeg 200 U/mL 3TW (morning) versus IGlar OD *(+ met ± DPP-4 inhib.)*	T2DM Insulin-naïve	met monotherapy met + [SU/Glin ± DPP 4 inhib. ± α -GI] in any combination	26	1:1	IDeg: 229 IGlar: 230

[§] IDeg 100 U/mL unless otherwise noted. [#]A second IDet dose could be added after 8 weeks in case of inadequate glycaemic control.
Abbreviations: 3TW: three times weekly; α -GI: alpha-glucosidase inhibitor; BID: twice daily; comp.: comparator; DPP-4 inhib.: dipeptidyl peptidase-4 inhibitor; FAS: full analysis set; FF: Flex (IDeg administered with alternating narrow (8–12 hours) and wide (36–40 hours) dosing intervals; Glin: glinide; IDeg: insulin degludec; IDegAsp: insulin degludec/insulin aspart; IGlar: insulin glargine; met: metformin; OAD: oral antidiabetic drug; OD: once daily; pio: pioglitazone; SU: sulphonylurea; T1DM: type 1 diabetes mellitus; T2DM; type 2 diabetes mellitus; TID: three times daily; TZD: thiazolidinedione

2.4.2. Pharmacokinetics

The pharmacokinetics of IDeg was investigated in 25 clinical pharmacology trials, out of which sixteen trials were conducted using the commercial IDeg formulation and are therefore considered key trials. IDeg has been quantified by a validated sandwich enzyme-linked immunosorbent assay (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.

Intra-individual variability in AUC was lower with IDeg (13 %) than with IGlar (24 %) in subjects with T1DM.

Distribution

Based on *in vitro* studies using surface plasmon resonance (SPR) methodology, IDeg seems to have high plasma protein binding >99%. The volume of distribution (Vd) of IDeg is unknown.

Elimination and time dependency

Subcutaneously administered IDeg has 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). IDeg exhibits 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). Across studies, no indication of time dependency is seen.

The dominating route of IDeg elimination appears to be 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.

Dose proportionality

No major differences in IDeg PK are observed between T1DM or T2DM populations but there is a trend towards lower Cmax in the T2DM population compared to the T1DM population. Dose proportionality, both for AUC and Cmax, between doses of 0.4, 0.6 and 0.8 U/kg in T1DM and T2DM populations has been demonstrated. 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 very small differences in the pharmacokinetic properties of IDeg between subjects with renal impairment (mild, moderate, severe and ESRD) and healthy subjects. The data further 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.

There were only minor differences in the pharmacokinetic properties (AUC and Cmax differed < 15 % in all comparisons) of IDeg between sexes, subjects of different race and ethnicity and between younger adults and elderly. The number of very old (aged 75 years and over) was very limited. However, the PK data available do not suggest dramatic differences compared to patients aged 65-74 years.

When comparing children with adults, IDeg AUC and Cmax was 48 % and 20 % higher in children compared to adult subjects. When comparing adolescents with adults, IDeg AUC and Cmax was 33 % and 23 % higher and in adolescents compared to adult subjects. However, the sought indication does not include children and adolescents and no further investigations are considered necessary at present.

Regarding BMI, 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.

In general, any observed differences in the pharmacokinetic exposure between different special populations are not believed to have any clinical implications considering that IDeg 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.

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 long pharmacokinetic and pharmacodynamic profiles.

Insulin degludec is a specific and full agonist at the human insulin receptor and the mode of action (post-receptor signalling) is identical to that of human insulin and other insulin analogues.

Primary and Secondary pharmacology

The dose-response Trials 1993 and 1987 are considered pivotal for describing the steady-state pharmacodynamic properties of IDeg in subjects with T1DM and T2DM, respectively. Results from other trials are included as supportive information.

All trials employed the euglycaemic clamp for the characterisation of the PD profile of IDeg. The euglycaemic clamp procedure used across the IDeg clinical pharmacology trials was standardised in a

systematic way. In the majority of the trials, continuous glucose infusion was automatically adjusted to maintain blood glucose at a pre-defined level using a Biostator (MTB Medizintechnik, Ulm, Germany).

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.

Steady-State Pharmacodynamic Properties

Subjects with Type 1 Diabetes

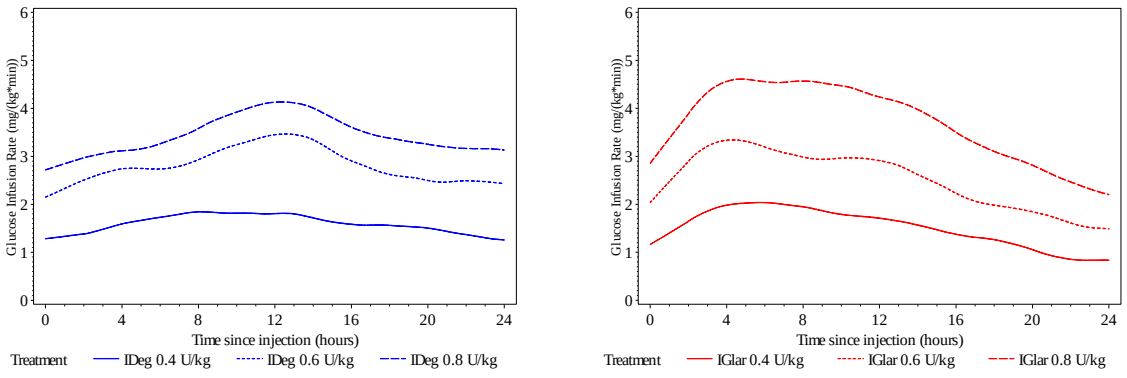
The steady-state pharmacodynamic properties of IDeg in subjects with T1DM were investigated in Trial 1993. This trial was a randomised, single-centre, double-blind, incomplete block cross-over, multiple-dose trial with 8 days of once-daily administration of IDeg or IGlar at doses of 0.4, 0.6 and 0.8 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.

Glucose-lowering Effect

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 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 1).

Descriptive statistics and statistical analyses confirmed that the glucose-lowering effect of IDeg increased with increasing dose (Table 1). 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 1 24-hour Mean Glucose Infusion Rate Profiles for IDeg (Left) and IGlar (Right) at Steady State in Subjects with T1DM



Trial 1993

Table 1 Glucose Infusion Rate Endpoints for IDeg at Steady State in Subjects with T1DM

Dose (U/kg)	N	$AUC_{GIR,\square\square SS}$ (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 ($AUC_{GIR\tau,SS}$ 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 a 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.

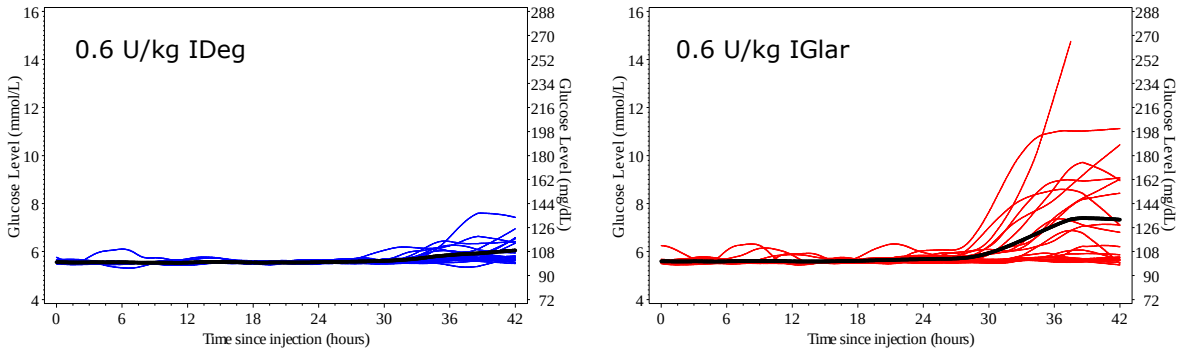
In addition, the fluctuation in glucose infusion rate ($AUCF_{GIR,\tau,SS}$) was calculated to illustrate how much the glucose infusion rate deviated from the individual mean. The estimated mean fluctuation values were lower for IDeg than for IGlar at all three dose levels, thus, the glucose infusion 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 2; data only shown for the 0.6 U/kg dose).

Figure 2 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 2).

Table 2 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. [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.N: number of subjects contributing to the analysis.

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. With the responses to the Day 120 List of Questions (LoQ) the Applicant 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

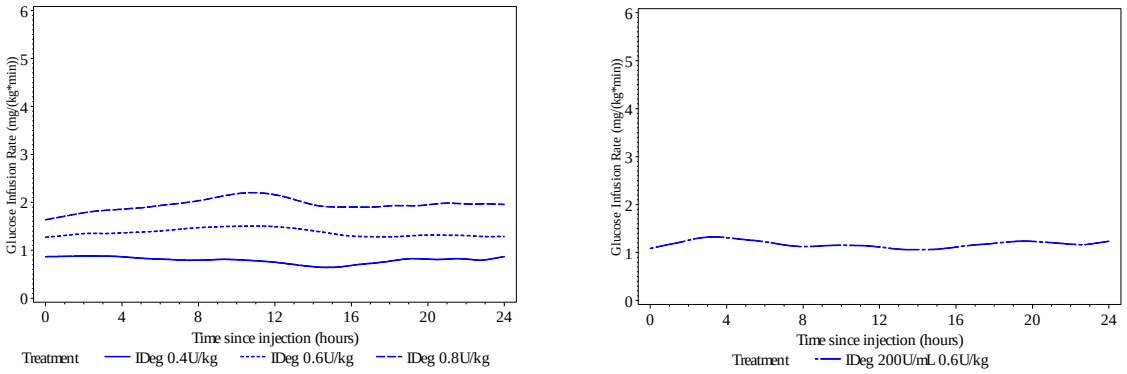
The steady-state pharmacodynamic properties of IDeg in subjects with T2DM were investigated in Trial 1987. This trial was a randomised, single-centre, double-blind, two-period, incomplete block cross-over, multiple-dose trial with 6 days of once-daily administration of IDeg at doses of 0.4, 0.6 and 0.8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

Glucose-lowering Effect

The mean 24-hour glucose infusion rate profiles obtained at steady state were flat at all three dose levels, and the glucose-lowering effect increased with increasing dose (Figure 3; left panel). The glucose-lowering effect of IDeg increased with increasing dose (Table 3), 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.

The mean glucose infusion rate profile for 0.6 U/kg IDeg 200 U/mL was flat and the glucose-lowering effect extended beyond 24 hours (Figure 3; right panel). Descriptive statistics are shown in Table 4. The glucose-lowering effect was distributed equally over the 24-hour period, which was supported by the ratio between $AUC_{GIR,0\text{-}12h,SS}$ and $AUC_{GIR,\tau,SS}$ estimated to 53%.

Figure 3 24-Hour Mean Glucose Infusion Rate Profiles for IDeg at Steady State in Subjects with T2DM, IDeg 100 U/ml (left panel) and 200 U/ml (right panel)



Trial 1987.

Table 3 Glucose Infusion Rate Endpoints for IDeg at Steady State in Subjects with T2DM, IDeg 100 U/ml

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	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 %.

Table 4 Glucose Infusion Rate Endpoints for IDeg 200 U/mL at Steady State in Subjects with T2DM

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%)	$AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,\tau,SS}$ Geom. mean (CV%)
0.6	16	1345 (64)	1.5 (44)	12.1 (74)	0.53 (17)

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

Due to the design of the trial, no formal comparison was performed between the 100 U/ml and 200 U/ml formulations within trial 1987. AUC_{GIR} and GIR_{max} were both slightly lower for the 200 U/ml formulation. However, in study 3678 (see below), which was adequately designed to compare the two formulations, no clinically relevant differences were observed.

Duration of Action

Duration of action of IDeg 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.

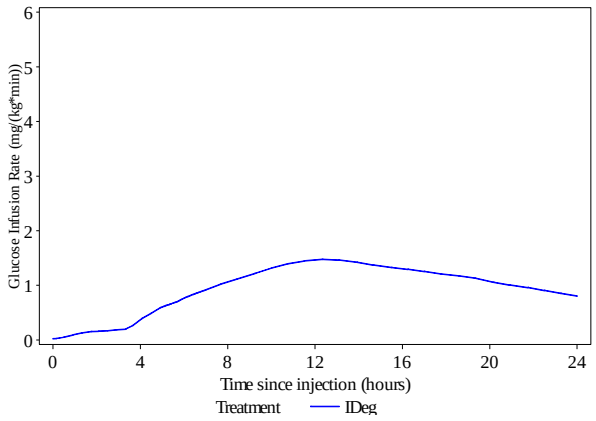
Single-Dose Pharmacodynamic Properties

Subjects with Type 1 Diabetes

The single-dose pharmacodynamic properties of IDeg in subjects with T1DM were investigated in Trial 3857. This trial was a randomised, single-centre, open-label, three-period cross-over trial with single-dose administration of 0.5 U/kg IDegAsp, 0.5 U/kg IDeg and 0.5 U/kg IAsp in subjects with T1DM. The pharmacodynamic properties were investigated during a 24-hour euglycaemic clamp (target glucose level of 5.5 mmol/L [100 mg/dL]).

The mean glucose infusion rate profile for IDeg is presented in Figure 4, and the corresponding glucose infusion rate endpoints are shown in Table 5. The single dose PD profile shows a rather slow onset of action with a peak at about 12 hours.

Figure 4 24-Hour Mean Glucose Infusion Rate Profile for IDeg after Single Dose in Subjects with T1DM



Trial 3857: 0.5 U/kg.

Table 5 Glucose Infusion Rate Endpoints for IDeg after Single Dose 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%)	$tGIR_{max,,SD}$ (h) Median (CV%)
0.5	26	1213 (47)	1.6 (41)	13.5 (35)

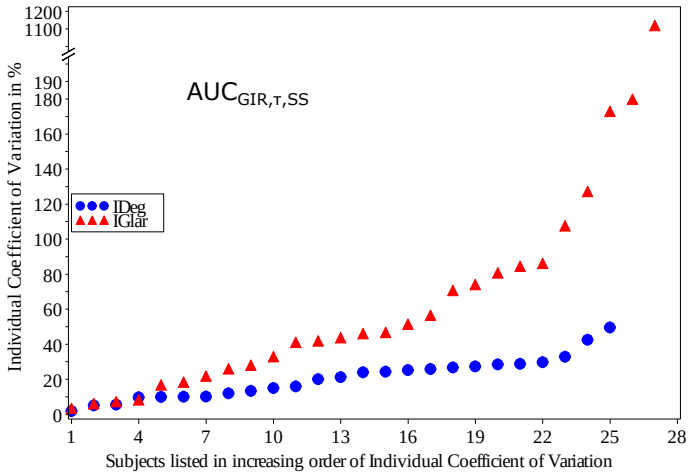
Trial 3857.
N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

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 5, 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 5).

Figure 5 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.

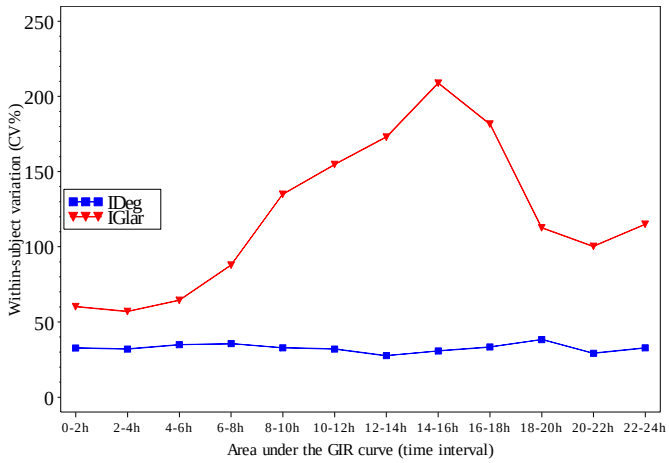
Table 6 Day-to-Day Variability in Glucose-Lowering Effect for IDeg and IGlar at Steady State in Subjects with T1DM

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 6). Mean CVs for IDeg were 33% for $AUC_{GIR,0\text{-}2h}$, 33% for $AUC_{GIR,10\text{-}12h}$ and 33% for $AUC_{GIR,22\text{-}24h}$, and mean CVs for IGlar were 60% for $AUC_{GIR,0\text{-}2h}$, 135% for $AUC_{GIR,10\text{-}12h}$ and 115% for $AUC_{GIR,22\text{-}24h}$).

Figure 6 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 vs. IGlar. The prediction intervals for both average and maximum glucose-lowering effect were narrower for IDeg than for IGlar. 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.

Furthermore, it was predicted that the risk of an individual with $GIR_{max,SS}$ of 3 mg/kg·min experiencing more than 133% of the usual $GIR_{max,SS}$ (i.e. $GIR_{max,SS}$ > 4 mg/kg·min) was 6% for IDeg and 30% for IGlar. Likewise, for a usual $GIR_{max,SS}$ of 2 mg/kg·min the risk of an individual experiencing more than twice the average $GIR_{max,SS}$ (i.e. $GIR_{max,SS}$ > 4 mg/kg·min) on any given day (i.e., potential hypoglycaemia) was <0.1% for IDeg and 11% for IGlar.

Thus, the data show that the variability, both with regards to $AUC_{GIR,\tau,SS}$ and GIR_{max} was significantly lower for IDeg compared to IGlar.

<u>IDeg 200 U/mL and IDeg 100 U/mL Interchangeability</u>

The pharmacodynamic properties of IDeg 100 U/mL and IDeg 200 U/mL at steady state in subjects with T1DM were compared in Trial 3678. This was a randomised, single-centre, double-blind, cross-over, multiple-dose trial with 8 days of once-daily administration of 0.4 U/kg IDeg 100 U/mL or 0.4 U/kg IDeg 200 U/mL. Pharmacodynamic properties were investigated during a 26-hour euglycaemic clamp (target glucose level of 5.5 mmol/L [100 mg/dL]) conducted at steady state.

The mean glucose infusion rate profiles obtained at steady state were similar for IDeg 100 U/mL and IDeg 200 U/mL. The glucose-lowering effect extended beyond the clamp duration of 26 hours both with IDeg 100 U/mL and IDeg 200 U/mL. Descriptive statistics showed that the two products provided similar glucose-lowering effect at steady state based on $AUC_{GIR,\tau,SS}$ and $GIR_{max,SS}$ (Table 7), and there was no statistically significant difference between the two treatments (IDeg 200 U/mL vs. IDeg 100 U/mL) for $AUC_{GIR,\tau,SS}$ (0.94 $[0.86; 1.03]_{95\%CI}$).

Table 7 Glucose Infusion Rate Endpoints for IDeg 100 U/mL and IDeg 200 U/mL at Steady State in Subjects with T1DM

Product and 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%)
100 U/mL 0.4	33	2255 (48)	2.4 (46)	12.4 (35)
200 U/mL 0.4	33	2123 (48)	2.1 (42)	13.9 (47)

Trial 3678.
N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %

Injection Regions and Routes of Administration

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.

Subcutaneous Injections in Thigh, Abdomen or Deltoid

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 8). 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 8 Glucose Infusion Rate Endpoints for IDeg after Single Dose in the Thigh, Abdomen and Deltoid in Healthy Subjects

Injection Region	N	$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg) Geom. mean (CV%)	$GIR_{max,SD}$ (mg/kg·min) Geom. mean (CV%)	$tGIR_{max,SD}$ (h) 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 %.

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 9). 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; this is reflected in section 4.2 of the SmPC.

Table 9 Glucose Infusion Rate Endpoints for IDeg after Single Dose i.m. and s.c. in Healthy Subjects

Administration Route	N	$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg) Geom. mean (CV%)	$GIR_{max,SD}$ (mg/kg·min) Geom. mean (CV%)	$tGIR_{max,SD}$ (h) 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

The effect of BMI and sex on total and maximum glucose-lowering effect of IDeg was investigated across trials in subjects with T1DM and in subjects with T2DM. Total and maximum glucose-lowering effect of IDeg at steady state decreased with increasing BMI in subjects with either T1DM or T2DM, and statistical analyses showed that the correlation was significant. The total and maximum glucose-lowering effect of IDeg was greater in women than in men, and this was confirmed by statistical analysis. These findings are in line with previous findings on the correlation between insulin sensitivity and BMI and gender, respectively.

Geriatric Subjects

When the steady-state pharmacodynamic properties of IDeg in geriatric subjects (≥65 years) in comparison to younger adult subjects (18–35 years) with T1DM were investigated during a 26-hour euglycaemic clamp, the mean 24-hour glucose infusion rate profiles for IDeg were slightly lower for geriatric subjects compared to younger adult subjects despite the fact that exposure of IDeg was comparable in the two age groups. Total and maximum glucose-lowering effect were approximately 20% lower in geriatric subjects; however, statistical analysis showed no difference in $AUC_{GIR,\tau,SS}$ or $GIR_{max,SS}$. These findings are in line with the decreased insulin sensitivity known to occur with increasing age.

Hypoglycaemic Response to IDeg in Subjects with Type 1 Diabetes

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 with 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 10). 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 10 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

The pharmacokinetic and pharmacodynamic properties of IDeg were characterised in the dose range 0.4 to 0.8 U/kg. This is adequate, although lower doses may sometimes be used in T1DM. 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

IDeg is present in the circulation for at least 120 hours and has an estimated $t_{½}$ of approximately 25 hours, supporting duration of action beyond 42 hours. Given the long duration of action and continuous and stable absorption, IDeg would allow flexibility in the timing of administration. This was further investigated in the clinical trials.

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. In addition, the glucose-lowering effect was essentially similar for the IDeg 100 U/mL and IDeg 200 U/mL products. The data are deemed sufficient to conclude that 1 U of IDeg 100 U/mL and 1 U of IDeg 200 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 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 IDeg, 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 was 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; these interactions are sufficiently reflected in section 4.5 of the SmPC.

IDegLira - IDeg Co-formulated with Liraglutide

In study NN9068–3632, the safety, tolerability, pharmacokinetics, and pharmacodynamics of IDeg co-formulated with liraglutide (IDegLira) was investigated. Results showed that the bioavailability of IDeg was unaltered when administered as part of IDegLira, and the pharmacodynamic effect of IDegLira seemed to be additive with no synergistic effects when combining IDeg and liraglutide in IDegLira. No safety or tolerability issues were observed with IDeg either administered alone or as part of IDegLira.

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.

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

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 glutamic acid spacer. The non-clinical data confirm that the mechanism of action is similar to that of other insulins, only with a slightly lower activity.

IDeg is a new insulin analogue and the pharmacokinetic studies should thus aim at describing the disposition of the new chemical entity. The influence of intrinsic factors (BMI, age, sex, race/ethnicity, renal and hepatic function) and extrinsic factors (drug interactions) should also be evaluated. 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 pharmacodynamic profile of IDeg has been investigated through a well-designed development program. The single dose PD profile in T1DM subjects shows a rather slow onset of action with a peak at about 12 hours. 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 and 1 U of IDeg 200 U/mL corresponds to 1 U of all other insulin analogues and to 1 IU of human insulin.

Steady state data in T1DM patients show that IDeg has a flatter PD profile than IGlar, with a slight peak observed about 10-12 hours after dosing especially at higher doses. The data on fluctuation of the effect indicate a more stable PD profile for IDeg compared to IGlar. The dose adjusted data across trials for AUC_{GIR} and GIR_{max} are consistent although with some variation especially within trial 1993. An appropriate dose range has been investigated and a proportional dose-response relationship has been established in T1DM.

Due to the long duration of action for IDeg, an exact duration of action could not be estimated. At the dose levels investigated the effects well exceeds 24 hours. The duration of action, however, 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.

The steady state PD profile obtained in T2DM subjects is similar to that observed in T1DM subjects, however with a less pronounced peak at 10-12 hours. In the shorter clamp used in T2DM subjects (26 h vs. 42 h in T1DM) no patient showed an escape of effect in the dose range 0.4-0.8 U/kg as would be expected. Since insulin requirements are usually higher in T2DM, 24 hour coverage with IDeg would be expected in clinical use. In T2DM the dose-response relationship was shown to be linear.

Intra-individual variability was investigated in a parallel group study where each subject underwent three euglycaemic clamps. The data show 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 more stable glucose control when IDeg is used in clinical practice remains to be shown.

The development of IDeg also included a new formulation of 200 U/ml. In T1DM subjects, the overall PD profile is comparable for the 100 U/ml and 200 U/ml formulations with no statistically confirmed difference in AUC.

The influence of injection site on the PD profile was investigated in healthy subjects. Very similar profiles were obtained irrespective of injection site, however, 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 with regards to this is considered adequate. When comparing i.m. and s.c. injection, the PD profile was essentially similar but with a higher peak observed with i.m. injection together with higher AUC and GIR. Due to the higher glucose-lowering effect, i.m. injections should be avoided. Adequate information is included in the SmPC to this respect.

The influence of the intrinsic factors BMI and gender were investigated in across-trial analyses without any unexpected findings. The influence of age and ethnicity was investigated in dedicated studies. None of these analyses did reveal any unexpected or clinically relevant findings.

The hypoglycaemic clamp was performed to investigate whether the counter-regulation to hypoglycaemia induced by IDeg was impaired relative to IGlar induced hypoglycaemia. No attenuation of the counter-regulation in response to hypoglycaemia with IDeg as compared to IGlar was observed. This is reassuring considering the long duration of IDeg action and the potential for protracted hypoglycaemia. Less glucose was needed to reverse the hypoglycaemia induced by IDeg, the clinical relevance of this finding is unknown.

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 section 4.5 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

Overall, the applicant has performed a very comprehensive clinical pharmacology program which clearly covers more than what could be considered the minimum requirements regarding PK characterisation.

The pharmacodynamic characteristics of IDeg have been thoroughly investigated and the PD profile has been adequately characterised. IDeg has been shown to have a flat and stable profile at steady

state with less intra-individual variability than the comparator IGlar. The duration of effect exceeds 24 hours with an estimated $t_{½}$ of 25 hours making OD dosing feasible.

2.5. Clinical efficacy

The clinical development programme of IDeg comprises nine therapeutic confirmatory trials with IDeg OD, two therapeutic confirmatory trials with IDeg three times weekly (3TW) and three therapeutic exploratory trials. The primary objectives of the therapeutic confirmatory trials were to confirm the efficacy of IDeg in controlling long-term glycaemia with IDeg used either alone or in combination with bolus insulin, with or without OADs in subjects with either T1DM or T2DM. Therapeutic confirmatory trials with the OD dosing are discussed in the following. Trials with the 3TW dosing will not be further discussed since the posology was not pursued as the primary objective was not met.

Table 11 Overview of Therapeutic Confirmatory Trials – T1DM

Trial (wks)	Trial Description	Treatment Combination	Subject Population	No. of Subjects Randomised	Antidiabetes Treatment at Screening	Randomisation (IDeg: Comparator)	Stratification
Basal-bolus therapy							
3583 (52)	IDeg 100 U/mL OD vs. IGlar OD	+IAsp	Insulin treated	IDeg: 472 IGlar 157	Any basal–bolus regimen	3:1	No stratification
3585 (26)	IDeg 100 U/mL OD vs. IDet OD[#]	+IAsp	Insulin treated	IDeg: 303 IDet: 153	Any basal–bolus regimen	2:1	Region: Europe/Japan/ India/South Asia
3770 (26)	IDeg FF 100 U/mL OD vs. IGlar OD and IDeg FF 100 U/mL OD vs. IDeg OD	+IAsp	Insulin treated	IDeg FF: 164 IDeg: 165 IGlar: 164	Any basal–bolus regimen[§]	1:1:1	No stratification

FF: Fixed Flexible, subjects treated with a rotating dosing schedule

#a second IDet dose could be added after 8 weeks in case of inadequate glycaemic control

§basal insulin (OD or BID) + any bolus insulin (≥3 daily injections)

Table 12 Overview of Therapeutic Confirmatory Trials – IDeg OD – T2DM

Trial (wks)	Trial description	Treatment Combination	Subject Population	No. of Subjects Randomised	Antidiabetes Treatment at Screening	Randomisation (IDeg: comparator)	Stratification
Basal-bolus therapy ± OADs							
3582 (52)	IDeg 100 U/mL OD vs. IGlar OD	+IAsp ±met ±pio	Insulin treated	IDeg: 755 IGlar 251	Any insulin regimen (with or without OADs): premix, self-mix, basal insulin only, basal-bolus (≥1 bolus), bolus only, CSII	3:1	Prior treatment: basal-bolus/ basal insulin only/other
OAD-insulin combination therapy							
3579 (52)	IDeg 100 U/mL OD vs. IGlar OD	+met ±DPP-4I	Insulin-naïve	IDeg: 773 IGlar: 257	met (mandatory) ±SU/glin, ±α-GI, ±DPP-4I in any combination	3:1	Prior treatment: DPP-4I Yes/No
3672 (26)	IDeg 200 U/mL OD vs. IGlar OD	+met ±DPP-4I	Insulin-naïve	IDeg: 230 IGlar: 230	met (mandatory) ±SU/glin, ±DPP-4I, ±α-GI in any	1:1	No stratification

Trial (wks)	Trial description	Treatment Combination	Subject Population	No. of Subjects Randomised	Antidiabetes Treatment at Screening	Randomisation (IDeg: comparator)	Stratification
					combination)		
3586 (26)	IDeg 100 U/mL OD vs. IGlar OD	±met ±SU/glin ±α-GI	Insulin-naïve	IDeg: 289 IGlar: 146	monotherapy or combination of SU/glin and met ±α-GI or DPP-4I	2:1	Region: Japan/ Asia (not Japan)
3580 (26)	IDeg 100 U/mL OD vs. Sita OD	+1-2 OADs: met, SU/glin, pio	Insulin-naïve	IDeg: 229 Sita: 229	±met ±SU/glin ±pio, 1–2 OADs in any combination	1:1	Prior treatment: TZD Yes/No
3668 (26)	IDeg Flex 100 U/mL OD vs. IGlar OD and IDeg Flex 100 U/mL OD vs. IDeg 100 U/mL OD	±met ±SU/glin ±pio	Insulin-naïve + insulin treated	IDeg Flex: 229 IDeg: 228 IGlar 230	OAD(s) only *or* basal insulin only *or* basal insulin + OAD(s) OADs could be any combination of met, SU/glin, pio	1:1:1	Prior treatment: OADs only/ basal insulin only/basal insulin + OADs

met: metformin; pio: pioglitazone; DPP-4I: dipeptidyl peptidase-4 inhibitor; SU: sulphonylurea; α-GI: alpha-glucosidase inhibitor; TZD: thiazolidinedione; glin: glinide; sita: sitagliptin; CSII: continuous subcutaneous insulin infusion

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 treat-to-target trials in which IDeg was compared to an active comparator (Table 11 and Table 12). Trial duration was either 26 weeks or 52 weeks, to ensure that stable glycaemic control was maintained for a sufficient time period. Five (5) of the therapeutic confirmatory trials (3 in T1DM and 2 in T2DM) were extended by an additional trial period of 26 or 52 weeks primarily to investigate long-term safety. Trial 3770 (T1DM) and Trial 3668 (T2DM) included a third treatment arm in which IDeg was dosed in the morning and in the evening on alternating days (the Fixed Flexible dose schedule), with the purpose to investigate the impact of extreme day-to-day variation in the dosing intervals. In study 3672, basal therapy with IDeg 200 U/ml was compared to IGlar in patients with T2DM. 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 IDeg and comparator insulin products. Because both the IDeg and the comparator treatment were adjusted to achieve glycaemic targets, a non-inferiority design was applied for all but one study where sitagliptin was the comparator. Focus was thus also on other parameters, especially the rate of hypoglycaemia. The clinical program is considered adequate as well as the overall design of the studies.

In total, 1578 subjects with T1DM (IDeg 1104, comparator products 474) and 4076 subjects with T2DM (IDeg 2733, comparator products 1343) were randomised to IDeg OD treatment in the therapeutic confirmatory trials. To ensure that most races and ethnic groups were exposed in the trial programme, trial sites were selected in geographical regions where the relevant populations were significantly represented. Trial subjects were from Asia, Europe, North America, South Africa and South

America. Trial 3586 only included sites in Hong Kong, Japan, Malaysia, South Korea, Thailand and Taiwan.

Study Participants

Inclusion Criteria

The inclusion criteria regarding diabetes duration and current antidiabetic treatment were set to ensure that all subjects qualified for intensified treatment. In Trial 3580, the HbA_{1c} limits were 7.5–11.0% (both inclusive) and in Trial 3668, the limits for insulin-naïve subjects were 7.0–11.0% (both inclusive). In these two trials, all subjects continued current OAD treatment and no OADs were discontinued at baseline. In the remaining trials subjects discontinued certain OADs at randomisation and hence, an upper HbA_{1c} limit of 10% was applied.

The upper limits for body mass index (BMI) were set high in order to introduce a broad population, representative of the global T2DM population. The upper limits for T2DM were higher than for T1DM (40.0 vs. 35.0 kg/m^2). An exception was in Trial 3586, in which the upper limit was 35.0 kg/m^2 since Asian subjects develop T2DM at a lower BMI than non-Asian subjects. The upper BMI limit of 45 kg/m^2 for trials using IDeg 200 U/mL allowed the inclusion of more obese subjects requiring high doses of insulin.

Exclusion Criteria

The exclusion criteria were set to ensure a population of subjects who required additional diabetes therapy. Subjects with significant concomitant illnesses, including renal impairment, were excluded. Antidiabetes 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

IDeg is developed as IDeg 100 U/mL (600 nmol/mL) and IDeg 200 U/mL (1200 nmol/mL). IDeg 200 U/mL contains the double amount of units of insulin in the same volume compared to IDeg 100 U/mL. Using IDeg 200 U/mL, it will be possible to administer large doses in a single injection rather than in two successive injections. The prefilled Flextouch pen injector has been developed for use with IDeg products. Two types of Flextouch prefilled pen injectors are available: Flextouch 100 U/mL and Flextouch 200 U/mL.

Insulin-naïve subjects with T2DM were to start OD basal insulin treatment at a dose of 10 U/day. For insulin-treated subjects, a unit-to-unit transfer was recommended, but adjustments were possible according to the investigator's discretion. This is supported by data from the PD studies.

Basal insulin doses were titrated individually to achieve optimal glycaemic control. Titration algorithms were developed to ensure treatment uniformity between trial sites and across trials. The same titration algorithm was used for IDeg and for comparator products. In basal–bolus trials, the main focus was on the titration of basal insulin, whereas the bolus dose was monitored less vigorously.

The IDeg development programme was designed to investigate a wide range of dosing times. In totality, IDeg was administered once daily in the entire period from early morning (wake-up) to late evening (bedtime). In all trials, comparator insulin products were dosed according to their approved label, hence at any time of the day, but at the same time every day. The Fixed Flexible dose schedule (The IDeg Flex arms in Trials 3668 and 3770) was employed to investigate the impact of extreme day-to-day variation in the dosing intervals. IDeg was administered with alternating narrow (8–12 hours) and wide (36–40 hours) dosing intervals. In Trial 3580, the subjects could inject IDeg flexibly at any

time of the day, and at varying time from day to day within a dosing window of a minimum of 8 hours and a maximum of 40 hours between IDeg injections.

In Trial 3585, in case of inadequate glycaemic control after ≥8 weeks of treatment and optimisation of dosing, a second dose of insulin detemir (IDet) could be added if fulfilling three prespecified criteria. At the end of trial, 32.9% of subjects in the IDet group administered the basal insulin twice daily.

Concomitant Antidiabetic Treatment

Concomitant treatment with mealtime IAsp was used in all trials in T1DM. No other concomitant antidiabetic treatment was allowed for subjects with T1DM.

The therapeutic confirmatory trials investigated the efficacy and safety of IDeg in combination with various types of OADs, for details see Table 12. Measures were taken to ensure that the dose of present antidiabetic therapy had been titrated to a maximum effect.

Choice of Comparator

IGlar was chosen as comparator in most of the therapeutic confirmatory trials since IGlar is one of the most widely used basal insulin analogues world-wide, and has a well-known efficacy and safety profile. IGlar is characterised by an activity profile of around 24 hours and is approved for OD dosing. IDet was the comparator in one trial in T1DM (Trial 3585) since 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. Sitagliptin was the comparator in one trial in T2DM (Trial 3580) in order to investigate the efficacy and safety of adding IDeg instead of an additional OAD in subjects inadequately controlled on 1–2 OADs.

Objectives and endpoints

Primary Objective/Endpoints

The primary objective in all of the therapeutic confirmatory trials was to confirm the efficacy of IDeg in controlling glycaemia, as measured by change from baseline in glycosylated haemoglobin A1c (HbA_{1c}) in subjects with T1DM or T2DM by comparing the difference in change from baseline in HbA_{1c} at end of treatment (26 or 52 weeks) between IDeg and the active comparator.

Secondary Objectives/Endpoints

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

- Proportion of subjects reaching prespecified HbA_{1c} targets with or without hypoglycaemic episodes. Subjects achieving the predefined HbA_{1c} targets at end of trial are designated as 'responders' and were recorded at end of trial.
- Laboratory-measured fasting plasma glucose (FPG). Blood samples for change in FPG from baseline to end of trial (26 or 52 weeks) were measured in fasting state (before breakfast) and prior to insulin injection.
- 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. For trials of 52 weeks' duration, SMPG profiles were also measured after 40 and 52 weeks.
- SMPG profiles for dose adjustments.
- Within-subject variability in pre-breakfast SMPG.

- 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 Trial 3583 (T1DM) and Trials 3579 and 3668 (T2DM). 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 IDeg and comparator products during the course of the trials.

The safety objectives of importance for the efficacy evaluation were to compare IDeg 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. IDeg-specific, IGlar- or IDet-specific and insulin antibodies cross-reacting to human insulin were measured in T1DM (Trials 3583 and 3585), and in T2DM (Trials 3579, 3586, 3668 and 3672). In the 52-week trials, insulin antibodies were measured at baseline (Week 0) and after 12, 26, 40, 52 and 53 weeks of treatment. In the 26-week trials, insulin antibodies were measured at baseline (Week 0) and after 12, 26 and 27 weeks of treatment.

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

Randomisation/Blinding (masking)

In four of the therapeutic confirmatory trials, subjects were randomised in equal numbers (i.e., 1:1) to each of the treatment arms, while five trials randomised more subjects to the IDeg arm than the comparator arm in order to obtain an adequate total of subjects exposed to IDeg. Six (6) of the therapeutic confirmatory trials were stratified according to prior anti-diabetic treatment or according to geographical region (see Table 11 and Table 12).

Site monitors and investigators were not blinded. The visual appearance of IDeg differed from that of the comparator products, and the insulin cartridges and pen injectors for IDeg, IDet and IGlar were easy to distinguish from each other. Use of a double-dummy design was not possible as a comparator placebo product cannot be obtained. In addition, such design would require a large number of daily injections, particularly in basal–bolus trials and in trials with alternating morning and evening dosing, which could increase the risk of medication errors (omission or double-dosing). Thus, for practical and ethical reasons, an open-label design was chosen for all the therapeutic confirmatory and therapeutic exploratory trials, which is acceptable.

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 summary of the subject disposition in the T1DM and T2DM therapeutic confirmatory trials is given below.

Table 13 Subject Disposition – T1DM

Trial (wks)	IDeg N	(%)	Comparator N	(%)	Total N	(%)
Randomised	1104	(100.0)	474	(100.0)	1578	(100.0)
Exposed	1102	(99.8)	467	(98.5)	1569	(99.4)
Withdrawn at/after Randomisation	140	(12.7)	47	(9.9)	187	(11.9)
Adverse Event	24	(2.2)	4	(0.8)	28	(1.8)
Ineffective Therapy	5	(0.5)	3	(0.6)	8	(0.5)
Non-Compliance With Protocol	22	(2.0)	10	(2.1)	32	(2.0)
Withdrawal Criteria	33	(3.0)	8	(1.7)	41	(2.6)
Other	56	(5.1)	22	(4.6)	78	(4.9)
Completed	964	(87.3)	427	(90.1)	1391	(88.1)
Full Analysis Set	1103	(99.9)	474	(100.0)	1577	(99.9)

N: Number of subjects; %: Proportion of randomised subjects
Ineffective Therapy: Either documented by HbA1c or undocumented at investigator discretion; Comparator: IDet (3585) and IGlar (3583, 3770)

The completion rate the T1DM trials ranged from 86% to 92% of randomised subjects. The overall number of withdrawals within each trial was similar among treatment groups, except in Trial 3770 where the withdrawal rate was higher in the two IDeg treatment groups (16%) than in the IGlar group (7%). In the 52-week trial (Trial 3583), most withdrawals occurred from Week 13 and onwards, and in the two 26-week trials, withdrawals were evenly distributed throughout the trial period.

A large proportion of patients completed the trials; however, withdrawal due to adverse events and withdrawal criteria (hypoglycaemia being one criterion) was somewhat more common in the IDeg group with T1DM (Table 13).

Table 14 Subject Disposition – T2DM

	IDeg N	(%)	Comparator N	(%)	Total N	(%)
Randomised	2733	(100.0)	1343	(100.0)	4076	(100.0)
Exposed	2713	(99.3)	1339	(99.7)	4052	(99.4)
Withdrawn at/after Randomisation	469	(17.2)	221	(16.5)	690	(16.9)
Adverse Event	70	(2.6)	25	(1.9)	95	(2.3)
Ineffective Therapy	15	(0.5)	6	(0.4)	21	(0.5)
Non-Compliance With Protocol	90	(3.3)	49	(3.6)	139	(3.4)
Withdrawal Criteria	45	(1.6)	27	(2.0)	72	(1.8)
Other	249	(9.1)	114	(8.5)	363	(8.9)
Completed	2264	(82.8)	1122	(83.5)	3386	(83.1)
Full Analysis Set	2716	(99.4)	1332	(99.2)	4048	(99.3)

N: Number of subjects; %: Proportion of randomised subjects
Ineffective Therapy: Either documented by HbA_{1c} or undocumented at investigator discretion; Comparator: IGlar (3582, 3579, 3672, 3586, 3668) and Sita (3580)

In the T2DM trials, the completion rate ranged from 76% of randomised subjects in Trial 3580 to 91% in Trial 3586 thus the completion rate was somewhat lower in the T2DM trials than in T1DM trials (Table 13).

Conduct of the study

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.

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.

Baseline data

Baseline Diabetes Characteristics

For subjects with T1DM, the mean diabetes duration was similar with IDeg and comparator products. In T2DM, the mean diabetes duration was 1 year longer in the IDeg group than in the comparator group. Mean diabetes duration was generally longer in T1DM (17.3 years) than in T2DM (10.5 years).

Mean baseline HbA_{1c} was around 8% and slightly higher in the T2DM subjects (8.4%) than in the T1DM subjects (7.8%). There were no major differences in baseline HbA_{1c} between treatment groups in the individual trials. Mean baseline FPG was similar in T1DM and T2DM. There were no major differences between groups in baseline FPG in any of the trials.

In the T1DM trials, 24% of all subjects had diabetes complications at baseline, which were mainly ophthalmic complications (16%) and neurological complications (10%). In the T2DM trials, the proportion of subjects with diabetes complications ranged from 11% in Trial 3580 in early T2DM to 39% in Trial 3586. The most frequent diabetes complications were neurological and ophthalmic.

The patients included in the trials were representative of the target diabetic population.

Pretrial Antidiabetes Treatment

Within trials, mean basal, bolus and total insulin dose at screening were comparable between treatment groups. Almost all the subjects who entered the T1DM trials were treated with basal–bolus therapy at screening.

The subjects with T2DM entered the trials with a wider range of pretrial insulin regimens than subjects with T1DM.

No OAD treatment was allowed in the T1DM trials. All T2DM trials required that the subjects had been treated with unchanged OAD regimens and doses for at least three months before trial inclusion. In the OAD-insulin combination trials, 61% of subjects were treated with 2 OADs at screening. The treatment groups were well balanced with regards to the different OADs (Table 15).

Table 15 Pre-trial OAD Treatment – T2DM – IDeg OD – FAS

Trial (wks)	IDeg N	(%)	Comparator N	(%)	Total N	(%)
Total						
Alpha-glucosidase inhibitor	83	(3.1)	35	(2.6)	118	(2.9)
Acarbose	59	(2.2)	20	(1.5)	79	(2.0)
Miglitol	10	(0.4)	5	(0.4)	15	(0.4)
Voglibose	14	(0.5)	10	(0.8)	24	(0.6)
Amylin	7	(0.3)	2	(0.2)	9	(0.2)
Pramlintide[#]	7	(0.3)	2	(0.2)	9	(0.2)
Biguanide	2310	(85.1)	1182	(88.7)	3492	(86.3)
Metformin	2310	(85.1)	1182	(88.7)	3492	(86.3)
DPP-4 inhibitor	205	(7.5)	106	(8.0)	311	(7.7)
Saxagliptin			1	(0.1)	1	(0.0)
Sitagliptin	187	(6.9)	97	(7.3)	284	(7.0)
Vildagliptin	18	(0.7)	8	(0.6)	26	(0.6)
Glinide	68	(2.5)	27	(2.0)	95	(2.3)
Mitiglinide	5	(0.2)	1	(0.1)	6	(0.1)
Nateglinide	3	(0.1)	2	(0.2)	5	(0.1)
Repaglinide	60	(2.2)	24	(1.8)	84	(2.1)
Sulphonylurea	1448	(53.3)	761	(57.1)	2209	(54.6)
Glibenclamide	420	(15.5)	234	(17.6)	654	(16.2)
Gliclazide	321	(11.8)	180	(13.5)	501	(12.4)
Glimepiride	521	(19.2)	254	(19.1)	775	(19.1)
Glipizide	177	(6.5)	91	(6.8)	268	(6.6)
Gliquidone	2	(0.1)			2	(0.0)
Glyburide	9	(0.3)	3	(0.2)	12	(0.3)
Tolazamide	1	(0.0)			1	(0.0)
Thiazolidinedione	94	(3.5)	44	(3.3)	138	(3.4)
Pioglitazone	93	(3.4)	43	(3.2)	136	(3.4)
Rosiglitazone[##]	1	(0.0)	1	(0.1)	2	(0.0)

Comparator: IGlar (3582, 3579, 3672, 3586, 3668) and Sita (3580); A subject can be on more than one OAD; #: pramlintide is not an OAD, but is included for completeness; ## 2 subjects were withdrawn due to treatment with rosiglitazone (protocol deviation)

In all T2DM trials except Trial 3586, the median metformin dose at screening was 2000 mg/day, and most subjects received doses corresponding to the maximum effective dose of 850–1000 mg twice daily. In Trial 3586, the median metformin dose at screening was 1500 mg/day. This is in line with a lower maintenance dose in some Asian. In those T2DM trials that allowed pretrial use of DPP-4 inhibitor, the median dose at screening of sitagliptin/vildagliptin was 100 mg/day. The mean and median pretrial dose of glimepiride was around 4–6 mg/day. Thus adequate doses of the different OADs were used.

It was further noted that patients could have been treated with other OADs which were not allowed in a respective trial, these were insulin secretagogues and α-glucosidase inhibitors in trials 3579 and 3668, and DPP4-inhibitors in trial 3586. These OADs were discontinued at randomization but as the trials did not have a run-in phase, an adequate baseline evaluation was not ensured. The applicant elaborated sufficiently on the fact that the lacking run-in phase of the trials did not have implications on the trials.

Baseline Concomitant Illness

The majority of subjects with T1DM (87.6%) had normal renal function at baseline (estimated creatinine clearance >80). A small proportion (10.6%) had mild renal impairment (estimated creatinine clearance 50–80, both included). In each trial, the number of subjects with renal impairment

was equal between treatment groups, except in Trial 3770, in which there were 5 subjects (3.0%) with mild renal impairment in the IDeg Flex group and 14 (8.5%) in the IGlar group. Very few subjects (0.8%) had hepatic impairment at baseline. A total of 86.4% of subjects with T1DM reported one or more concomitant illnesses at baseline for both IDeg and comparator. In addition to diabetes complications, the most commonly reported concomitant illnesses at baseline (≥10% of subjects) were hypertension (27.5%), hyperlipidaemia (18.1%), hypothyroidism (12.2%) and seasonal allergy (10.8%). The frequencies of these illnesses were similar between IDeg and comparator.

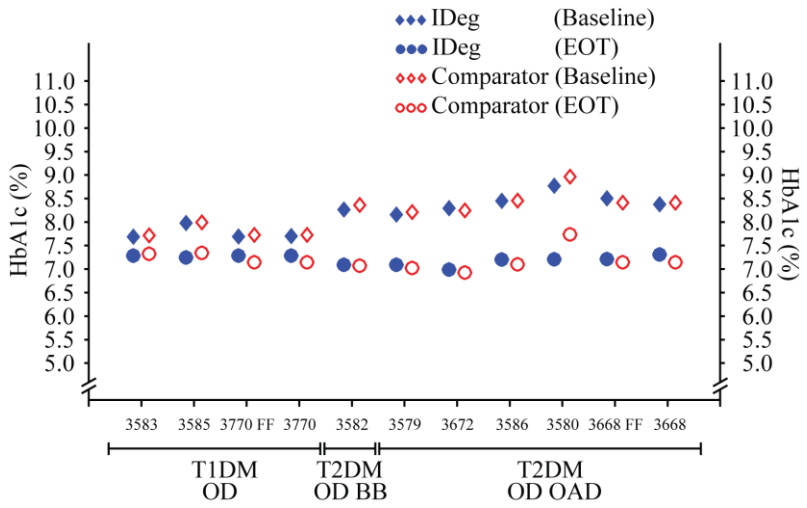
In the T2DM Trial 3582, 88.2% of subjects had normal renal function at baseline, while 11.5% had mild renal impairment. In the OAD-insulin trials, a total of 82.5% of subjects had normal renal function and 15.9% had mild renal impairment at baseline. In Trials 3582, 3586 and 3580, there was a higher proportion of subjects with mild renal impairment in the IDeg groups than in the comparator groups. A total of 0.3–0.4% of subjects with T2DM had hepatic impairment at baseline. Overall, 96.5% of subjects with T2DM reported one or more concomitant illnesses at baseline for both IDeg and comparator. In addition to diabetic complications, the most commonly reported concomitant illnesses at baseline (≥10%) were hypertension (69.0%), hyperlipidaemia (28.6%), dyslipidaemia (20.7%), hypercholesterolemia (13.7%), obesity (10.8%), osteoarthritis (10.5%) and gastro-oesophageal reflux disease (10.5%). The frequencies of these illnesses were similar between IDeg and comparator, and are characteristic for subjects with T2DM requiring intensified treatment.

Outcomes and estimation

Primary Efficacy Endpoint: Change in HbA1c

The change in HbA1c for all trials is summarised in Figure 7. Efficacy of IDeg in terms of HbA_{1c} reduction was confirmed across different age groups, BMI groups and racial groups, different degrees of hepatic and renal function, and in combination with different OADs.

Figure 7 HbA1c (%) at Baseline and End of Trial – Plot of Mean Values – FAS

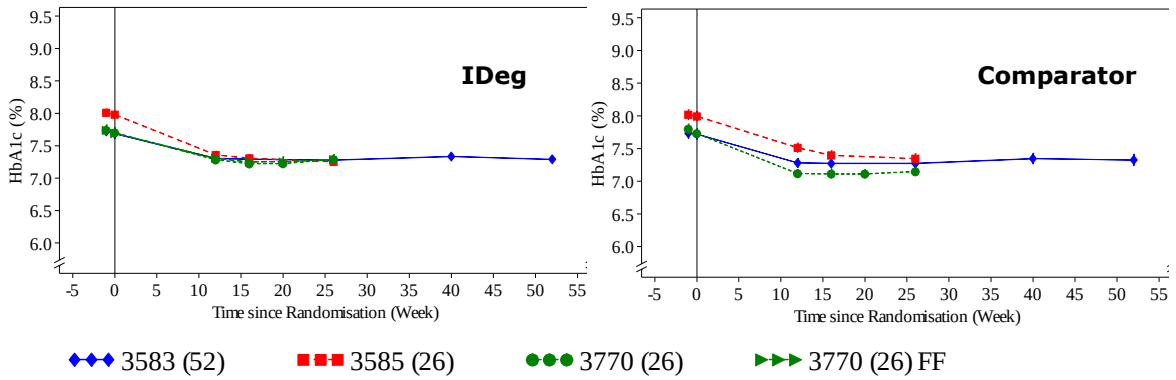


FF: Fixed Flexible, subjects treated with a rotating dosing schedule; Comparator: IGlar, except IDet (3585) and Sita (3580); LSMeans with 95%CI; missing values are imputed by LOCF

In subjects with T1DM, treatment with IDeg in a basal–bolus regimen improved glycaemic control as assessed by reduction in HbA_{1c} (non-inferior to comparator). The reduction in mean HbA_{1c} was evident

after the first 12 weeks of treatment, and the lower HbA_{1c} level was maintained for at least 52 weeks based on the results from Trial 3583 (Figure 8).

Figure 8 (%) – Mean (±SEM) by Treatment Week – T1DM – FAS



FF: Fixed Flexible, subjects treated with a rotating dose schedule; LOCF imputed data; Comparator: IDet (3585) and IGlar (3583, 3770)

The change in observed HbA_{1c} from baseline to end of trial ranged from approximately 0.4 to 0.7% points for both IDeg and comparator, thus clinically relevant reductions in HbA1c were observed taking the relatively low baseline HbA1c into account. Mean HbA_{1c} of 7.2–7.4% at end of trial was obtained with both IDeg and comparator products in all trials. Similar reductions in HbA_{1c} were obtained whether IDeg was dosed in the evening every day or flexibly with alternating, narrow and wide time intervals between dose administrations, simulating the extremes of what might happen in terms of insulin administration in individuals with diabetes mellitus (IDeg Flex).
Non-inferiority of IDeg to IGlar was confirmed in Trial 3583, non-inferiority of IDeg Flex to IGlar was confirmed in Trial 3770, and non-inferiority of IDeg to IDet was confirmed in Trial 3585 as the upper limits of the 95% CIs were ≤0.4% for all the estimated treatment differences of change in HbA_{1c}.

The primary analysis was repeated for the PP analysis set supporting the conclusions of the primary analysis in all three trials. In addition, the analysis was repeated for subjects who completed the trials, and the results supported the conclusions from the primary analysis. Results from a repeated measurement analysis, which was carried out to assess the sensitivity of the LOCF method, also confirmed the conclusions of the primary analysis.

Table 16 HbA1c (%) Change from Baseline at End of Trial – T1DM – Statistical Analysis – FAS

	IDeg		Comparator		IDeg - Comparator	
Trial (wks)	N	LSMEAN (SE)	N	LSMEAN (SE)	Contrast	95% CI
3583 (52)	472	-0.36 (0.05)	157	-0.34 (0.07)	-0.01	[-0.14; 0.11]
3585 (26)	302	-0.71 (0.06)	153	-0.61 (0.07)	-0.09	[-0.23; 0.05]
3770 (26) IDeg FF - IGlar	164	-0.40 (0.05)	164	-0.57 (0.05)	0.17	[0.04; 0.30]*
3770 (26) IDeg FF - IDeg			165	-0.41 (0.05)	0.01	[-0.13; 0.14]

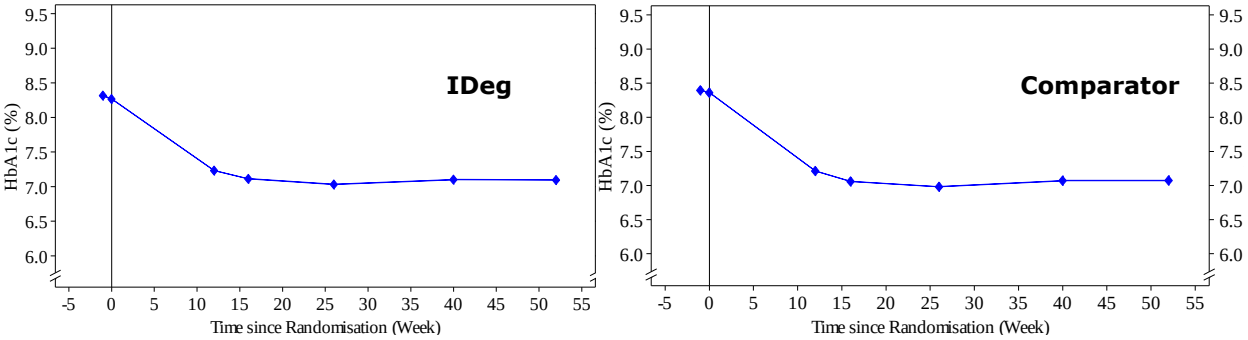
N: Number of subjects contributing to analysis; FF: Fixed Flexible, subjects treated with a rotating dosing schedule; LSmean: least-square mean; SE: standard error

*Difference statistically significantly different from 0; Endpoint was analysed by an ANOVA model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors and age and baseline HbA_{1c} as covariates; Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); The primary treatment contrast of interest in 3770 was IDeg FF – IGlar, the comparison IDeg OD vs. IGlar was not specified in the

protocol; End of Trial: a subject's last trial visit excluding the follow-up visit; Comparator: IDet (3585) and IGlar (3583, 3770); Missing values are imputed by LOCF;

In T2DM subjects (Trial 3582; basal–bolus treatment ±OADs in subjects who already were treated with insulin at baseline), mean HbA_{1c} improved by 1.2% points with IDeg and by 1.3% points with IGlar. After 52 weeks, the mean observed HbA_{1c} was close to 7.1% in both treatment groups. IDeg was non-inferior to IGlar (see Table 17 and Figure 9).

Figure 9 HbA1c (%) – Mean (±SEM) by Treatment Week – T2DM – Basal–bolus Therapy – Trial 3582 – FAS

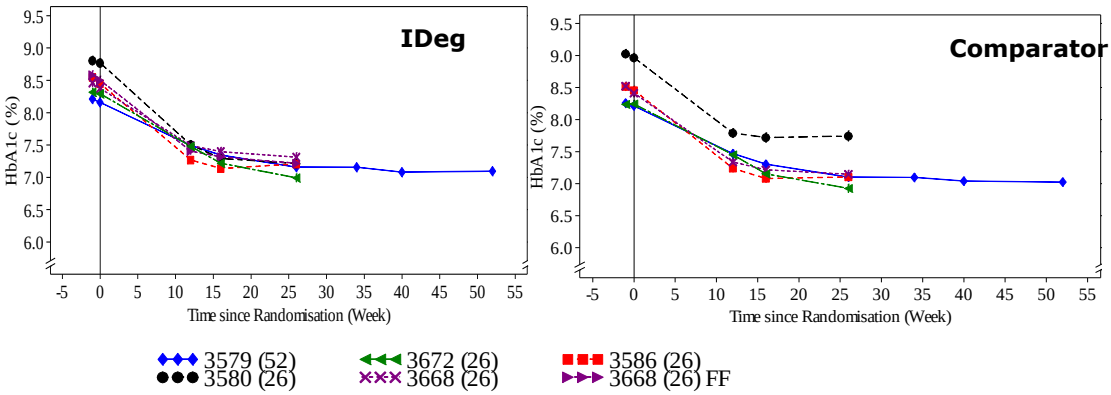


Comparator: IGlar; missing values are imputed by LOCF

♦♦♦ 3582 (52)

Used alone, or in combination with OADs, treatment with IDeg resulted in clinically relevant reductions in mean HbA_{1c} ranging from approximately 1.1 to 1.6% points compared to 1.2–1.4% points with comparator products. The mean observed HbA_{1c} at end of trial was between 7.0 and 7.3% with IDeg and between 7.0 and 7.2% with IGlar (7.7% with sitagliptin); see Figure 10.

Figure 10 HbA1c (%) – Mean (±SEM) by Treatment Week – T2DM – OAD-insulin Combination – FAS



FF = Fixed Flexible, subjects treated with a rotating dose schedule. Missing data are imputed by LOCF; Comparator = IGlar (3579, 3672, 3586, 3668) and Sita (3580);

The largest reduction in HbA_{1c} happened during the first 12 weeks of treatment, which was the period during which the basal insulin dose was adjusted the most (see Figure 10). Glycaemic control improved to a similar extent in the IDeg OD treatment arm with evening injections and in the IDeg Flex treatment arm with alternating wide and narrow dosing intervals (Trial 3668). Similar HbA_{1c} was achieved with IDeg dosed at any time of the day (Trial 3580).

Non-inferiority to IGlar was confirmed in all trials as the upper limits of the 95% CIs for the estimated treatment difference (IDeg – comparator products) were ≤ 0.4% for all the estimated treatment differences of change in HbA_{1c}. Superiority to sitagliptin was confirmed in Trial 3580 as the upper limit of the 95% CI was ≤0% (Table 17). Thus the primary endpoint was met in all trials.

The primary analysis was repeated both for the PP analysis set and for the completer analysis set, and the results of these analyses supported the conclusions of the primary analysis in all the trials. Results from repeated measurements analyses, which were carried out to assess the sensitivity of the LOCF method, also confirmed the results of the primary analyses.

Table 17 HbA1c (%) Change from Baseline at End of Trial – T2DM – Statistical Analysis – FAS

	IDeg		Comparator		IDeg - Comparator	
Trial (wks)	N	LSMEAN (SE)	N	LSMEAN (SE)	Contrast	95% CI
Basal-bolus therapy ± OADs						
3582 (52)	744	-1.10 (0.06)	248	-1.18 (0.08)	0.08	[-0.05; 0.21]
OAD-insulin combination therapy						
3579 (52)	773	-1.06 (0.04)	257	-1.15 (0.06)	0.09	[-0.04; 0.22]
3672 (26)	228	-1.18 (0.09)	229	-1.22 (0.08)	0.04	[-0.11; 0.19]
3586 (26)	289	-1.42 (0.06)	146	-1.52 (0.07)	0.11	[-0.03; 0.24]
3580 (26)	225	-1.52 (0.10)	222	-1.09 (0.10)	-0.43	[-0.61; -0.24]*
3668 (26) IDeg FF - IGlar	229	-1.17 (0.08)	230	-1.21 (0.08)	0.04	[-0.12; 0.20]
3668 (26) IDeg FF - IDeg			228	-1.03 (0.08)	-0.13	[-0.29; 0.03]

N: Number of subjects contributing to analysis; FF: Fixed Flexible, subjects treated with a rotating dosing schedule; LSmean: least-square mean; SE: standard error

*Difference statistically significantly different from 0; Endpoint was analysed by an ANOVA model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors and age and baseline HbA_{1c} as covariates; Non-

inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); The primary treatment contrast of interest in 3668 was IDeg FF – IGlar, the comparison IDeg OD vs. IGlar was not specified in the protocol; End of Trial: a subject's last trial visit excluding the follow-up visit; Comparator: IGlar (3582, 3579, 3672, 3586, 3668) and Sita (3580); Missing values are imputed by LOCF;

Secondary Efficacy Endpoints

Subjects with T1DM Achieving HbA1c Targets

Similar proportions of subjects achieved the target of HbA_{1c} <7.0% at end of trial in the three therapeutic confirmatory T1DM trials, ranging from 37 to 43% of subjects (Table 18). The proportion of subjects who achieved the target was similar when IDeg was injected with alternating wide and narrow dosing intervals (IDeg Flex) or at the same time every day (IDeg OD). There were no statistically significant differences between IDeg and the comparator (IGlar or IDet) in any of the trials, as assessed by the estimated odds of achieving the HbA_{1c} target of <7.0% at end of trial, however, responder rates were numerically lower with IDeg in two out of three trials.

Table 18 HbA1c<7.0% at End of Trial – T1DM – FAS

	IDeg			Comparator		
Trial (wks)	N	n	(%)	N	n	(%)
3583 (52)	472	188	(39.8)	157	67	(42.7)
3585 (26)	302	124	(41.1)	153	57	(37.3)
3770 (26) FF	164	61	(37.2)	164	67	(40.9)
3770 (26)	165	61	(37.0)			

N: Number of subjects; n: Number of subjects with HbA_{1c}<7.0%; FF: Fixed Flexible, subjects treated with a rotating dosing schedule

End of Trial: a subject's last trial visit excluding the follow-up visit; Comparator: IDet (3585) and IGlar (3583, 3770); Missing HbA_{1c} values are imputed by LOCF;

Between 87 and 90% of subjects in the T1DM trials did not report any episodes of severe hypoglycaemia during treatment. Between 37 and 42% of the subjects achieved HbA_{1c} <7.0% at end of trial without any episodes of severe hypoglycaemia during the last 12 weeks of treatment or within 7 days after last randomised treatment. The proportion of responders was similar for IDeg and comparator-treated subjects (albeit numerically lower for IDeg except in trial 3585), and the proportions were also similar across trials. There were no statistically significant differences between IDeg and comparator in any of the trials.

About 90% of subjects with T1DM experienced at least one episode of confirmed hypoglycaemia during the T1DM trials. Thus, the proportions of subjects who achieved HbA_{1c} <7.0% without confirmed hypoglycaemia during the last 12 weeks were low. There were no statistically significant differences between IDeg and comparator.

Subjects with T2DM Achieving HbA1c Targets

With IDeg OD in a basal–bolus regimen ±OADs, approximately 50% of subjects with T2DM achieved the target of HbA_{1c} <7.0% after 52 weeks of treatment (Table 19). The proportion of subjects who attained the stricter target of ≤6.5% was 31% for IDeg and 33% for IGlar. There were no statistically significant differences in the estimated odds of achieving the two targets.

With IDeg OD treatment in combination with OAD(s), between 39 and 52% of subjects achieved the target of HbA_{1c} <7.0% (Table 19). With comparator, the proportion ranged from 28 to 56%, lowest with sitagliptin in Trial 3580. In Trial 3580, the estimated odds of achieving the target of HbA_{1c} <7.0%

were statistically significantly higher with IDeg (estimated odds ratio 1.60 [1.04; 2.47]$_{95\%CI}$). There were no statistically significant differences between the treatment groups in any of the other trials. The proportions of subjects who attained the target of HbA_{1c} ≤6.5% at end of trial ranged from 18 to 38% with IDeg and from 15 to 43% with comparator products. There was no statistically significant difference between the treatment groups in any of the trials in which IDeg was compared to another basal insulin.

Thus in all trials, except when compared to sitagliptin, responder rates were numerically lower for IDeg versus the comparator.

Table 19 HbA1c<7.0% at End of Trial – T2DM – FAS

	IDeg			Comparator		
Trial (wks)	N	n	(%)	N	n	(%)
Basal-bolus therapy ±OADs						
3582 (52)	744	368	(49.5)	248	124	(50.0)
OAD-insulin combination therapy						
3579 (52)	773	400	(51.7)	257	139	(54.1)
3672 (26)	228	119	(52.2)	229	128	(55.9)
3586 (26)	289	118	(40.8)	146	71	(48.6)
3580 (26)	225	92	(40.9)	222	62	(27.9)
3668 (26) FF	229	89	(38.9)	230	101	(43.9)
3668 (26)	228	93	(40.8)			

N: Number of subjects; n: Number of subjects with HbA_{1c}<7.0%; FF: Fixed Flexible, subjects treated with a rotating dosing schedule

End of Trial: a subject's last trial visit excluding the follow-up visit; Comparator: IGlar (3582, 3579, 3672, 3586, 3668) and Sita (3580); Missing HbA_{1c} values are imputed by LOCF;

After 52 weeks of treatment with a basal–bolus regimen ±OADs, approximately 51% of subjects in both groups achieved the HbA_{1c} target <7.0% without severe hypoglycaemia, and 32–34% attained the target of ≤6.5% without severe hypoglycaemia with no statistically significant treatment differences between IDeg and IGlar. HbA_{1c} <7.0% without confirmed hypoglycaemia was achieved by 23–24% of subjects in both groups, and HbA_{1c} ≤6.5% without confirmed hypoglycaemia was achieved by 14–15% with no statistically significant treatment differences between groups. Note that the requirements for ≥12 weeks' exposure for this endpoint may result in a lower N and hence a higher responder rate compared to the endpoint 'subjects achieving HbA_{1c} <7.0%'.

In the OAD-insulin combination trials, the number of episodes of severe hypoglycaemia was very low. Therefore the proportions of subjects who achieved HbA_{1c} <7.0% without severe hypoglycaemia at end of trial approximated the percentage of subjects who achieved the target level of HbA_{1c} (range 41–56% with IDeg and 32–59% with comparator products). There were no statistically significant treatment differences between the two groups in any of the trials.

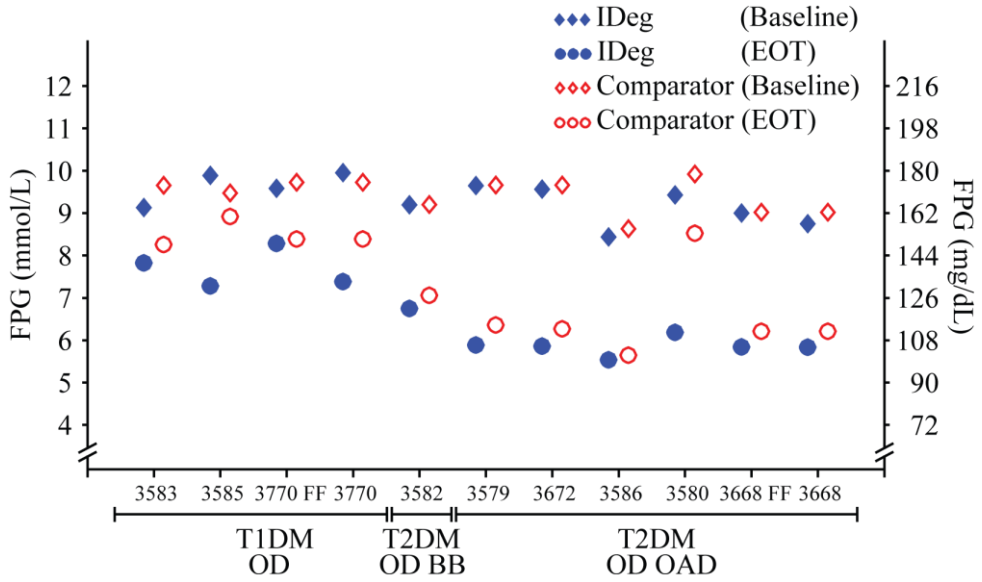
For subjects treated with basal insulin alone or in combination with OADs, the proportion of subjects achieving HbA_{1c} <7.0% without confirmed hypoglycaemia ranged from 25–45% with IDeg and from 23–46% with comparator products. In these trials a slightly different pattern was observed with responder rates being higher for IDeg in three out of six trials. There were no statistically significant differences between IDeg and comparator products. The proportions of subjects who attained HbA_{1c} ≤6.5% without confirmed hypoglycaemia ranged from 12–32% with IDeg and from 12–35% with comparator products, with no statistically significant treatment differences between IDeg and comparator for any of the trials.

The highest proportions of subjects achieving HbA_{1c} <7.0% without confirmed hypoglycaemia were in Trials 3579 and 3672, where SUs were not permitted, and lowest in Trial 3582, which applied the most intensive treatment regimen in all of the T2DM trials.

FPG (Central Laboratory)

FPG decreased with both IDeg and comparator in all trials, and the reduction was generally larger with IDeg, both in T1DM and T2DM. The observed FPG was lower with IDeg than with comparator products at end of trial (Figure 11). The lower FPG was not accompanied by a lower HbA_{1c}.

Figure 11 FPG at End of Trial – Plot of Estimated Values – FAS

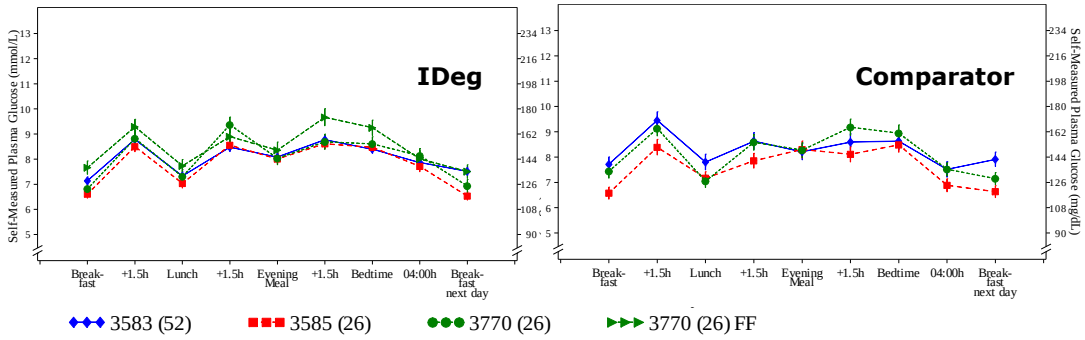


FF: Fixed Flexible, subjects treated with a rotating dosing schedule; Comparator: IGlar, except IDet (3585) and Sita (3580); LSMeans with 95%CI; missing values are imputed by LOCF

9-Point SMPG Profiles

In T1DM subjects, treatment with IDeg in a basal–bolus regimen resulted in similar 9-point SMPG profiles at end-of-trial in all trials, except in Trial 3770 where the 9-point profile for the IDeg Flex arm was above that of the IDeg (evening dosing) arm particularly after the evening meal (Figure 12).

Figure 12 9-point SMPG Profile – Mean (±SEM) – End of Trial – T1DM – FAS



FF: fixed flexible, subjects treated with a rotating dose schedule
Comparator: IDeg (3583, 3770) IDet (3585); missing values are imputed by LOCF

In Trial 3585, the estimated mean prandial increment at end of trial was greater with IDeg than with IDet for lunch, evening meal and all meals (statistically significant), reflecting that the mean SMPG

value with IDet was at a constant high level during this time interval. There were no other statistically significant treatment differences in mean prandial increment or nocturnal change in SMPG from bedtime to breakfast.

In T2DM subjects, treatment with IDeg in a basal–bolus regimen ±OADs for 52 weeks resulted in a similar pattern of SMPG compared to IGlar. There was no statistically significant treatment difference in mean prandial increment or nocturnal change in SMPG from bedtime to breakfast.

Treatment with IDeg OD ±OADs resulted in similar end-of-trial PG levels in the 9-point SMPG curves between trials. Apart from trial 3580 where sitagliptin was the comparator, no statistically significant treatment difference in mean prandial increment or nocturnal change in SMPG from bedtime to breakfast was observed.

Pre-breakfast SMPG

In T1DM subjects, treatment with IDeg OD in a basal–bolus regimen for 26 or 52 weeks reduced the pre-breakfast SMPG level in all three T1DM trials, in line with the findings for FPG. At end of trial, the pre-breakfast SMPG ranged from 6.6 to 7.6 mmol/L (119.1–136.1 mg/dL) with IDeg and from 6.7 to 7.8 mmol/L (120.0–141.3 mg/dL) with comparator. In Trial 3770, the estimated mean pre-breakfast SMPG was statistically significantly higher with IDeg Flex than with IDeg OD.

In trial 3583, the median time to achieve the titration target (SMPG <5.0 mmol/L or <90 mg/dL) for the first time was shorter with IDeg (5.0 weeks) than with IGlar (10.0 weeks). The treatment difference was statistically significant. In Trials 3585 and 3770, the median time ranged from 4.0 to 7.0 weeks before the titration target was met for the first time with no statistically significant treatment differences between IDeg and comparator products. In the IDeg Flex arm of Trial 3770, subjects took a longer time (median 7.0 weeks) to reach the target than in the IDeg OD arm (median 4.0 weeks).

A total of 11 to 24% of subjects treated with IDeg reached the titration target at the end-of-trial visit compared to 13 to 24% with comparator products. Overall, the proportion of subjects who achieved the target was similar between treatment arms within each trial, except from the proportion of responders in Trial 3770, which was lower in the IDeg Flex (11%) compared to IDeg (24%) and IGlar (18%).

With IDeg treatment, the estimated day-to-day variation within subjects in prebreakfast SMPG (CV%) ranged from 36 to 42%, and with IGlar, the range was 35–42%. The estimated values for within-subject variability were close to the values for comparator products in all T1DM trials. There were no statistically significant treatment differences in CV% in any of the T1DM trials.

In T2DM subjects (Trial 3582), the observed reduction in prebreakfast SMPG was similar with IDeg and IGlar. Prebreakfast SMPG was statistically significantly lower in the IGlar group than in the IDeg group after 52 weeks of treatment. In the OAD-insulin trials, the observed reduction in prebreakfast SMPG from baseline to end of trial ranged from 3.0 to 4.1 mmol/L (53–74 mg/dL) with IDeg and from 1.9 to 4.0 mmol/L (34–71 mg/dL) with comparator. Prebreakfast SMPG at end of trial was statistically significantly lower with IDeg than with sitagliptin in Trial 3580.

The median time to achieve the titration target (SMPG <5.0 mmol/L or < 90 mg/dL) for the first time ranged from 5.0 to 12.0 weeks with IDeg and from 7.0 to 14.0 weeks with IGlar. There were no statistically significant treatment differences for IDeg versus IGlar. The titration target was not relevant for sitagliptin in Trial 3580.

In the T2DM basal–bolus Trial 3582, 19% and 21% of subjects had achieved the titration target at the end-of-trial visit with IDeg and IGlar, respectively. In the OAD-insulin combination trials, from 28% to

45% of subjects treated with IDeg and from 33% to 46% of subjects treated with IGlar achieved the titration target. In most of the OAD-insulin combination trials, the proportion of subjects achieving the titration target at end of trial was slightly higher with IDeg than with comparator. In Trial 3580, 1.8% of subjects treated with sitagliptin achieved prebreakfast SMPG <5.0 mmol/L (< 90 mg/dL) at Week 26.

In the T2DM trials, the estimated day-to-day variation within-subject in prebreakfast SMPG (CV%) ranged from 16% (Trial 3586) to 21% (Trial 3582) with IDeg. With comparator, the estimated CV% ranged from 12% (Trial 3580) to 23% (Trial 3582). Statistically significantly lower CV% was found with IDeg in Trial 3586. Statistically significantly lower CV% was found with sitagliptin in Trial 3580. Also, in Trial 3668 the CV% was statistically significantly lower with IGlar than with IDeg Flex. Thus, no consistent differences in the day-to-day variability were observed between IDeg and the comparators.

Interstitial Glucose Profiles by Continuous Glucose Monitoring (CGM)

In Trial 3583 (T1DM), CGM was employed in a total of 158 of the 629 randomised subjects (IDeg 119 and IGlar 39). There was no statistically significant difference between IDeg and IGlar in the means of the overall and nocturnal IG profiles. Estimated mean fluctuation in the overall IG profile was similar with IDeg and IGlar at end of trial, whereas the estimated mean fluctuation of the nocturnal profile was 11% lower with IDeg than with IGlar (not statistically significant). There were no statistically significant differences between IDeg and IGlar at end of trial in duration of low (<3.5 mmol/L [63 mg/dL]) or high (>12.0 mmol/L [216 mg/dL]) nocturnal IG episodes.

In Trial 3579, CGM was employed in 193 of the 1030 randomised subjects (IDeg 145, IGlar 48, corresponding to the 3:1 randomisation). In Trial 3668, CGM was measured in 239 of the 685 randomised subjects (IDeg Flex 79, IDeg OD 79, IGlar 81). The mean of the overall and nocturnal IG profiles improved in all treatment groups with no statistically significant treatment differences (IDeg vs. IGlar) at end of trial. In Trial 3668, the mean IG profile was statistically significantly lower with IDeg Flex than with IDeg OD. Estimated fluctuation in the overall IG profile was similar with IDeg and IGlar at end of trial, while the estimated fluctuation of the nocturnal profile was 13% lower with IDeg than with IGlar in Trial 3579 (not statistically significant). In Trial 3668, the estimated fluctuation was similar for IDeg Flex and IGlar. There were no statistically significant treatment differences between IDeg and IGlar in the duration of low (<3.5 mmol/L [63 mg/dL]) or high (>12.0 mmol/L [216 mg/dL]) nocturnal IG episodes at end of trial.

Health Economics and Patient-reported Outcome

Treatment satisfaction and health-related quality of life was assessed by one generic questionnaire (SF-36v2) and three disease-specific questionnaires developed for Novo Nordisk A/S (DiabMedSat, DPM, TRIM-D). Results from SF-36v2 showed that changes from baseline to end of trial were marginal with both IDeg and comparator products.

Safety Endpoints as Part of Efficacy Evaluation

Overview of all hypoglycaemic episodes by classification in T1DM

In Table 20, an overview of all hypoglycaemic episodes in T1DM patients across the IDeg clinical programme are summarized.

Table 20 Hypoglycaemic Episodes by Classification – T1DM – SAS

Trial (wks)		IDeg N	IDeg (%)	IDeg E	IDeg R	Comparator N	Comparator (%)	Comparator E	Comparator R
3583	Number of subjects	472				154			
3585	Number of subjects	301				152			
3770 FF	Number of subjects	164				161			
3770	Number of subjects	165							
3583	Severe	58	(12.3)	90	20.8	16	(10.4)	23	15.9
3585	Severe	32	(10.6)	45	30.9	16	(10.5)	28	38.8
3770 FF	Severe	17	(10.4)	25	34.4	16	(9.9)	37	47.1
3770	Severe	21	(12.7)	28	36.7				
3583	Confirmed	451	(95.6)	18389	4253.6	147	(95.5)	5796	4017.7
3585	Confirmed	280	(93.0)	6673	4583.1	139	(91.4)	3295	4568.9
3770 FF	Confirmed	154	(93.9)	5988	8237.7	156	(96.9)	6263	7973.4
3770	Confirmed	164	(99.4)	6724	8825.1				
3583	Nocturnal severe	18	(3.8)	23	5.3	3	(1.9)	3	2.1
3585	Nocturnal severe	12	(4.0)	13	8.9	5	(3.3)	6	8.3
3770 FF	Nocturnal severe	5	(3.0)	5	6.6	5	(3.1)	13	16.6
3770	Nocturnal severe	5	(3.0)	5	6.9				
3583	Nocturnal confirmed	341	(72.2)	1905	440.7	114	(74.0)	845	585.7
3585	Nocturnal confirmed	176	(58.5)	603	414.1	89	(58.6)	428	593.5
3770 FF	Nocturnal confirmed	111	(67.7)	453	623.2	117	(72.7)	782	995.6
3770	Nocturnal confirmed	121	(73.3)	732	960.7				

Treatment Emergent Hypoglycaemic Episodes in T1DM

Between 10 and 13% of subjects with T1DM reported one or more episodes of severe hypoglycaemia. Observed rates of severe episodes ranged from approximately 21 to 37 episodes per 100 PYE with IDeg and from approximately 16 to 47 episodes per 100 PYE with comparator. Nocturnal severe episodes were reported by approximately 3–4% of subjects treated with IDeg (observed rate 5–9 episodes per 100 PYE) and by 2–3% of subjects treated with comparator products (observed rate 2–17 episodes per 100 PYE). There were no statistically significant treatment differences IDeg vs. comparator in the estimated rates of severe or nocturnal severe hypoglycaemia. The absolute number of episodes of severe hypoglycaemia was low, which adversely affected the ability to demonstrate differences between treatment regimens.

A total of 3 subjects (all IDeg) withdrew from the trials at least partly due to hypoglycaemia where the withdrawal reason was reported as 'adverse event'. A total of 12 subjects treated with IDeg and 3 subjects treated with comparator products withdrew due to the withdrawal criterion 'Hypoglycaemia Causing a Safety Problem'. Also, 7 subjects (all IDeg) withdrew from the trials due to the withdrawal reason 'Other' including a comment mentioning hypoglycaemia. Of these 25 withdrawals, 4 occurred during the first month (30 days) of treatment (all IDeg), thus the transfer to IDeg from previous treatment was not the primary cause of withdrawal due to hypoglycaemia. Kaplan Meier curves provided show that withdrawals were evenly distributed over time and there is no indication that they occurred more frequently in the transition period. It is thus most likely that an increased awareness of the investigational drug in the open-label trials as well as the fact that a large part of subjects from the comparator groups were randomised to their pre-trial insulin therapy were responsible for the differences observed.

Between 91% and 99% of subjects with T1DM experienced at least one episode of confirmed hypoglycaemia. Thus, clinically apparent hypoglycaemia is inherent for most individuals with T1DM on basal-bolus insulin therapy. The high percentage reflects the underlying disease state and, as illustrated by the temporal pattern of hypoglycaemia over the day, the effect of the bolus insulin. The distribution of hypoglycaemic episodes over the 24-hour period show that the vast majority (up to 90%) of confirmed hypoglycaemic episodes occur in the daytime (from 06:00 to 00:00). The largest

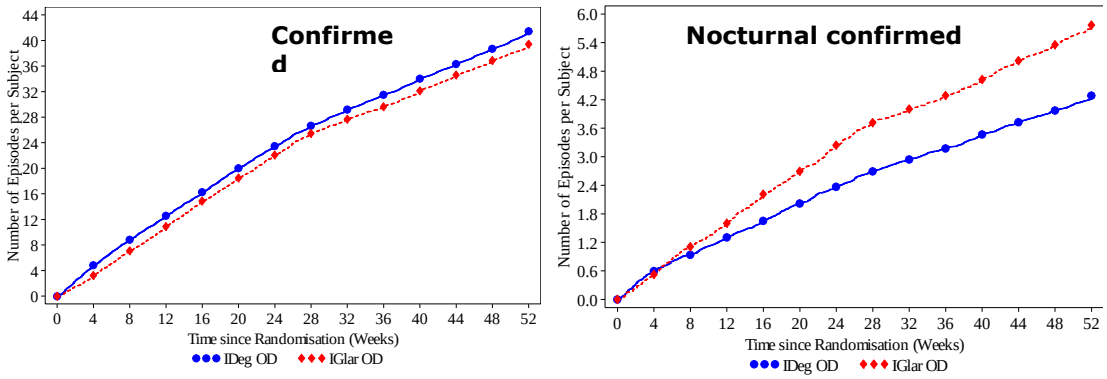
proportion of confirmed hypoglycaemic episodes occurred during the daytime, especially around the mealtimes.

Numerically higher rates of confirmed hypoglycaemia were observed with IDeg than with comparator products. The estimated rate ratio (IDeg/comparator) for confirmed hypoglycaemia ranged from 0.98 to 1.07 with no statistically significant treatment differences between IDeg and comparator. There was no statistically significant difference in terms of rates of confirmed hypoglycaemia between IDeg dosed at alternating narrow and wide time intervals (IDeg Flex) and IDeg dosed continuously in the evening (Trial 3770). In Trial 3770, subjects were to perform 4-point SMPG profiles every day, while in Trials 3583 and 3585, subjects were only required to measure three 4-point SMPG profiles per week. This difference could explain the higher rates of hypoglycaemia reported in Trial 3770 compared to Trials 3583 and 3585. Furthermore, the similar rates of severe hypoglycaemia with IDeg and IGlar in Trial 3770 indicate that the higher rates are due to increased measuring frequency as opposed to increased spontaneous reporting of hypoglycaemia.

Between 59 and 74% of subjects with T1DM reported nocturnal confirmed hypoglycaemia. The observed rates of nocturnal confirmed hypoglycaemia were consistently lower with IDeg than with comparator products. Overall, IDeg was associated with a 25–40% lower risk of nocturnal confirmed hypoglycaemic episodes than IDet or IGlar. Based on the hierarchical testing, superiority of IDeg over comparator products was confirmed in Trials 3583 and 3585. In Trial 3770, where this was not a confirmatory endpoint, the estimated rate of nocturnal confirmed hypoglycaemia was statistically significantly lower with IDeg than with IGlar.

Exemplified by the 52-week Trial 3583 (Figure 13), the cumulated number of confirmed hypoglycaemic episodes was similar for IDeg and IGlar both in the titration period (week 0–15) and in the maintenance period (from week 16 to end-of-trial). The lower rate of nocturnal confirmed hypoglycaemia became increasingly apparent over time. A similar pattern was seen in Trial 3585, while in Trial 3770, the cumulative curves for IDeg OD and IDeg Flex were above IGlar in terms of number of confirmed episodes. For nocturnal confirmed episodes, the curve for IDeg Flex was lower than IDeg OD and IGlar.

Figure 13 Hypoglycaemic Episodes – T1DM – Trial 3583 – Mean Cumulative Function – SAS



Nocturnal period: the period between 00:01 and 05:59 (both included);

Thus in the T1DM population, more hypoglycaemic episodes were reported for IDeg than for IGlar. Nocturnal hypoglycaemia was less common with IDeg, this difference was statistically significant.

Overview of all hypoglycaemic episodes by classification in T2DM

In Table 21, an overview of all hypoglycaemic episodes in T1DM patients across the IDeg clinical programme are summarized.

Table 21 Hypoglycaemic Episodes by Classification – T2DM – SAS

		IDeg				Comparator			
Trial (wks)		N	(%)	E	R	N	(%)	E	R
Basal-bolus therapy ± OADs									
3582 (52)									
Number of subjects		753				251			
Severe		34	(4.5)	41	6.1	11	(4.4)	12	5.2
Confirmed		609	(80.9)	7437	1108.9	206	(82.1)	3120	1363.4
Nocturnal confirmed		298	(39.6)	930	138.7	119	(47.4)	422	184.4
OAD-insulin combination therapy									
3579	Number of subjects	766				257			
3672	Number of subjects	228				228			
3586	Number of subjects	284				146			
3580	Number of subjects	226				228			
3668 FF	Number of subjects	230				229			
3668	Number of subjects	226							
3579	Severe	2	(0.3)	2	0.3	5	(1.9)	5	2.3
3672	Severe	0				0			
3586	Severe	0				1	(0.7)	1	1.4
3580	Severe	1	(0.4)	1	1.0	0			
3668 FF	Severe	1	(0.4)	2	1.9	2	(0.9)	2	1.9
3668	Severe	2	(0.9)	2	1.9				
3579	Confirmed	356	(46.5)	1014	152.0	119	(46.3)	403	184.9
3672	Confirmed	65	(28.5)	129	122.1	70	(30.7)	152	142.1
3586	Confirmed	142	(50.0)	397	297.6	78	(53.4)	260	369.9
3580	Confirmed	96	(42.5)	311	307.0	29	(12.7)	123	126.1
3668 FF	Confirmed	117	(50.9)	388	364.3	113	(49.3)	368	348.4
3668	Confirmed	99	(43.8)	378	362.6				
3579	Nocturnal confirmed	106	(13.8)	169	25.3	39	(15.2)	84	38.5
3672	Nocturnal confirmed	14	(6.1)	19	18.0	20	(8.8)	30	28.1
3586	Nocturnal confirmed	58	(20.4)	104	78.0	35	(24.0)	87	123.8
3580	Nocturnal confirmed	29	(12.8)	53	52.3	13	(5.7)	29	29.7
3668 FF	Nocturnal confirmed	31	(13.5)	67	62.9	49	(21.4)	79	74.8
3668	Nocturnal confirmed	24	(10.6)	58	55.6				

Confirmed Hypoglycaemia in T2DM

In Trial 3582 (basal–bolus treatment), about 5% of subjects experienced one or more episodes of severe hypoglycaemia during the 52-week trial period. The rates of severe episodes were low: 6.1 episodes per 100 PYE with IDeg and 5.2 episodes per 100 PYE with IGlar. In the OAD-insulin combination trials, the number of severe hypoglycaemic episodes was low ranging from 0 to 2 episodes with IDeg and from 0 to 5 episodes with IGlar. Due to the low number of events, no statistical analyses are performed for severe hypoglycaemia in T2DM.

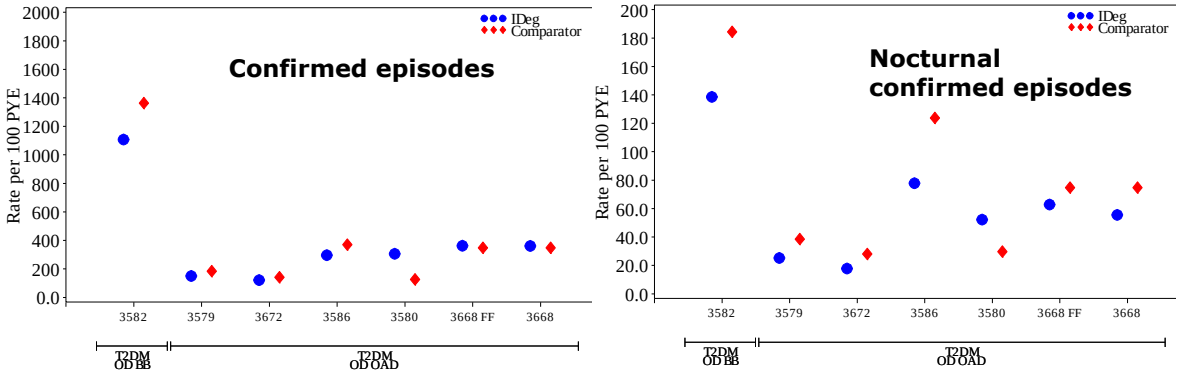
Two (2) subjects (both IDeg) withdrew from the trials at least partly due to hypoglycaemia, with the withdrawal reason 'Adverse Event'. A total of 13 subjects (IDeg 9, comparator 4) withdrew from the trials due to withdrawal criterion 'Hypoglycaemia Causing a Safety Problem'. In addition, 4 subjects (all IDeg) withdrew from the trials due to the withdrawal category 'Other' including a comment mentioning hypoglycaemia. As for T1DM, the rate of serious adverse events related to hypoglycaemia was similar across treatments. It is thus most likely that an increased awareness of the investigational drug in the open-label trials was responsible for the differences observed. Of the 19 withdrawals, 6 occurred during the first month of treatment (5 in the IDeg group and 1 in the comparator group). The Kaplan Meier curves show that withdrawals were evenly distributed over time and there is no indication that they occurred more frequently in the transition period.

In Trial 3582, episodes of confirmed hypoglycaemia were reported by approximately 80% of subjects. The observed rates of confirmed hypoglycaemia were 1109 and 1363 episodes per 100 PYE with IDeg and IGlar. The estimated rate of confirmed hypoglycaemia was 18% lower with IDeg than with IGlar, and superiority was demonstrated.

In the OAD-insulin combination trials, between 13 and 53% of subjects experienced at least one episode of confirmed hypoglycaemia. The estimated rates of confirmed hypoglycaemia were consistently lower (by 14–18%) with IDeg than with IGlar in Trials 3579, 3672 and 3586 (not statistically significant). The estimated rates of confirmed hypoglycaemia were similar whether IDeg was dosed at alternating time intervals or in the evening. As predicted from the comparison of a DPP-4 inhibitor versus an insulin product, the estimated rate of confirmed hypoglycaemia was lower (by 74%) with sitagliptin than with IDeg in Trial 3580. In this context, the comparison of rates of confirmed hypoglycaemia between IDeg and sitagliptin is not considered valid.

The observed rates of nocturnal confirmed hypoglycaemia were consistently lower with IDeg than with IGlar in T2DM (Figure 14). Also, the rates of confirmed hypoglycaemia were numerically lower with IDeg than with IGlar in four of the five trials where IGlar was the comparator. In general, the rates of hypoglycaemia were higher in trials where IDeg and comparator was combined with insulin secretagogues (Trials 3586, 3580 and 3668) than in trials where insulin secretagogues were not used.

Figure 14 Confirmed and Nocturnal Confirmed Hypoglycaemic Episodes – T2DM – Plot of Observed Rates – SAS



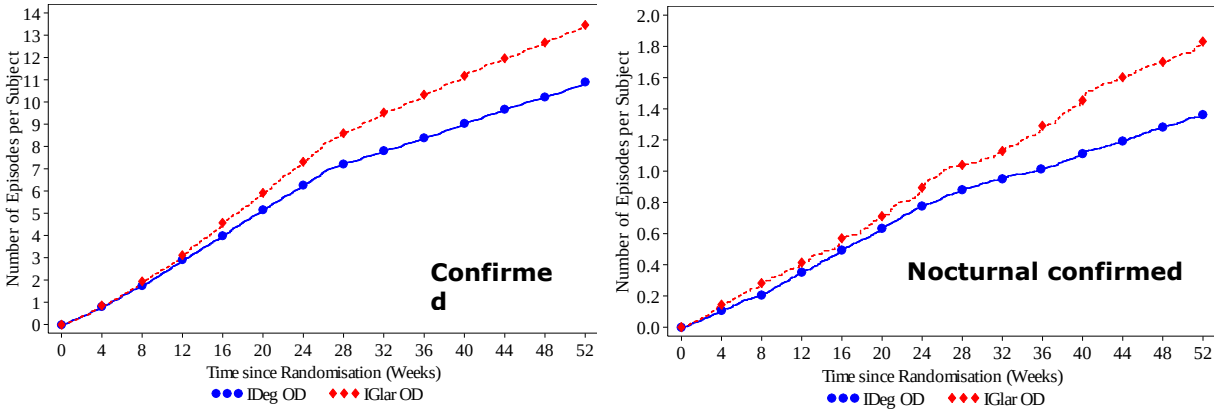
FF: Fixed Flexible, subjects treated with a rotating dose schedule; Comparator: IGlar and Sita (3580); note different scales on y-axes of right and left panel; Nocturnal period: the period between 00:01 and 05:59 (both included);

In Trial 3582, episodes of nocturnal confirmed hypoglycaemia were reported by 40% with IDeg and 47% with IGlar. After 52 weeks of treatment, the estimated rate of nocturnal confirmed hypoglycaemia was 25% lower with IDeg than with IGlar (statistically significant).

In the OAD-insulin combination trials, the number of subjects who reported nocturnal confirmed hypoglycaemia were comparable, being 6–20% of IDeg-treated subjects and 6–24% of comparator-treated subjects. Based on results from Trials 3579, 3672, 3586 and 3668, the estimated rates of nocturnal confirmed hypoglycaemic episodes were 23–38% lower with IDeg than with IGlar. The treatment difference was statistically significant in Trial 3579. Of note, nocturnal confirmed hypoglycaemia was a confirmatory endpoint in Trial 3586. In Trial 3580, the estimated rate of nocturnal confirmed hypoglycaemia was lower (by 48%) with sitagliptin than with IDeg, this was not statistically significant. Consistently lower rates of nocturnal hypoglycaemia with IDeg were observed together with similar reductions in SMPG over night with IDeg and IGlar.

In Trial 3582, the cumulated rates of confirmed and nocturnal confirmed episodes clearly separate from around Week 20–28 (Figure 15). At this time, glycaemic control and insulin dose were at a stable level. The majority of confirmed hypoglycaemic episodes occurred during the daytime and evening (06:00 to 00:00), with a higher proportion around 12:00.

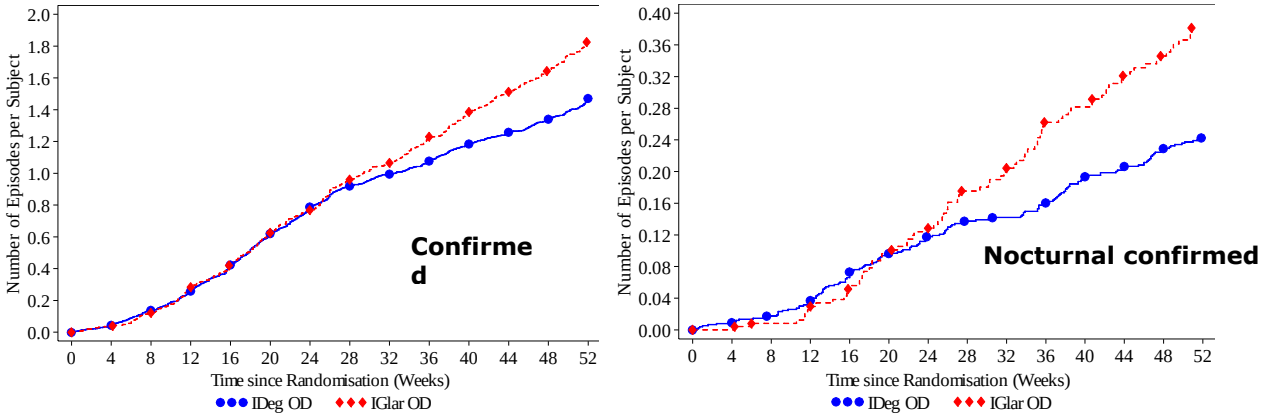
Figure 15 Hypoglycaemic Episodes – T2DM – Basal-bolus Therapy – Trial 3582 – Mean Cumulative Function – SAS



Nocturnal period: the period between 00:01 and 05:59 (both included);

Rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were similar with IDeg and IGlar in the first half of the 52-week Trial 3579 (Figure 16). During the second half of the trial period the slope of the IDeg curve levelled off while it continued to increase with IGlar.

Figure 16 Hypoglycaemic Episodes – T2DM – OAD-insulin Combination – Trial 3579 – Mean Cumulative Function – SAS



Nocturnal period: the period between 00:01 and 05:59 (both included)

Results from the 26-week OAD-insulin trials were similar to Trial 3579 in terms of the development of cumulated numbers of confirmed and nocturnal confirmed hypoglycaemic episodes. An exception was Trial 3580, in which rates of hypoglycaemia were lower with sitagliptin than with IDeg. In Trial 3672, the rate for IDeg was higher than that for IGlar for the first 18 treatment weeks, after which the IDeg rate was less than the IGlar rate. In Trial 3668, the lower rates of hypoglycaemia with IDeg were seen for nocturnal confirmed hypoglycaemia and not for confirmed hypoglycaemia.

Confirmed hypoglycaemic episodes were dispersed throughout the 24-hour period with a cluster around 06:00–08:00 for both IDeg and comparator products.

In conclusion, the estimated rates of confirmed and nocturnal confirmed hypoglycaemia were statistically significantly lower with IDeg than with IGlar when used as part of basal-bolus treatment in subjects with T2DM. A consistent pattern of numerically lower rates of confirmed and nocturnal confirmed hypoglycaemic episodes was observed with IDeg in most T2DM trials with OAD-insulin combination compared to IGlar; statistically significant in Trial 3579. The lower rates of hypoglycaemia

were consistent across a variety of administration times, with different OAD combinations and with different doses of basal insulin.

Body Weight

Mean body weight increased for both IDeg and comparator in all trials in T1DM. With IGlar, the observed mean weight gain was approximately 1.6 kg in both Trial 3583 and 3770, while with IDeg, the observed mean weight gain ranged from 0.8 kg to 1.8 kg. There were no statistically significant differences between IDeg and IGlar in terms of weight change. The observed mean weight gain with IDet was 0.4 kg. At end of trial, the estimated change in body weight was less with IDet than with IDeg (statistically significant) confirming previous observations with IDet compared to either NPH insulin or IGlar. The statistical analysis was repeated for subjects who completed the trials and the results supported the findings of the analysis on the FAS.

In T2DM subjects, after 52 weeks of basal–bolus treatment with IDeg or IGlar in combination with IAsp, the mean observed weight gain was approximately 3.6 kg with IDeg and 4.0 kg with IGlar. There was no statistically significant difference in weight gain between the treatment groups. In subjects treated with basal insulin in combination with OADs, body weight gain ranged from 1.3 kg to 2.3 kg with IDeg and from 1.3 kg to 2.1 kg with IGlar. With sitagliptin, the mean body weight decreased by 0.4 kg from baseline to end of trial (Trial 3580). No statistically significant treatment differences (IDeg – IGlar) in estimated change in body weight were detected. With sitagliptin, the estimated change in body weight was statistically significantly less than with IDeg. Results of the statistical analyses for subjects who completed the trials were in support of the analysis on the FAS.

Ancillary analyses

Comparison of Results in Subpopulations

Comparison of the efficacy of IDeg in sub-populations was assessed through statistical analysis of interaction between treatment effect and intrinsic/extrinsic factors. The intrinsic factors were demographic factors (age group, sex, BMI group, race and ethnicity) and disease factors (diabetes duration category, baseline HbA_{1c} category, estimated creatinine clearance category and ALAT percentile). The extrinsic factors were pretrial antidiabetic treatment, concomitant medication and concomitant OAD medication class. The analyses were based on pooled data from therapeutic confirmatory trials in T1DM and T2DM, respectively. These analyses were performed in order to evaluate whether the treatment difference (measured by HbA_{1c} and hypoglycaemia) depended on any intrinsic or extrinsic factors.

In summary, there were no statistically significant treatment-by-demographic interactions or treatment-by-disease factor interactions. Except for a statistically significant interaction for subjects using TZDs, the treatment difference (IDeg – comparator) in HbA_{1c} and rate of confirmed hypoglycaemia was independent of intrinsic and extrinsic factors. With IDeg, there was no difference in observed HbA_{1c} reduction between subjects treated with TZDs and those not treated with TZDs, the reduction was 1.17% points for both. For comparator products, the reduction in HbA_{1c} was greater for subjects treated with TZDs (1.5% points) than for subjects not treated with TZDs (1.3% points). This was only seen for the pooled trials, whereas the results for the individual trials were inconsistent. Hence, the analysis result was considered a chance finding.

Thus, no clinically relevant findings were observed in the subgroup analyses.

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).

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) Confirmatory secondary 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) 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/IGlar) was entirely below one.
	3) 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.
	4) 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.
	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.	
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; FAS: full analysis set; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; 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) Confirmatory secondary 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.	
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; HbA1c: glycosylated haemoglobin A1c; 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

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 treatment	Comparison groups	IDeg FF – IGlar	IDeg FF – IDeg OD
		Treatment contrast	-0.44	0.33
		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.		
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; FAS: full analysis set; FF: fixed flexible, subjects treated with a rotation dosing schedule; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A1c; 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 weeks of treatment	Comparison groups	IDeg – IGlar
		Treatment contrast	-0.31
		95% CI	[-0.98; 0.37]
	Supportive secondary endpoint: Total daily insulin dose after 52 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; 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 A1c; 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	Comparison groups	IDeg – IGlar

	endpoint: Change from baseline in FPG after 52 weeks of treatment	Treatment contrast	-0.43
		95% CI	[-0.74; -0.13]*
	3) Confirmatory secondary endpoint: Within-subject variability in SMPG (CV%) after 52 weeks of treatment	Comparison groups	IDeg/IGlar
		Treatment ratio	0.99
		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.	
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; 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 A1c; 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 HbA1c (%) 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 HbA1c (%) 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 endpoint: HbA_{1c} < 7.0% at end of trial without confirmed hypoglycaemia	Comparison groups	IDeg/IGlar
		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.	
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; 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 A1c; 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	Comparison groups	IDeg – IGlar

	endpoint: Change from baseline in FPG after 26 weeks of treatment	Treatment contrast	-0.09
		95% CI	[-0.41; 0.23]
	4) Confirmatory secondary endpoint: Within-subject variability in SMPG (CV%) after 26 weeks of treatment	Comparison groups	IDeg/IGlar
		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.	
Notes			

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 A1c; 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 administered 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.	
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; 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 A1c; 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.		
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; FAS: full analysis set; FF: fixed flexible, subjects treated with a rotation dosing schedule; FPG: fasting plasma glucose; glin: glinides; HbA_{1c}: glycosylated haemoglobin A1c; 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

Clinical studies in special populations

N/A

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

Meta-analysis of Hypoglycaemic Episodes

A prospectively planned meta-analysis, pooling all therapeutic confirmatory trials (T1DM and T2DM) with IDeg OD and IGlar as comparator (excluding the IDeg Flex arms of Trials 3770 and 3668) was performed. The analyses were based on the FAS, which included a total of 2899 subjects treated with IDeg and 1431 subjects treated with IGlar.

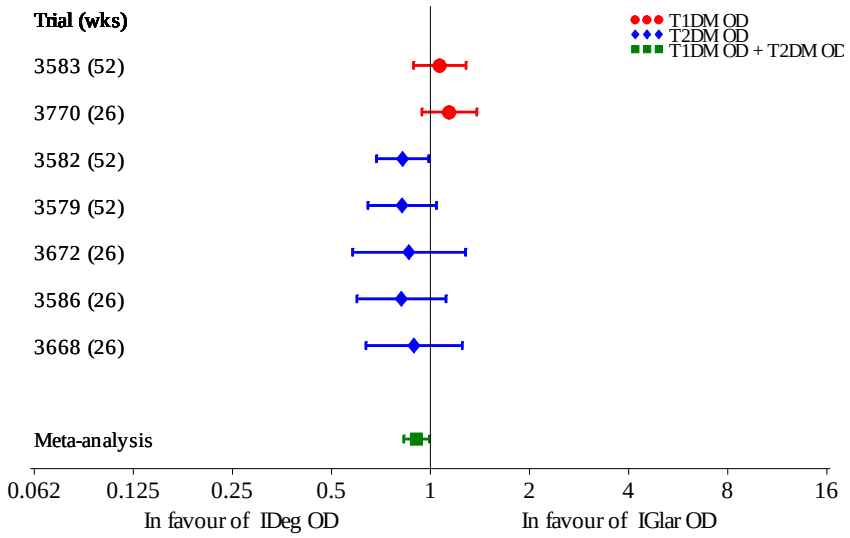
Severe Hypoglycaemia

A total of 11.7% of subjects with T1DM and 1.7% of subjects with T2DM reported severe hypoglycaemia during the trial period. The majority of the severe hypoglycaemic episodes for subjects with T2DM were reported in Trial 3582 (basal/bolus treatment regimen), where 4.5% of the subjects experienced at least one severe hypoglycaemic episode. The observed rate of severe hypoglycaemia were approximately the same for subjects treated with IDeg compared to IGlar and there were no statistically significant difference between the treatments in the pooled analysis; estimated rate ratio 0.98 $[0.66; 1.45]_{95\%CI}$.

Confirmed Hypoglycaemia

The primary analysis demonstrated that IDeg was superior to IGlar in terms of a lower rate of confirmed hypoglycaemic episodes with an estimated rate ratio of 0.91 $[0.83; 0.99]_{95\%\ CI}$. For trials in T2DM, all point estimates were to the left of 1.0, which demonstrates the consistency of response. In T1DM, the point estimate was either at 1.0 or slightly above (i.e., favouring the comparator insulin product); see Figure 17.

Figure 17 Confirmed Hypoglycaemic Episodes - Therapeutic Confirmatory Trials – IDeg vs. IGlar – Plot of Treatment Contrasts – FAS



Estimates with 95% confidence interval; the comparison for Trial 3668 is IDeg OD vs. IGlar

In an additional (*post-hoc*) statistical analysis on the incidence (incident cases) of confirmed hypoglycaemia (pooling T1DM and T2DM), the estimated incidence of confirmed hypoglycaemia (odds ratio of 0.93 $[0.79; 1.08]_{95\%CI}$) was consistent with the primary analysis as well as the additional analyses of sub-populations (rate ratios). In the two types of analyses the ratios were similar and below 1, meaning that not only the rate of hypoglycaemic episodes was lower with IDeg OD, but also the proportion of subjects experiencing hypoglycaemia were lower compared to IGlar OD. The difference was not statistically significant in the incidence analysis due to the lower number of observations when evaluating only the incident cases and disregarding the number of hypoglycaemic episodes experienced by the subjects.

Based on the stratified Wilcoxon rank-sum test, there was no difference between the treatment groups in the incidence rate of confirmed hypoglycaemia, that is, the number of subjects with at least one hypoglycaemic episode divided by the extent of exposure.

The results of a pre-specified secondary analysis in elderly subjects (≥65 years) were in line with the findings of the primary analysis; estimated rate ratio (IDeg/IGlar) of 0.82 $[0.66; 1.00]_{95\%\ CI}$ (not statistically significant).

The statistical analyses were repeated for the titration period and for the maintenance period to explore the changes in the rate of hypoglycaemic episodes across the trial period. A cutting point of 16 weeks was chosen as the time point where a stable dose of basal insulin and stable glycaemic control was considered obtained for the majority of subjects. There was no statistically significant difference in rates of confirmed hypoglycaemia between the two treatments in the titration period, (estimated rate ratio IDeg/IGlar 1.00 $[0.90; 1.10]_{95\%CI}$). During the maintenance period (from Week 16 and onwards), subjects treated with IDeg had a statistically significantly lower rate of confirmed hypoglycaemic episodes compared to subjects treated with IGlar; estimated rate ratio IDeg/IGlar 0.84 $[0.75; 0.93]_{95\%CI}$.

The demonstrated superiority of IDeg compared to IGlar in terms of a lower rate of confirmed hypoglycaemic episodes rate was primarily driven by results in T2DM, whereas there was no statistically significant treatment difference in T1DM (estimated rate ratio 1.10 $[0.96; 1.26]_{95\%CI}$). In

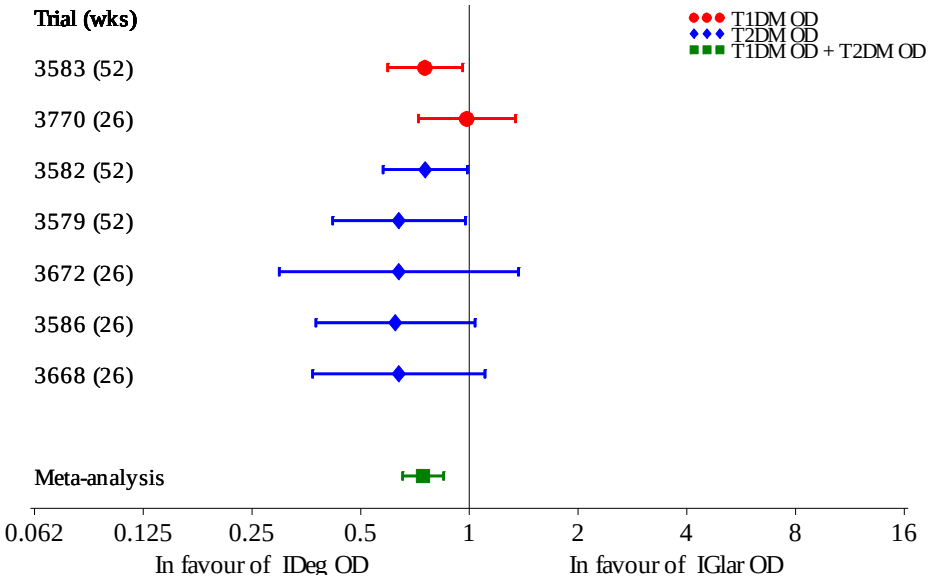
T2DM, the rate of confirmed hypoglycaemia was statistically significantly lower with IDeg than with IGlar (estimated rate ratio 0.83 [0.74; 0.94]$_{95\%CI}$). Also, in insulin-naïve subjects with T2DM treated with basal insulin in combination with OADs (Trials 3579, 3672 and 3586), the rate of confirmed hypoglycaemia was lower with IDeg compared to IGlar; the estimated rate ratio for confirmed hypoglycaemia was 0.83 [0.70; 0.98]$_{95\%CI}$.

Since the outcome differed between the two populations (T1DM and T2DM) the data do not support a general claim regarding a lower risk of hypoglycaemia with IDeg. Data concerning hypoglycaemia in these 2 populations is included in section 5.1 of the SmPC. In two studies, where the time of dosing was recorded for IGlar, confirmed hypoglycaemias were most common when IGlar was admininstered before breakfast. However, since both these studies were performed in comparison with IDegAsp, no direct comparisons with IDeg can be made.

Nocturnal Confirmed Hypoglycaemia

The meta-analysis confirmed that IDeg was superior to IGlar in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes with a ratio of 0.74 [0.65; 0.85]$_{95\%\ CI}$ for the estimated rates of nocturnal confirmed hypoglycaemia; see Figure 18.

Figure 18 Nocturnal Confirmed Hypoglycaemic Episodes - Therapeutic Confirmatory Trials – IDeg vs. IGlar – Plot of Treatment Contrasts – FAS



Estimates with 95% confidence interval; Nocturnal period: the period between 00:01 and 05:59 (both included)

The result of the *post-hoc* analysis of incidence of nocturnal confirmed hypoglycaemic episodes showed that a statistically significantly smaller proportion of subjects in the IDeg group experienced at least one episode of nocturnal confirmed hypoglycaemia compared to subjects treated with IGlar (odds ratio of 0.78 [0.67; 0.92]$_{95\%CI}$. As for the results of confirmed hypoglycaemia, results of incidence of nocturnal confirmed hypoglycaemia were consistent with analysis results of rates, altogether suggesting a lower rate of nocturnal confirmed hypoglycaemia as well as a lower proportion of subjects with nocturnal confirmed hypoglycaemia.

In a pre-specified analysis, elderly subjects treated with IDeg had a statistically significantly lower rate of nocturnal confirmed hypoglycaemic episodes than elderly subjects treated with IGlar (estimated rate ratio 0.65 [0.46; 0.93]$_{95\%CI}$).

Subjects treated with IDeg had a statistically significantly lower rate of nocturnal hypoglycaemic episodes in the titration period compared to subjects treated with IGlar (estimated rate ratio 0.86 $[0.74; 1.00]_{95\%CI}$). The difference was substantiated throughout the maintenance period: estimated rate ratio IDeg/IGlar 0.68 $[0.58; 0.80]_{95\%CI}$ (*post-hoc* analysis).

Results for subjects with T1DM pointed to a lower rate of nocturnal confirmed hypoglycaemia for subjects treated with IDeg than for subjects treated with IGlar, thus supporting the confirmatory secondary analysis on nocturnal confirmed hypoglycaemic episodes; estimated rate ratio 0.83 $[0.69; 1.00]_{95\%CI}$. The result was not statistically significant. For subjects with T2DM, the additional analysis also supported the confirmatory secondary analysis, since IDeg was superior to IGlar in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes (estimated rate ratio 0.68 $[0.57; 0.82]_{95\%CI}$).

In insulin-naïve subjects with T2DM treated with basal insulin in combination with OADs (Trials 3579, 3672 and 3586), the rate of nocturnal confirmed hypoglycaemia was also statistically significantly lower with IDeg compared to IGlar. The estimated rate ratio for nocturnal confirmed hypoglycaemia was 0.64 $[0.48; 0.86]_{95\%\ CI}$.

The findings were consistent for both T1DM and T2DM patients, although not statistically significant for T1DM. This information is included in section 5.1 of the SmPC. As for confirmed hypoglycaemias, data on how the comparator IGlar was administered is only available for two studies comparing IGlar to IDegAsp.The majority of patients administered IGlar before the evening meal/at bedtime, but a substantial propostion of patients took their insulin before breakfast. In one study, (somewhat surprisingly) the rate of nocturnal hypoglycaemias was highest with breakfast dosing compared to evening meal/bedtime dosing whereas the opposite was observed in the other study.

Supportive studies

Three therapeutic exploratory trials were conducted with IDeg 600 nmol/mL and IDeg 900 nmol/mL. The composition of IDeg 600 nmol/mL used in the therapeutic exploratory trials is identical to IDeg 100 U/mL used in the therapeutic confirmatory trials.

Two trials were conducted in T1DM patients; trials 1835 and 3569. Trial 3569 included only six Japanese patients and will not be further discussed. One trial (1836) was conducted in T2DM patients on 1-2 OADs. The overall pattern was the same as in the therapeutic confirmatory trials: a high number of subjects completed the trials, and the main reason for withdrawal was 'Other'. 'Ineffective Therapy' was the cause of withdrawal for 3 subjects in Trial 1835, 2 with IDeg 900 nmol/mL OD and 1 with IDeg OD, and for 1 subject with IDeg OD in Trial 1836.

The primary endpoint in Trial 1835 (T1DM) and Trial 1836 (T2DM) was HbA_{1c} after 16 weeks of treatment. In Trial 1835, the observed mean reduction in HbA_{1c} was approximately 0.6% points after 16 weeks of IDeg treatment, and in Trial 1836, the observed mean reduction in HbA_{1c} was approximately 1.3% points with IDeg OD.

In the therapeutic exploratory Trial 1835 (T1DM), the observed proportion of subjects who achieved the HbA_{1c} target <7.0% after 16 weeks of treatment was about 15% in all treatment groups. The composite responder endpoints were defined as proportion of subjects (exposed for ≥8 weeks) who achieved HbA_{1c} <7.0% or ≤6.5% after 16 weeks without hypoglycaemic episodes (confirmed or severe) during the last 4 weeks of treatment. With IDeg, 14.5% of subjects reached the <7.0% target without severe hypoglycaemia and 3.6% achieved the target without confirmed hypoglycaemia. With IGlar, the corresponding proportions were 14.8% and 1.9%, respectively.

In the therapeutic exploratory Trial 1836 (T2DM), the proportions of subjects achieving HbA_{1c} <7.0% after 16 weeks of treatment were 47% for IDeg OD and 45% for IGlar, thus in support of the results of

the therapeutic confirmatory trials. The composite responder endpoints were defined in the same way as in Trial 1835. With IDeg OD, 52.8% of subjects reached the <7.0% target without severe hypoglycaemia, and 49.1% achieved the target without confirmed hypoglycaemia. With IGlar, the corresponding proportions were 48.2% and 42.9%, respectively.

In the therapeutic exploratory trials, hypoglycaemic episodes were defined as nocturnal if the time of onset was between 23:00 and 05:59 (both included), thus, the nocturnal period was 1 hour longer than in the confirmatory trials.

In Trial 1835 (T1DM), the estimated rate of confirmed hypoglycaemia was 28% lower with IDeg than with IGlar after 16 weeks of treatment. A total of 7 episodes of severe hypoglycaemia were reported with IDeg and 6 episodes with IGlar. The observed rates of confirmed hypoglycaemia were markedly higher in Trial 1835 than in the therapeutic confirmatory trials both for IDeg and for IGlar. In Trial 3569 (T1DM), the rate of confirmed hypoglycaemia was 22% lower with IDeg than with IDet after 6 weeks of treatment (not statistically significant). No severe episodes were reported. The estimated rate of nocturnal confirmed hypoglycaemic episodes was distinctively lower with IDeg than with comparator in Trials 1835 and 3569.

In Trial 1836 (T2DM), the estimated rate of confirmed hypoglycaemia was 56% lower with IDeg than with IGlar. In total, 8% of subjects treated with IDeg and 23% of IGlar-treated subjects reported episodes of confirmed hypoglycaemia during the 16-week period with no episodes classified as severe in the IDeg and IGlar treatment groups. The estimated rates of nocturnal hypoglycaemic episodes (defined as for Trial 1835) were low and similar for IDeg and IGlar in this trial.

Conclusion

The exploratory trials were of shorter duration and differed also in other respects from the confirmatory trials. The effect on HbA1c was comparable to that achieved in the confirmatory trials whereas responder rates were lower, especially in the T1DM trial. A similar pattern with regards to hypoglycaemias as observed in the confirmatory trials was seen.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of IDeg has been investigated in nine confirmatory studies, three in T1DM patients and six in T2DM patients. The T1DM trials included 1578 subjects and 4076 subjects were included in the T2DM trials. All trials were of 26-52 weeks duration. One of the T2DM trials (3672) investigated the 200 U/ml formulation. In addition three 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. It should be noted that patients treated with GLP-1 analogues or with 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 were excluded. The key withdrawal criteria included pregnancy, hypoglycaemia (as judged by investigator) and lack of effect as defined by an FPG of more than 13.3 mmol/l (240 mg/dl). It had been recommended to strengthen this criterion, however, considering that titration of insulin was possible (according to a pre-specified algorithm) in the trials this does not appear to be a major issue. An adequate justification for the criterion applied has been provided.

The T2DM trials allowed all OAD background therapies (where concomitant insulin therapy is included in the labelling) in different combinations. All trials were performed with active comparator and the choice of comparators (IDet or IGlar in the T1DM trials, IGlar or sitagliptin in the T2DM trials) was

adequate and in line with the given advice. All trials, except the trial where sitagliptin was used as comparator, were designed as non-inferiority, treat-to-target trials and insulin doses were titrated according to predefined titration algorithms. In one of the T2DM trials (3672) the 200 U/ml formulation was used. This study included 460 patients (230 on IDeg). Prefilled pens were used throughout the trials and a new pen was developed for the 200 U/ml formulation. Within the clinical program different dosing times for IDeg were systematically investigated, whereas the comparators were dosed according to their labelling.

The chosen primary and secondary outcomes are acceptable an 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 studies were generally well conducted. Due to the difference in appearance of IDeg, IDet 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 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. A total of 137 patients >75 were included in the trials. This is considered sufficient. About 36 % of T1DM patients and 39 % of T2DM patients were recruited from Europe. Thus the populations recruited are considered representative for the target population. The pretrial 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 pretrial to ensure that these patients were true treatment failures. It is, however, a weakness that metformin was not a requirement in all T2DM trial, being the cornerstone in antidiabetic treatment of T2DM patients. Overall, in all T2DM trials metformin was used by 86% of patients, but percentages were as low as approximately 60% in trial 3582. Withdrawal rates were rather low and balanced between study groups; however, withdrawal due to adverse events and withdrawal criteria (hypoglycaemia being one criterion) was somewhat more common in the IDeg group both in the T1DM and the T2DM population. Withdrawals were evenly distributed over the course of the trials. It is likely that an increased awareness of the investigational drug in the open-label trials as well as the fact that a large part of T1DM subjects from the comparator groups were randomised to their pre-trial insulin therapy were responsible for the differences observed.

In both T1DM and T2DM trials, the primary efficacy endpoint was met. In all trials but one the aim was to show non-inferiority vs. the comparator IGlar. The predefined delta was 0.4 %, which may be considered too large and was not in accordance with the CHMP Scientific Advice, however, in all trials the 95 % confidence interval lay between 0.2 and 0.3 % both in the ITT- and the PP-population. In study 3580 superiority was shown for IDeg vs. sitagliptin.

Clinically relevant reductions in HbA1c were observed taking the baseline HbA1c into account (0.4-0.7 % in T1DM trials; 1.1-1.6 % in T2DM trials). The rate of responders did not differ between groups, the rate being numerically slightly lower for IDeg in most trials. Similar observations were made when the occurrence of hypoglycaemia was taken into account. Subgroup analyses in T2DM trials did not suggest a relevant difference in HbA1c for the subgroups of patients with/without metformin, while confirmed hypoglycaemic and to a smaller extent also nocturnal hypoglycaemic episodes were clearly reduced in those patients treated with metformin, in both the IDeg and the comparator group. However, efficacy in terms of lowering HbA1c has been adequately shown in both T1DM and T2DM.

Notably, the lower FPG observed with IDeg across trials was not accompanied by a lower HbA1c. The Applicant argues that this may be explained by lower blood glucose levels, especially at night, with comparator products as indicated by higher numbers of nocturnal hypoglycaemic episodes. These periods of low plasma glucose may have contributed to HbA1c reduction beyond what could be appreciated from the FPG and postprandial glucose values alone. This may be true, however the discrepancy makes claims regarding lowering of FPG debatable since long-term outcome is largely associated with normalisation of HbA1c.

Analysis of the 9-point profiles did not reveal any clinically relevant differences between IDeg and the comparators.

The reductions in pre-breakfast SMPG were largely in line with the FPG observations. Time to reach target was estimated and was generally shorter in the IDeg groups. The proportion of patients that reached target was in the same range for both IDeg and comparators, with the exception of sitagliptin where few patients reached target. The outcome in the IDegFlex group differed in that the pre-breakfast SMPG was higher than for the comparator and the time to reach target was longer than for the IDeg OD group. In spite of the lower variability with IDeg observed in the PD studies, no differences in the day-to-day variability of the pre-breakfast SMPG was observed between IDeg, IDegFlex and the comparators.

Similar observations were made in the subgroups where CGM was applied with no significant differences between groups with regards to the IG profile fluctuations or the duration of hypoglycaemic or hyperglycaemic episodes. 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. However, hypoglycaemias were also recorded applying the stricter cut-off of 3.9 mmol/l in line with the scientific advice. Analyses according to the 3.9 mmol/l limit (documented symptomatic and asymptomatic) largely confirm the analyses with the lower cut-off, although statistical significance in favour of IDeg was only shown for nocturnal documented hypoglycaemia in T1DM and T2DM using basal bolus therapy. 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 no differences were observed between study groups.

In the T1DM population, numerically more confirmed hypoglycaemic episodes were reported for IDeg than for IGlar. Statistically significant differences were only observed with regards to nocturnal hypoglycaemia, which were less common with IDeg.

The rates of confirmed hypoglycaemia varied across trials in T2DM depending on the insulin regimen and OAD treatment. As expected, higher rates of hypoglycaemia was observed for IDeg compared to sitagliptin, but in this context, the comparison of rates of confirmed hypoglycaemia between IDeg and sitagliptin is not considered valid. In the other trials, lower rates of confirmed hypoglycaemia were consistently observed with IDeg compared to IGlar. Nocturnal hypoglycaemias were consistently lower for IDeg across trial except in comparison to sitagliptin.

A pre-planned meta-analysis of hypoglycaemic events was performed. The analysis confirmed that no differences were observed in the rates of severe hypoglycaemia either in the T1DM or T2DM populations. The meta-analysis further showed a lower risk for hypoglycaemia with IDeg, however, this result was driven by the T2DM trials, whereas for T1DM the point estimates were in favour of the comparator. Since there is an apparent difference between the two populations, no general statement regarding the risk of confirmed hypoglycaemia could be made.

With regards to nocturnal hypoglycaemia, this result was consistent for both T1DM and T2DM showing a lower risk with IDeg treatment. The lower risk of nocturnal hypoglycaemia may be due to the flatter profile obtained with IDeg compared to IGlar which when dosed in the evening will result in a peak during the night.

Data on how the comparator IGlar was administered was requested during the procedure, i.e. at what time of the day IGlar was administered and how administration time was distributed among patients and further how the time of administration was related to the occurrence of hypoglycaemias. Such data are only available for the T2DM trials 3593 and 3896, where IGlar was compared to IDegAsp.

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 can not be explained by a choice of time of dosing disfavouring IGlar.

Across the study program, no significant differences in weight gain were observed between treatment groups. The weight gain was as expected considering the HbA1c lowering achieved during the trials.

Comparison of the efficacy of IDeg in sub-populations was assessed through statistical analysis of interaction between treatment effect and intrinsic/extrinsic factors. Elderly with T2DM had a lower HbA1c response and a higher rate of confirmed hypoglycaemia in both treatment groups, but there was no significant interaction. Females had also a higher rate of confirmed hypoglycaemia (no significant treatment by sex interaction). No other potentially relevant differences between IDeg and the comparators were observed in the subpopulations studied.

Insulin dose is determined by individual need and the dose therefore has to individually titrated. In the clinical trials IDeg 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 IDeg was performed on a unit-to-unit basis without increase in hypoglycaemic event or deterioration of glycaemic control. In Trial 3583, including T1DM patients, the rates of hypoglycaemia per month were slightly higher within the first month of treatment, particularly pronounced in subjects in good glycaemic control (HbA1c <8.0%) and subjects transferring from BID treatment. The SmPC of Tresiba

adequately addresses that a cautious transfer should be done in these patients. Data from trials 3770 and 3668 with the basal component IDeg supports that flexible dosing is feasible, although the outcome in the flexible dose groups appears less favourable compared to taking the dose at the same time every day. With respect to insulin doses in the T1DM trial 3770 IDeg doses in the FF arm were higher than in the IDeg OD arm. The flexible dose schedule may thus be at the expense of a slightly higher dose but seems still comparable to IGlar. The SmPC therefore recommends that Tresiba be given preferably at the same time every day, however, on occasions when this is not possible flexibility in dose of time is considered acceptable (section 4.2 of the SmPC).

Also in trial 3582, the mean basal insulin was higher with IDeg compared to IGlar after 52 weeks of treatment (74 U vs. 67 U). Otherwise insulin doses during and at the end of the trials seemed comparable.

The exploratory trials differed in a number of aspects with regards to design and endpoints, thus results cannot be easily compared. The effect on HbA1c was comparable to that achieved in the confirmatory trials whereas responder rates were lower, especially in the T1DM trial.

The findings in study 3672, investigating the 200 U/ml formulation, was consistent with the findings in the studies with IDeg 100 U/ml.

2.5.4. Conclusions on the clinical efficacy

The glucose-lowering effect of IDeg has been adequately shown in both T1DM and T2DM patients. In addition, the glucose-lowering effect of IDeg 200 U/ml has been adequately shown in T2DM patients. The data further support the proposed dosing recommendations. The data indicate that the risk of developing hypoglycaemia may be less with IDeg 100 U/ml and IDeg 200 U/ml as compared to IGlar in particular in T2DM.

2.6. Clinical safety

The safety and tolerability of IDeg as monotherapy (+IAsp) or in combination with other antidiabetic agents (metformin, sulfonylurea/glinide, alpha-glucosidase inhibitors, pioglitazone and DDP-4 inhibitors) in subjects with T1DM and T2DM was evaluated. A co-formulation of IDeg and insulin aspart (IAsp), named IDegAsp, was developed in parallel with IDeg in a separate clinical development programme. In the IDegAsp clinical trials there was a considerable exposure to IDeg, and for the purpose of this application the IDegAsp 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 were based on the full analysis set.

Patient exposure

The clinical development programme for IDeg consisted of a total of 41 completed trials. In these trials 5624 subjects were exposed to IDeg. The assessment of safety in subjects with T1DM and T2DM was mainly based on the 11 completed therapeutic confirmatory trials, representing the major part of the exposure. In these trials 4275 subjects were exposed to IDeg, 3758 subjects for at least 6 moths and 1635 subjects for at least 12 months. T2DM accounted for 74 % of the exposure (2101 PYE) and T1DM

accounted for 26 % of the exposure (727 PYE). The exposure of patients with T1DM and T2DM to IDeg at dose levels intended for clinical use has been sufficient to assess the safety of the product.

Table 22 Exposure Time (Months) – All Therapeutic Confirmatory Trials – All Subjects – IDeg vs. Comparator – Safety Analysis Set

	Any exposure		>= 6 months		>= 9 months		>= 12 months		TotalExposure in Subject Years
	N	%	N	%	N	%	N	%	
Therapeutic Confirmatory Trials									
All Subjects									
IDeg	4275	(100.0)	3758	(87.9)	1686	(39.4)	1635	(38.2)	2828.2
Comparator	2269	(100.0)	2010	(88.6)	565	(24.9)	548	(24.2)	1339.1
Subjects with T1DM									
IDeg	1102	(100.0)	991	(89.9)	418	(37.9)	404	(36.7)	726.8
Comparator	467	(100.0)	436	(93.4)	140	(30.0)	137	(29.3)	294.9
Subjects with T2DM									
IDeg	3173	(100.0)	2767	(87.2)	1268	(40.0)	1231	(38.8)	2101.4
Comparator	1802	(100.0)	1574	(87.3)	425	(23.6)	411	(22.8)	1044.2
Insulin-naïve Subjects with T2DM									
IDeg	1964	(100.0)	1702	(86.7)	633	(32.2)	611	(31.1)	1219.9
Comparator	1322	(100.0)	1144	(86.5)	205	(15.5)	199	(15.1)	709.7
Insulin-treated Subjects with T2DM									
IDeg	1209	(100.0)	1065	(88.1)	635	(52.5)	620	(51.3)	881.4
Comparator	480	(100.0)	430	(89.6)	220	(45.8)	212	(44.2)	334.5

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

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 sulphanylurea 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 has been added as missing information in the EU-RMP. This was considered acceptable by the CHMP.

Adverse events

Safety data from the 11 completed therapeutic trials were pooled for the following subgroups: All subjects; subjects with T1DM and subjects with T2DM.

Overall the incidence of AEs and AEs assessed as possibly or probably related to IDeg was slightly higher in the IDeg group than in the comparator group. The difference between groups was more pronounced in the group of subjects with T2DM (IDeg 68.3 %, 412.9 events per 100 PYE and comparator 65.1 %, 403.9 events per 100 PYE). Compared to subjects with T2DM, a larger proportion of subjects with T1DM experienced AEs, but the AE rate was similar between groups (IDeg 77.3 %, 471.9 events per 100 PYE and comparators 76.2%, 469.9 events per 100 PYE).

The vast majority of AEs were of mild or moderate severity and the pattern of AEs was generally similar between groups. Hypoglycaemic episodes were only recorded as AEs if they fulfilled the definition of a SAE or severe hypoglycaemia.

Table 23 Adverse Events – Treatment-emergent – All Therapeutic Confirmatory Trials – All Subjects – IDeg vs. Comparator – Summary – Safety Analysis Set

	IDeg				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	4275				2269			
All Adverse Events	3018	(70.6)	12106	428.1	1530	(67.4)	5603	418.4
Serious Adverse Events	337	(7.9)	427	15.1	147	(6.5)	181	13.5
Adverse Events leading to Death	14	(0.3)	17	0.6	7	(0.3)	8	0.6
Adverse Events Possibly or Probably Related to IMP	646	(15.1)	1093	38.6	305	(13.4)	472	35.2
Severity								
Mild	2649	(62.0)	8654	306.0	1327	(58.5)	3958	295.6
Moderate	1282	(30.0)	2877	101.7	658	(29.0)	1361	101.6
Severe	405	(9.5)	574	20.3	178	(7.8)	282	21.1
Unknown	1	(0.0)	1	0.0	2	(0.1)	2	0.1
Adverse Events withdrawals	98	(2.3)	132	4.7	30	(1.3)	32	2.4

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

	IDeg				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	4275				2269			
Total Exposure (yrs)	2828.2				1339.1			
All Adverse Events	3018	(70.6)	12106	428.1	1530	(67.4)	5603	418.4
Infections and infestations								
Nasopharyngitis	642	(15.0)	855	30.2	278	(12.3)	371	27.7
Upper respiratory tract infection	373	(8.7)	499	17.6	174	(7.7)	226	16.9
Influenza	151	(3.5)	166	5.9	64	(2.8)	76	5.7
Bronchitis	146	(3.4)	166	5.9	64	(2.8)	74	5.5
Sinusitis	132	(3.1)	167	5.9	63	(2.8)	71	5.3
Gastroenteritis	126	(2.9)	137	4.8	55	(2.4)	56	4.2
Urinary tract infection	120	(2.8)	140	5.0	48	(2.1)	54	4.0
Gastrointestinal disorders								
Diarrhoea	244	(5.7)	310	11.0	152	(6.7)	184	13.7
Nausea	157	(3.7)	188	6.6	95	(4.2)	107	8.0
Vomiting	122	(2.9)	135	4.8	65	(2.9)	77	5.1
Musculoskeletal and connective tissue disorders								
Back pain	198	(4.6)	239	8.5	98	(4.3)	130	9.7
Pain in extremity	137	(3.2)	155	5.5	66	(2.9)	74	5.5
Arthralgia	135	(3.2)	151	5.3	63	(2.8)	80	6.0
Nervous system disorders								
Headache	408	(9.5)	699	24.7	171	(7.5)	259	19.3
Dizziness	85	(2.0)	101	3.6	65	(2.9)	76	5.7
General disorders and administration site conditions								
Fatigue	92	(2.2)	114	4.0	52	(2.3)	55	4.1
Oedema peripheral	104	(2.4)	123	4.3	39	(1.7)	43	3.2
Injury, poisoning and procedural complications								
Wrong drug administered	112	(2.6)	119	4.2	22	(1.0)	23	1.7
Respiratory, thoracic and mediastinal disorders								
Cough	183	(4.3)	197	7.0	85	(3.7)	103	7.7
Oropharyngeal pain	131	(3.1)	149	5.3	63	(2.8)	71	5.3
Metabolism and nutrition disorders								
Hypoglycaemia	132	(3.1)	185	6.5	57	(2.5)	84	6.3
Eye disorders								
Diabetic retinopathy	91	(2.1)	94	3.3	44	(1.9)	45	3.4
Vascular disorders								
Hypertension	118	(2.8)	125	4.4	50	(2.2)	52	3.9

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 observed for the PTs "headache", "wrong drug administered", "muscle spasm" and "weight increased" where AEs were reported at a slightly higher frequency in the IDeg group than in the comparators.

The distribution of AEs in subjects with T1DM and T2DM was generally similar. However, a larger proportion of subjects with T1DM reported, "upper respiratory tract infection", "gastroenteritis", "urinary tract infection", "constipation" "depression" and "insomnia" in the IDeg group than in the comparator group, whereas in patients with T2DM "nasopharyngitis", "peripheral oedema" and "dyspnoea" were more common in the IDeg group than in the comparators.

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 IDeg 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 similar rate in both treatment groups (IDeg: 7.6 events per 100 PYE and comparator: 8.4 events per 100 PYE). The majority of injection site reactions were mild or moderate in severity. None of the injection site reactions were serious. The rates of *lipodystrophy* were low for both IDeg (0.5 events per 100 PYE) and comparators (0.4 events per 100 PYE).

No difference was seen in the rate of injection site reactions between the IDeg 100 U/ml product and IDeg 200 U/ml.

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

Peripheral oedema was reported at a similar rate for IDeg and comparators for all subjects (4.3 events per 100 PYE and 3.2 events per 100 PYE, respectively) and for subjects with T1DM (1.7 events per 100 PYE and comparators 1.4 events per 100 PYE). In subjects with T2DM, the rate was higher for IDeg than comparators (5.3 events per 100 PYE and 3.7 events per 100 PYE, respectively). Most events were mild or moderate in severity. No serious events were reported. The majority of events assessed as possibly or probably related to IDeg occurred later than one month after initiation of IDeg (in 15 of 19 subjects) or occurred in subjects with a confounding medical history (14 of 19 subjects). The rather late onset of symptoms and the fact that only one patient discontinued treatment due to the adverse event supports that alternative aetiologic factors might be involved. However, the skewed randomisation of studies and the presence of several confounders do not allow conclusive conclusions to be drawn. Further analyses of the data will not provide further evidence.

Peripheral oedema has been included in section 4.8 of the SmPC. At present, this is considered sufficient by the CHMP.

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]).

Upon request of the CHMP the Applicant submitted 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 (see Summary table of MACE analysis below).

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 were acknowledged by the CHMP.

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), gastrointestinal (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 gastrointestinal 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. Skin cancer and colon 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 populations. 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, neoplastic events have not been included in the RMP, and no additional pharmacovigilance activities are proposed. This was accepted by the CHMP. The Applicant will closely monitor as reflected in the RMP events of colon cancer in future PSURs; this is reflected in the RMP.

Medication errors were reported at a rate of 4.4 % (7.3 events per 100 PYE) and 2.2 % (4.2 events per 100 PYE) in the IDeg group and the comparator group, respectively. The medication errors were mainly due to mix-ups between bolus and basal insulin, occurring in 2.6 % in the IDeg group and 1 % in comparators. Approximately 40% of the mix-ups led to a hypoglycaemic episode, but in most cases the subjects managed their low blood glucose themselves. Reasons for mistaking basal insulin for bolus insulin were reported as patient distraction, injecting in the dark room, lack of training in relation to a new regimen or similar appearance of the trial devices.

In addition to the risk of mix ups-between basal and bolus insulin, a concern specific for IDeg, is the introduction of a new strength (200U/ml), with the potential for mix ups between Tresiba 200U/ml and an insulin preparation with the 100U/ml strength, which could result in a doubled dose. These medication errors could lead to severe hypoglycaemia and has the potential to be fatal. These concerns were subject to discussion at different stages of the procedure (see "Additional expert consultations"). During the procedure the Applicant justified that there is a medical need in EU for the 200U/ml Tresiba product, estimating the number of diabetics in the EU using ≥80 daily units of basal insulin to currently be between 200,000 – 700,000 patients. Furthermore, there are several clinical advantages with the higher strength product including potentially increased compliance, lesser medication errors linked to having to be split the dose into two injections and that the injection volume is lesser. This is supported by data from the clinical trial programme for IDeg, where the rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia, were in fact lower with the 200U/ml strength than with Tresiba 100 U/ml or IGlar, despite similar glycaemic control.

A third concern with regards to the IDeg products is the risk of mix-ups in patients with visual impairment. For subjects with inherited colour vision disorders, there may be an increased risk of mix-ups between basal and bolus insulin. Particularly, there may be an increased risk with NovoRapid, as the colour code for Novo Rapid is in the in the yellow colour range of the red, whereas Tresiba is in the yellow/green colour range. Furthermore, in subjects with impaired visual acuity, who may rely on the clicking sound made by the device rather than the visual dose read-out, there may be an increased risk of mix-ups between IDeg 200U/ml and insulins with the 100U/ml strength as IDeg 200 units/ml provides 2 units per click vs 1 unit per click in IDeg 100 units/ml. These concerns were discussed during the Diabetes/Endocrinology Scientific Advisory Group meeting. To address these concerns the Applicant further investigate the the impact of red-green colour blindness on the risk of mix-ups as

noted above in the post-marketing setting. The Applicant will also include that the patient should not count the pen clicks to select the dose as part of their educational material (see Risk Management Plan).

Several risk minimisation measures have been undertaken by the Applicant to minimise the potential risk for mix-ups. With regards to the 200U/ml strength, the design of the pens ensures that the display shows the number of units to be given no matter the strength of the product. Furthermore, the IDeg 200U/ml will be marketed as a prefilled pen injector only. The table below shows the differentiation features that have been applied in order to clearly differentiate Tresiba 100 units/ml from Tresiba 200 units/ml.

Regarding visually impaired patients the Applicant has revised the SmPC, the PL and the instructions for use (IFU), stating that patients with visual impairment should get assistance from a person with good vision who is trained in using the device. The Tresiba product therefore contains differentiation features other than the colour scheme.

	Prescriber	Pharmacy	Patient	Visually impaired
Withdrawal of 5 piece pack for Tresiba 200 units/ml – only 2 and 3 piece pack applied for	+	+	+	+
Coloured side panels on the carton		+	+	+
Stripes in dark green colour on all sides of the carton except bottom		+	+	+
Strength clearly visible on red background adjacent to the invented name		+	+	+
Strength prominently included on red background on all faces of the outer carton except bottom and additionally on the pen label		+	+	+
"Caution. The pen shows the dose - One step equals 2 units" added in box with red borders on the front panel ("Caution" printed in red)		+	+	+
Different pen orientation/presentation on front panel		+	+	(+)
Front panel on the carton without hexamer		+	+	
Double smart bar on front and back of carton		+	+	(+)
Difference in text lay-out on carton: size/weight		+	+	
Tactile elements on pen push button			+	+

Despite all the risk minimisation measures put in place, it is acknowledged that there will always be a potential risk of mix-ups between basal and bolus insulin and between the 200U/ml and 100U/ml strengths. Therefore, "Medication Errors Due to Mix-up between Basal and Bolus Insulin" and "mix-up between the two different strengths of Insulin degludec" are included in the RMP as potential risks and additional risk minimisation activities have been agreed by the CHMP (see section Risk Management Plan). This is accepted by the CHMP.

Diabetic retinopathy related events occurred at a similar rate with IDeg (5.1 events per 100 PYE) and comparators (5.6 events per 100 PYE). The majority of the events occurred after 6 months of treatment. Two events reported with IDeg, (one event of retinal haemorrhage in a subject with T1DM, and one event of diabetic retinopathy in a subject with T2DM), were assessed as serious. The event of retinal haemorrhage was assessed probably related to IDeg by the investigator while the event of diabetic retinopathy was assessed as unlikely related to IDeg.

A higher rate of diabetic retinopathy was reported in the Japanese subjects than the non-Japanese subjects; however, the rate was lower in the IDeg group than in the comparators. 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.

Peripheral neuropathy was reported at a lower rate in the IDeg group than in the comparators (IDeg: 5.8 events per 100 PYE and comparator: 7.1 events per 100 PYE). The majority of the events were mild and few were of moderate severity. The rates of peripheral neuropathy were higher in subjects with T2DM than in subjects with T1DM for both treatment groups.

Hyperglycaemia were reported at a similar rate in both treatment groups (IDeg: 1.1 events per 100 PYE and comparators: 1.0 events per 100 PYE). As expected, due to the nature of the disease, more events were reported in the subjects with T1DM than in the subjects with T2DM for both IDeg and comparators. Five (5) serious hyperglycaemia related events were reported with IDeg. One SAE of hyperglycaemia was reported with comparators. No events of hyperglycaemia were reported with IDeg, administered in a flexible regimen, in Trials 3668 and 3770.

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 was similar in the IDeg group and the comparators for subjects with T1DM (26 and 30 episodes per 100 PYE, respectively) and T2DM (2.6 and 2.7 episodes per 100 PYE, respectively). The rates of nocturnal severe hypoglycaemia were also similar between treatment groups.

In subjects with T2DM the majority of severe hypoglycaemia events were reported in the basal bolus trial. In subjects with T1DM the rate of severe hypoglycaemia was higher in the first three months whereas in T2DM the rate was constant throughout the 12 months. The occurrence of severe hypoglycaemia over time of day was similar with IDeg and the comparator. Among subjects reporting at least one episode of severe hypoglycaemia, the rate of confirmed hypoglycaemic episodes was similar between IDeg and comparator, but higher than that observed in the full population. Furthermore, in subjects with T2DM, the rate of nocturnal confirmed hypoglycaemic episodes was higher with IDeg than with comparator (393 vs. 278 episodes per 100 PYE, respectively), whereas in subjects with T1DM, the opposite was true (IDeg: 488 and comparator: 789 episodes per 100 PYE).

Also, episodes of severe hypoglycaemia was 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 (described in the efficacy section). 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). 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 event and deaths

The rate of SAEs was higher in the IDeg group (7.9%, 15.1 events per 100 PYE) than in the comparators (6.5%, 13.5 events per 100 PYE). As for all AEs, the difference between groups was more pronounced in subjects with T2DM (IDeg 7.8 %, 14.9 events and comparators 6.3%, 13.1 events per 100 PYE) than in subjects with T1DM (IDeg 8%, 15.5 events and comparators 7.1%, 14.9 events per 100 PYE). However, the number of events was low, and except for hypoglycaemia (see below), there was no significant differences in the distribution of SAEs between treatment groups.

In subjects with T1DM, ≥1% of subjects (both IDeg and comparators) reported SAEs in the *SOC Metabolism and nutrition disorders* (mostly related to hypoglycaemia), whereas in subjects with T2DM, ≥1% of subjects (IDeg and/or comparators) reported SAEs in the *SOCs Cardiovascular disorders* and *Infection and Infestations.*

In subjects with T1DM, the combined rate of *hypoglycaemic episodes* reported as SAEs was similar in both treatment groups. In subjects with T2DM, however, the rate was higher in the IDeg group than in the comparators (approximately 1.2 events per 100 PYE in the IDeg group and 0.6 events per 100 PYE in the comparator group). However, the number of serious events was low (IDeg n=27, comparator n=6) and the difference in reporting rate could, at least partly, be explained by the fact that more patients in the IDeg group than in the comparators reported events occurring after the administration of IAsp (44% vs. 33%) and events due to intentional overdose (n=2).

In total, 21 deaths were reported, 14/4275 (0.3%, 0.6 events per 100 PYE) in IDeg treated subjects and 7/2269 (0.3%, 6 events per 100 PYE) in subjects treated with comparators. One further death (sudden cardiac arrest) occurred 11 days after stopping treatment in the IDeg group and was not included in the analysis.

All deaths occurred in the therapeutic confirmatory trials. Of the 14 subjects who died in the IDeg group, 9 subjects died due to cardiovascular events. The other five subjects died due to different causes (haematemesis, anaemia secondary to myelodysplastic syndrome, drowning, traffic accident and suicide (hypoglycaemic coma)). Five subjects in the comparator arm died because of cardiovascular events.

The event of suicide (subject with T1DM) and the event of drowning was assessed as probably and possibly related to IDeg. The other fatal events with IDeg were assessed as unlikely related to IDeg.

The event of drowning concerned a 69-year-old male subject with T2DM, treated with IDeg with no reported medical history. The subject did not experience any hypoglycaemic event prior to entering the trial and after entering the trial the subject experienced 10 asymptomatic hypoglycaemic events with blood glucose values ranging from 43 to 68 mg/dl. The subject was reported to have drowned after 31 days of drug initiation. The subject had multiple traumatic injuries and the drowning was thought to have occurred as a consequence of the subject falling off a cliff.

In the pooled population of IDeg + IDegAsp, a total of 27 deaths were reported, 18 in the IDeg/IDegAsp group (0.3%) and 9 in the comparators (0.2%). There was no difference between treatment groups with respect to the type of events leading to death.

A total of 7 deaths have been reported in ongoing trials. All deaths were assessed as unlikely related to IMP.

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). 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. This 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, serious adverse events 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 T2DM and mild renal impairment, the rate of adverse events and serious adverse was similar in both treatment groups. Serious hypoglycaemic events were few, and the event rate was comparable between groups. The observed rates of confirmed hypoglycaemia were slightly higher for subjects with mild renal impairment than for subjects with normal renal function, but there was no

difference between IDeg and comparator (IDeg 664 vs. 527 episodes per 100 PYE and comparator products 661 vs. 582 episodes per 100 PYE).

In subjects with T1DM and mild renal impairment, the rate of AEs and SAEs was higher in the IDeg group than in the comparator group (AE's: IDeg 521.2 events/100 PYE vs. comparator 353.0 events/100 PYE). Adverse events related to hypoglycaemia, were more common with IDeg than with comparator (Hypoglycaemia: IDeg 16.3 events/100 PYE vs. comparator 0, hypoglycaemic unconsciousness: IDeg 8.2 events/10 PYE vs. comparator 6.7 events/100 PYE, hypoglycaemic coma: IDeg: 6.8 events/100 PYE vs. comparator 0). This difference was not seen with IDeg+IDegAsp.

Confirmed hypoglycaemic episodes were also more frequent in subjects with T1DM and mild renal impairment than in subjects with normal renal function in the IDeg group (6305 vs. 5108 episodes per 100 PYE). This difference was not seen with comparator products (5229 vs. 5252 episodes per 100 PYE). The difference may have been driven by between-trial differences in the proportion of subjects who had renal impairment at baseline. For IDegAsp, the results were somewhat conflicting, with a higher event rate of confirmed hypoglycaemia in the IDegAsp group than in the comparator group when the analysis was based on creatinine clearance (IDegAsp: 4254.0 events/100 PYE vs. comparator: 3975.5 events/100 PYE) but not when the analysis was performed using baseline serum creatinine (IDegAsp: 2909.9 events/100 PYE vs. comparator: 3573.5 events/100 PYE).

Overall, the differences in reporting rate seen with IDeg were relatively small and are not considered to impact the risk-benefit profile of the product in subjects with T1DM and 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. Hypoglycaemia associated with abnormal renal function is included as an identified risk in the RMP.

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 programme, 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 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 suspected 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 IDeg and the comparator group (IDeg n= 220, comparator n=145), and there was no difference between the treatment groups.

Two immunogenicity related events (both urticaria) were reported for these subjects, one in each treatment group. Both events were mild, non-serious and considered unlikely to be related to trial product by the investigator and the subjects continued in the trials.

There was no clinically relevant influence of insulin antibodies on HbA1c or dose calculated using Spearman correlation coefficients. Furthermore, the rates of severe hypoglycaemia and nocturnal severe hypoglycaemia were lower in the IDeg than in the comparator group in patients with antibodies. It is acknowledged that the clinical programme for IDeg and IDegAsp is extensive with 3733 subjects in the IDeg/IDegAsp group tested for antibodies at week 0, 2261 subjects tested at week 27 and 1233 subjects tested at week 53. 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, in line with what has been requested of other insulin products, "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. This risk has also been reflected in section 4.4 of the SmPC.

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 proportion of all subjects discontinuing due to AEs were low for both IDeg (2.3%, 4.7 events per 100 PYE) and comparators (1.3%, 2.4 events per 100 PYE), but was higher in the IDeg group. A possible explanation for this difference is that in the comparator group many patients continued on

their usual treatment. Nearly half of the AEs leading to withdrawal in IDeg group and the majority of AEs in the comparators group were SAEs.

Hypoglycaemia was the most common reason for withdrawal in subjects with T1DM, and was reported with a higher frequency in the IDeg group than in the comparator group for both patients with T1DM and T2DM (see below). The AEs leading to withdrawal in subjects with T2DM were mainly cardiovascular disorders and increase in weight. These events were reported in a similar proportion of patients in both treatment groups.

Discontinuation due to hypoglycaemia was more common in the IDeg group than in comparators particularly in subjects with T1DM (T1DM: IDeg 2.5%, comparator 0.9%, T2DM: IDeg 0.6%, comparator 0.3%). However, the number of subjects withdrawn due to hypoglycaemia was generally very low. Furthermore, in the IDeg group (T1DM), two SAEs leading to withdrawal were due to intentional overdose. Also, the withdrawals were evenly distributed over time and there is no indication that they occurred more frequently in the transition period. It is thus most likely that an increased awareness of the investigational drug in the open-label trials as well as the fact that a large part of subjects from the comparator groups were randomised to their pre-trial insulin therapy were responsible for the differences observed.

In the IDeg FF trials where IDeg was administered with alternating narrow and wide dosing intervals, the rates of hypoglycaemia in subjects with T1DM and T2DM were similar between treatment groups. Slightly more patients with T1DM withdrew due to events of hypoglycaemia in the IDeg groups than in the comparators, but the withdrawal rate was similar with IDeg OD and IDeg FF.

2.6.1. Discussion on clinical safety

In the 41 completed clinical trials constituting the clinical development program for IDeg, a total of 5624 subjects were exposed to IDeg. The assessment of safety in subjects with T1DM and T2DM was mainly based on the 11 completed therapeutic confirmatory trials, representing the major part of the exposure. In these trials 4275 subjects were exposed to IDeg, 3758 subjects for at least 6 moths and 1635 subjects for at least 12 months. The exposure of patients with T1DM and T2DM to IDeg at dose levels intended for clinical use is considered sufficient to assess the safety of the product.

Overall the incidence of AEs, SAEs, AEs assessed as possibly or probably related to IDeg and AEs leading to withdrawal was slightly higher in the IDeg group than in the comparator group. However, the vast majority of AEs were mild or moderate in severity and the distribution of AEs was similar between groups. 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 IDeg group than in the comparators. These differences were most pronounced for the PTs headache, wrong drug administered, muscle spasm, weight increased, upper respiratory tract infection (T1DM), gastroenteritis (T1DM), urinary tract infection (T1DM), constipation (T1DM), depression (T1DM), insomnia (T1DM), nasopharyngitis (T2DM), peripheral oedema (T2DM) and dyspnoea (T2DM). 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. SAEs were slightly more common in the IDeg group than in the comparators, but (except for hypoglycaemia) there was no specific pattern or clustering of events.

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). Serious events of hypoglycaemia (mainly in T2DM) were slightly more common in the IDeg group than in the comparator group. This could, at least partly, be explained by the fact that more patients in the IDeg group than in the comparators reported events occurring after the administration of IAsp (44 % vs. 33%) and events due to intentional overdose (n=2). Discontinuations due to hypoglycaemia were slightly more common in the IDeg group than in the comparator group in subjects with T1DM (due to hypoglycaemia, withdrawal criteria and "other reasons"), while withdrawals were comparable between IDeg and comparator in T2DM patients. The withdrawals were, however, evenly distributed over time and there is no indication that they occurred more frequently in the transition period. It is thus most likely that an increased awareness of the investigational drug in the open-label trials as well as the fact that a large part of subjects from the comparator groups were randomised to their pre-trial insulin therapy were responsible for the differences observed.

The rate of severe hypoglycaemia was similar in both treatment groups, in subjects with T1DM and T2DM. 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 higher frequency in the IDeg group than in the comparator group, and lead to a hypoglycaemic episode in approximately 40 % of cases. 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. Another concern with IDeg, however, is the potential for mix up between IDeg 200U/ml and other insulin products with the strength 100U/ml. Furthermore, there may be an increased risk of mix-ups in subjects with impaired visual acuity or in subjects that are colour-blind. To minimise these risk for mix-ups, the Applicant has implemented several risk minimization measures. In addition to this the applicant will investigate in the post-marketing setting, the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness (see Risk Management Plan and Pharmacovigilance measures). With regards to visually impaired patients, relevant information has been included in the SmPC and PIL, stating that these patients should get assistance from a person with good vision who is trained in using the device. With regards to the 200U/ml strength, the design of the pens ensures that the display shows the number of units to be given no matter the strength of the product. Furthermore, the IDeg 200U/mL will be marketed as a prefilled pen injector only. In addition, comprehensive differentiation features, have been applied to the injection pen intended for marketing.

These risk minimisation activities are considered appropriate. However, the risk minimisation measures will not completely eliminate the risk of mix-ups between basal and bolus insulin and between the 200U/ml and 100U/ml strengths. Therefore, "Medication Errors Due to Mix-up between Basal and Bolus Insulin" and "mix-up between the two different strengths of Insulin degludec" have been included in the RMP as potential risks, which is endorsed.

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, as reflected in the RMP, 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. Furthermore, the development of antibodies did not appear to affect clinical efficacy or safety. However, the low number of subjects developing antibodies may not have been sufficient to establish any efficacy or safety issues; therefore, immunological events 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 in response to the second D180 LoOI including 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 and >75 years is in accordance with the ICH E7 guideline. Exposure to IDeg + IDeg/Asp in the subgroup of subjects with T1DM >75 years was low 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. In subjects with T2DM, there was no between group differences in the safety profile of IDeg+IDegAsp in subjects with mild renal impairment. In type 1 diabetics with mild renal impairment, there were more adverse events including hypoglycaemic adverse events and confirmed hypoglycaemic episodes in the IDeg group than in the comparator group. For IDegAsp the data on hypoglycaemic episodes in mild renal impairment was conflicting. Overall, the differences were relatively small and are not considered to impact the benefit-risk profile of the product in subjects with T1DM and 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. 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.

Additional expert consultations

During the initial marketing authorisation procedure for Tresiba concerns were raised with regards to the introduction of a new strength (i.e. 200 units/ml), and whether sufficient measures had been put in place to ensure the safe and correct use of the new high strength concentration (see "Medication errors"). As such a first Healthcare Professional and Patient Organisation consultation was launched to request feedback on these issues. The comments received in this consultation prompted the CHMP to further discuss the introduction of the new strength and lead to the introduction of a major objection with regards to the benefit/risk of the new strength and the risk minimisation measures put in place to avoid medication errors.

The Applicant responses to the major objection addressed both the need for the new high strength in the EU and also included a differentiation strategy to reduce medication errors between the two insulin degludec strengths, insulin degludec and insulin degludec/aspart, and with other insulins products (see "Medication errors"). After assessment this strategy there remained concerns with regards to the risk minimisation and medication errors, and a second Healthcare Professional and Patient Organisation consultation was initiated, in particular with regards to reviewing the educational materials proposed by the applicant. The comments from the second consultation were more positive than the first, and it was acknowledged that clear steps had been taken to differentiate the new strength from other 100 units/ml insulins. The CHMP however, acknowledging that the introduction of a new strength into the market was an important change in the way diabetic patients were treated requested one last formal consultation by the Diabetes/Endocrinology SAG. The SAG was asked to address questions on

the benefit/risk of the new 200 units/ml formulation and the risk minimisation put in place to reduce the risk of medication errors. The SAG concluded as follows:

1) **Please discuss the benefits and risks of the introduction of a new insulin strength in clinical practice taking into account the current use of insulin pen devices versus the more extended use of insulin syringes in the past.**

The SAG almost unanimously agreed to the need and welcomed the introduction of higher strength insulins. It was pointed out that already higher strength insulins (500 unit/ml) are in use, even though not approved in the EU, and this situation was unsatisfactory. One expert still remained unconvinced and maintanined that one strength was still the simpler solution with less possibility of leading to medication errors, and that if 200 units/ml were to be introduced this should be done with a well planned communication campaign.

However, the SAG pointed out that this represents an important change for all parties involved in the treatment of diabetes and that there is a need to prepare the market for the introduction of the new strength. It was emphasized by some experts that health care systems may be not fully be prepared for the change as only 100 unit/ml insulins are currently used in the EU. A particular concern was raised that electronic prescribing systems, paper charts etc. would need to be modified for that purpose. It should be avoided launching the product without the healthcare professional community being fully aware of the change. Some members of the SAG expressed that this should be a joint effort between the EMA, Applicant and relevant Scieintific and Professional Societies and that some time may be needed to achieve this. The EMA expressed that at the time of approval a dedicated press release would be prepared emphasizing the risk minimisation to be put in place and possible points to consider by healthcare providers. The EMA will further discuss internally what actions can be taken to further prepare the market.

It was agreed that the use of a prefilled pens for this strength was the best solution to avoid errors. However it was stressed that in some instances nurses for example did not know how to use the pen properly and it may occur that the product is extracted from the pen into a syringe leading to potential medication errors. The SAG also agreed that the highest risk of error would be due to attempts by the user to perform a conversion of the dose with the new strength, which should be more explicitly warned against. It was also considered that there could be more medication errors at patient level if the patient had just been transferred to the high concentration and had the 2 pens with different strengths at home.

The SAG agreed on the fact that "what you dial is what you get" will minimise the risk of medication errors at patient level and that more risk would be found at the level of prescribing and dispensing. There was concern with regards to the use of this new strength in visually impaired patients and the fact that 2 units equals 1 click, vs. the usual 1 unit 1 click, and that if patients relied on this audible cue this would be a problem. However, patient representatives pointed out that with this pen it would be very unlikely that dose selection by the patient could be performed relying on clicks only anyhow. The SAG agreed that dosing in 1 unit steps would be preferable. Questions were raised as to whether studies in colour blind patients had been performed.

There were discussions about the difference of effect seen between using the 200 unit/ml and the 100 unit/ml presentations. These differences were probably due to better compliance; this was noted as speculation by the Applicant who confirmed that bioequivalence between the 2 Tresiba strengths had been shown. Some patient representatives in the meeting noted that using a lower injection volume is seen as advantageous as often injections are painful. On the other hand, they also noted that the speed at which the pen administered the dialed dose was rather high, and could be more painful and would perhaps lead to more injection site reactions.

One expert considered the consequence of receiving the 100 U/mL instead of the 200 U/mL pen and vice versa for the patient as rather minimal compared with the risk resulting from receiving a different type of insulin. The same expert also suggested that the main message of warning in the educational material should be directed to the warning not to do a dose conversion, which is not needed, but which was required in the past when using different strength insulins with the same syringes.

Participants questioned the suitability of the suggested pen system for paediatric use. During the discussion the Applicant confirmed that Tresiba 100 unit/ml and 200 unit/ml will only be indicated in adult patients until the ongoing paediatric study is finalized.

Having taken into account the above reservations, the general view of the SAG was that the benefit/risk of the new 200 unit concentration was positive and welcomed the introduction of the new strength, in particular due to the fact that "what you dial is what you get" with both strengths.

2) Please discuss the adequacy of the proposed risk minimisation measures with the aim to mitigate the risk of mix up between the 200 U/ml strength and 100U/ml insulin preparations. In order to do so, please review the following documents and propose possible improvements if necessary:

a. The wording of the product information: summary of product characteristics (SmPC), package leaflet and labelling.

b. The pre filled pen: labelling, tactile features, pen dosing in 2 units versus 1 unit.

c. Pack design/Layout of the product information.

There were discussions about the name the product would have and how this would translate into prescribing errors. Some participants suggested that 2 different names may reduce the frequency of wrong prescriptions. Different options for naming the product such as having a different name for each strength, having the strength linked to the name, or having a qualifier such as "forte" were discussed, together with how these would affect the risk of medication errors. The fact that other companies will also have new and possibly different strengths on the market in the future was also noted. None of the proposals however seemed to be able to address the issue of potential medication errors and hence it was agreed that at this point in time it may be best to leave the name as it currently stands.

The difference in pack sizes between Tresiba 100 unit/ml and 200 unit/ml was noted, and some experts commented on the fact that having a bigger box (5 prefilled pens) for the 100 unit/ml, vs. a smaller box (3 prefilled pens) for the 200 unit/ml seemed somewhat counterintuitive. The SAG however finally concluded that the important fact was that the pack sizes were actually different, which was supported unanimously. No further recommendation on this point was given. It was mentioned that the red box highlighting the 200 unit/ml was a good way to differentiate the 2 strengths and that ultimately the important points were the dose counter and the steps.

Some members raised the possibility of including restrictions in the SmCP to limit the target population to receive the 200 unit/ml (e.g. BMI; doses higher than 80 units, type 2 DM patients). It was however agreed that this decision was best left to the prescriber, rather than limit the indication and restrict the use of product for patients who could potentially benefit from it.

It was noted that the packaging of the product did not include a barcode and that this was key in order to ensure that the right product was being dispensed. The SAG stressed that the barcode should be present on both the carton and the pen (particularly important in hospital setting). The Applicant responded that the final version of the carton will include a 2D barcode but that the pen label would be limited by the size and would not include it, unless other features would be made smaller

One of the experts noted that there was no wording in the information to patients regarding non-medical diabetes treatment, and also that with the current mobility patients have it would be good to give some instructions about whether they would be able to obtain the product in other countries.

The dose window and the numbers on the pen were said to be too small by some experts, although other experts agreed that this was better than some other pens on the market. The SAG agreed that it would be of interest to user test this in the future.

3) **The Applicant has also proposed, as part of their established educational program in diabetes several educational leaflets for patients and healthcare professionals. Could you please comment on whether you consider these materials adequate or if they could be further improved?**

During the discussions it was noted that the use of the words "strength", "concentration" and "formulation" were used interchangeably and that the Applicant should consider using only one of these. The use of the term "formula" was also proposed instead of strength. It was stressed that the key message was that 1 unit of 100 units/ml equals 1 unit of 200 units/ml, but that 200unit/ml delivers the same units in half the volume.

The main patient educational leaflet was considered to be too promotional and was not endorsed by the SAG. The experts agreed that the letter to healthcare professionals and the one page information leaflet for patients were acceptable. As important improvements the SAG suggested that the leaflet should mention that the patient should dial the dose recommended by their healthcare provider (this wording would perhaps induce fewer errors than saying "do not convert the dose yourself") and that an attempt to use the product in syringes should never be undertaken. It was also stated that a better understanding of pen usage was sometimes needed at hospital level.

4) **Would you consider useful the development of any additional educational materials for patients and for HCP (prescribers, nurses and pharmacists) aiming to increase awareness and prevent medications errors and to support educational of patients. For example: dosing or reminder cards?**

The SAG did not identify the need for any additional education material.

5) **The applicant has proposed the use of a follow-up questionnaire in case of reports of medication errors (with or without adverse drug reactions). Could you please comment on the proposed questionnaire?**

The follow-up questionnaire was considered to be in need for improvement, according to some experts, and that the coding of medication errors needed to be taken into account. An expert from the SAG also noted that medication error information could not be included in the standard AE reporting form. On the suggestion of one expert, information from the WHO Pharmacovigilance programme in collaboration with the Uppsala Monitoring centre will be provided to the Applicant to review and help to improve the follow up form.

2.6.2. Conclusions on the clinical safety

Overall, the results of the clinical studies demonstrate that the use of IDeg in patients with T1DM and T2DM as monotherapy or in combination with oral antidiabetic agents is 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, which included a risk minimisation plan.

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 (see sections 4.5, 4.8 and 4.9). • 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 symptoms may disappear in patients with long-standing diabetes. • Concomitant illness, especially infections and fever, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose. • As with other basal insulin products, the prolonged effect of Tresiba 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 glucose metabolism. • The following substances may reduce the insulin requirements: Oral anti-diabetic medicinal products, GLP-1 receptor agonists,

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides. • The following substances may increase the insulin requirements: Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone 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' • 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, 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 or other products containing sugar. 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 healthcare professional. Glucose must be given

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		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 'Contraindications' • Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. • 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 Tresiba, hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.
Important potential risks		
Medication errors due to mix-up between basal and bolus insulin	Routine pharmacovigilance (including structured follow-up forms) Additional pharmacovigilance: • A study/survey to investigate the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness	Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder, as well as tactile elements on the pen push button SmPC • Section 4.4 'Special warnings and precautions for use' • Avoidance of medication errors: Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two concentrations of Tresiba and other insulin products. 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

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		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. • Tresiba 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 the insulin you need, 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 and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Tresiba FlexTouch pen.
Medication errors due to mix-up between the different concentrations of Tresiba	Routine pharmacovigilance (including structured follow-up forms) Additional pharmacovigilance: • A study/survey to investigate the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness.	Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder, as well as tactile elements on the pen push button SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • Tresiba is available in 2 concentrations. For both, the needed dose is dialled in units. The dose steps, however differs between the two concentrations of Tresiba. • With Tresiba 100 units/ml a dose of 1-80 units per injection, in steps of 1 unit, can be administered. • With Tresiba 200 units/ml a dose of 2-160 units per injection, in steps of 2 units, can be administered. The dose is provided in half the volume of 100 units/ml basal insulin products. • The dose selector shows the number of units regardless of concentration and no dose conversion should be done when transferring a patient to a new concentration. • Section 4.4 'Special warnings and precautions for use' • Avoidance of medication errors: Patients must be instructed to always check the insulin label before each injection to avoid

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		accidental mix-ups between the two concentrations of Tresiba and other insulin products. 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. Patient Information • Start by checking your pen to make sure that it contains the insulin you need, then look at the illustrations to get to know the different parts of your pen and needle. • For Tresiba 100U/ml: Check the name and concentration on the label of your pen, to make sure that it contains Tresiba 100 U/ml. • For Tresiba 200U/ml: Check the name and concentration on the label of your pen, to make sure that it contains Tresiba 200 U/ml. • Do not use your pen without proper training from your doctor or nurse. • If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Tresiba FlexTouch pen. Direct healthcare professional communication, a poster for display in pharmacies/diabetic units and a patient education leaflet are being prepared to help mitigate the risk of medication errors
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/limited information		
Pregnant and lactating women	Routine pharmacovigilance	SmPC, Product Label and Patient Information Section 4.6 'Fertility, pregnancy and lactation' • Pregnancy • There is no clinical experience from the use of Tresiba 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 decrease in the first trimester and increase subsequently during the second and third trimester. After delivery, insulin requirements usually return rapidly to pre-pregnancy values. • Breast-feeding • There is no clinical experience with Tresiba 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 is excreted in human milk. No metabolic effects of insulin degludec are anticipated in the breast-fed newborn/infant. • Fertility • Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility.
Children and adolescents < 18 years	Routine pharmacovigilance and 3b trial	SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • Safety and efficacy of Tresiba 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' • Tresiba has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties. (see Section 5.2 of SmPC). Safety and efficacy have not been investigated

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		in children and adolescents. • Section 5.2 'Pharmacokinetic properties' • Pharmacokinetic properties of insulin degludec were investigated in children (6–12 years) and adolescents (12–17 years) and compared to adults with type 1 diabetes mellitus. The properties of Tresiba seen in adults are preserved in children and adolescents. Total exposure after a single dose is higher in children and adolescents than in adults with type 1 diabetes mellitus.
Hepatic impairment	Routine pharmacovigilance	SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • Tresiba 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 is no difference in the pharmacokinetics of insulin degludec 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	SmPC, Product Label and Patient Information • Section 4.2 'Posology and method of administration' • Tresiba 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 elderly patients and in patients with renal or hepatic impairment do not

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		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 Tresiba between elderly and younger adult subjects.
Co-administration with GLP-1	Routine pharmacovigilance Additional pharmacovigilance: • Clinical trial 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 the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
A protocol for a study/a survey with the objective of investigating the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness.	18 July 2013
A final study report for a study/a survey with the objective of investigating the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness.	Within 6 months of approval of protocol by CHMP
A draft follow-up questionnaire in case of reports of medication errors (with or without adverse drug reactions) within 1 month of Commission Decision.	Within a month of Commission Decision (Jan 2013)

The following additional risk minimisation activities were required:

Educational pack which should contain the following elements:

- Dear Healthcare Professional Communication letter as described below;
- Summary of Product Characteristics and Package Leaflet;

- Poster for display in pharmacies/diabetic units;
- Patient Brochures.

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

- That Tresiba is available in 2 strengths;
- Key differences in the design of the packages and the prefilled pen devices;
- When prescribing to make sure that the correct strength is mentioned in the prescription slip;
- Always check the insulin label before dispensing to make sure the correct strength is delivered to the patient;
- Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;
- Do not use outside of the prefilled pen device (e.g. syringes);
- Reporting of medication errors or any side effects.

The patient brochure shall contain the following key elements:

- That Tresiba is available in 2 strengths;
- Key differences in the design of the packages and the prefilled pen devices;
- Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;
- Patients who are blind or have poor vision must be instructed always to get help/assistance from another person who has good vision and is trained in using the insulin device;
- Always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose;
- Check how many units were selected before injecting the insulin;
- The dose counter shows the number of units regardless of strength and no dose conversion should be done;
- Reporting of medication errors or any side effects.

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

Insulin degludec (IDeg) is a new 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 glutamic acid spacer.

Insulin degludec is intended for once-daily dosing in subjects with type 1 diabetes mellitus (T1DM) and subjects with type 2 diabetes mellitus (T2DM). To accommodate the wide range of insulin requirements, insulin degludec has been developed both as IDeg 100 units/ml and IDeg 200 units/ml.

Benefits

Beneficial effects

The pharmacodynamic profile has been investigated in both T1DM and T2DM patients, confirming a flat profile. Dose-response was investigated in an adequate dose range and was shown to be proportional in T1DM patients and linear in T2DM patients. The potency of 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. The intra-individual variation of IDeg was studied in T1DM patients at steady state, and was shown to be significantly lower than for the comparator insulin glargine (IGlar). A lower variability may indicate a lower risk for both hypo- and hyperglycaemia; this however would have to be confirmed in clinical use. The pharmacodynamic properties of IDeg 200 U/ml did not differ from those observed for IDeg 100 U/ml when compared in a cross-over trial in T1DM patients.

The efficacy and safety of IDeg has been investigated in an extensive clinical program comprising nine confirmatory trials in both T1DM and T2DM subjects. The T1DM trials include 1578 patients and the T2DM trials include 4076 patients.

The populations recruited are considered representative for the target population. European patient were well represented (more than 30 % of patients) both in the T1DM trial and the T2DM trials. The pre-trial 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 pre-trial to ensure that these patients were true treatment failures. Co-administration of all OADs in different combinations (excluding GLP-1 inhibitors where coadministration with insulin is not included in the label) were allowed in the T2DM studies.

Efficacy in terms of HbA1c-lowering effect was confirmed in both T1DM and T2DM patients in clinical trials of 26 to 52 weeks duration. One trial in T2DM patients investigated IDeg 200 U/ml as basal insulin therapy. When IDeg was introduced to insulin-naïve patients a staring dose of 10 U was applied whereas patients already on insulin treatment were switched on an unit-to-unit basis. IDeg was shown to be non-inferior to the insulin comparator in all trials. In one trial in T2DM patients, sitagliptin was used as comparator and in this trial IDeg showed superiority. Clinically relevant HbA1c reductions were achieved (0.6% in T1DM trials and 1.2 % in T2DM trials).

The secondary endpoints that concerned the glucose-lowering effect were in support of the primary endpoint. A larger decrease in FPG was observed with IDeg compared to IGlar. This was, however, not transformed into a larger decrease in HbA1c and the Applicant hypothesises that this may be due to lower nocturnal glucose levels with the comparator. The benefits of lowering FPG without a concomitant decrease in HbA1c could be debated.

Since all but one of the studies was 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 3.9 mmol/l in line with the scientific advice; these data were in line with the data using the lower cut-off. In both T1DM and T2DM patients, the rate of nocturnal hypoglycaemia was lower with IDeg than with the comparator. This was confirmed in a pre-planned meta-analysis. Confirmed hypoglycaemias were less common with IDeg in T2DM patients whereas no significant lowering was observed in T1DM patients. A reduction in nocturnal hypoglycaemias has been consistently shown across 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.

An increase in body weight is expected when insulin therapy is intensified and results in lower HbA1c. No difference in the effect on body weight was observed compared to IGlar.

The current application includes a new strength of insulin (200 U/ml) in a prefilled pen allowing the administration of 160 U in one single injection. There are increasing numbers of diabetes patients using high insulin doses due to obesity causing high insulin resistance. The higher strength in combination with the possibility to administer up to 160 U/injection reduce the need for double injections at the same dosing occasion which is likely to increase treatement compliance and reduce the risk of dosing errors. Furthermore the volume to be injected is reduced.

Uncertainty in the knowledge about the beneficial effects

The Applicant proposed that the reduced variability observed with 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 variability in SMPG or fluctuations in interstitial glucose levels were not different with IDeg 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 IDeg the most commonly reported AEs in both treatment groups were nasopharyngitis (IDeg: 15.0 % vs. comparator 12.3%), headache (IDeg: 9.5% vs. comparator 7.5%), upper respiratory tract infection (IDeg: 8.7% vs. comparator 7.7%) and diarrhoea (IDeg 5.7% vs. comparator 6.7%).

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, there were no major differences between treatment groups in the rate of serious or severe hypoglycaemic events in subjects with T1DM (IDeg 13.1% and 27.1 events per 100 PYE vs. comparator 11.7% and 30.5 events per 100 PYE) or T2DM (IDeg 1.4% and 2.4 events per 100 PYE vs. comparator 1.3% and 2.2 events per 100 PYE). The proportion of subjects with serious hypoglycaemic events was slightly higher for IDeg than comparators in subjects with T2DM (IDeg 0.7% vs. comparator 0.4%), as was the proportion of subjects with T1DM discontinuing due to hypoglycaemia (IDeg 2.5%, comparator 0.9%) and T2DM (IDeg 0.6%, comparator 0.3%).

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%). There were three cases assessed as serious with IDeg and none with comparators.

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 incidence was similar between treatment groups (IDeg: 3.8% vs. comparator 3.7%).

The incidence of peripheral oedema was comparable in both IDeg and comparators arms (2.4% vs. 1.7%, 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 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 current application includes a new strength of insulin (200 U/ml) compared to all currently approved insulin products, which have the strength 100 U/ml. This could potentially lead to a risk of mix-up between Tresiba 200U/ml and other insulin preparations, which may result in a doubled dose potentially causing severe hypoglycaemia. The medical need for the 200 U/ml strength has been justified and several risk minimisation measures, including differentiation features to the insulin pens, has been implemented. These are considered sufficient. However, the introduction of a new insulin strength is a significant change and careful consideration should be given to how this product is introduced safely on the market. Furthermore, the risk minimisation measures introduced are unlikely to completely eliminate the risk of mix-ups. Therefore, "Medication Errors Due to Mix-up between Basal and Bolus Insulin" and "mix-up between the two different strengths of Insulin degludec" have been included in the RMP as potential risks. Additional risk minimisation activities will also be put in place by the Applicant to raise awareness of the introduction of the new strength and to reduce the risk of medication errors.

The development of specific IDeg antibodies or insulin cross reacting antibodies was generally low in both treatment groups (IDeg n=220, comparator n=145). No clinically relevant 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 ability of an insulin to maintain normal glucose levels without large fluctuations in blood glucose is of great importance in both T1DM and T2DM patients. The predictability of the effect is of importance and thus the lower variability shown for IDeg may therefore be beneficial.

As the aim of insulin treatment is to normalise glucose levels, especially in younger patients, the risk of experiencing hypoglycaemia hampers successful treatment. The lowered risk for nocturnal hypoglycaemias shown for IDeg is therefore of importance. In T2DM the overall risk for hypoglycaemias was also reduced.

Overall, the results of the clinical studies demonstrate that the use of IDeg 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 there are no indications of increased CV risk.

The medical need for the 200U/ml strength has been justified and several risk minimisation measures have been implemented. However, with the new strength, there will be a potential risk of mix-ups, and these cases should be closely monitored post marketing. Also, considering that this is the first time in many years that a new insulin strength is introduced on the EU market, it is important to ensure that relevant information is communicated promptly and effectively, as such additional risk minimisation in the form of an educational programme (DHPC, posters, patient leaflets) will be put in implemented by the Applicant. Relevant stakeholders (i.e. patient organisations and health care professionals) have been consulted regarding the need for, and the content of the information to prescriber and patients.

Conclusion on the benefit-risk balance

In view of all the above considerations the CHMP concluded that the overall benefit risk balance for the Tresiba 100 units/ml strength and the 200 units/ml strength is 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 Tresiba in the treatment of 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 7) 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

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

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

The educational pack should contain:

- Direct Healthcare Professional Communication letter as described below;
- Summary of Product Characteristics and Package Leaflet;

- Poster for display in pharmacies/diabetic units;
- Patient Brochures.

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

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

- That Tresiba is available in 2 strengths;
- Key differences in the design of the packages and the prefilled pen devices;
- When prescribing to make sure that the correct strength is mentioned in the prescription slip;
- Always check the insulin label before dispensing to make sure the correct strength is delivered to the patient;
- Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;
- Do not use outside of the prefilled pen device (e.g. syringes);
- Reporting of medication errors or any side effects.

The patient brochure shall contain the following key elements:

- That Tresiba is available in 2 strengths;
- Key differences in the design of the packages and the prefilled pen devices;
- Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;
- Patients who are blind or have poor vision must be instructed always to get help/assistance from another person who has good vision and is trained in using the insulin device;
- Always use the dose recommended by your healthcare provider;
- Always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose;
- Check how many units were selected before injecting the insulin;
- The dose counter shows the number of units regardless of strength and no dose conversion should be done;
- Reporting of medication errors or any side effects.

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

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 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/44/2010 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).