Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for insulin degludec (rys)

Proprietary Product Name: Tresiba Penfill, Tresiba FlexTouch

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Report: March 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee for Prescription Medicines
ACS	Acute coronary syndrome
ACSOM	Advisory Committee on the Safety of Medicines
AE	Adverse event
AMI	Acute myocardial infarction
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration time curve
BIAsp 30	Biphasic insulin aspart
BD	Twice daily
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD-Epi	Chronic kidney disease epidemiology collaboration
CRF	Case report form
CSR	Clinical study report
CVOT	Cardiovascular Outcomes Trial
DPP4	Dipeptidyl peptidase-4
DPP4i	Dipeptidyl-peptidase 4 inhibitor
EAC	Event adjudication committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full analysis set

Abbreviation	Meaning
FDA	Food and Drug Administration
FF	Fixed flexible
GIR	Glucose infusion rate
glin	Glinide
GLP1	Glucagon-like peptide-1
HbA_{1c}	Glycated haemoglobin
IAsp	Insulin aspart
IDeg	Insulin degludec
IDegAsp	Insulin degludec (rys)/insulin aspart (rys)
IDet	Insulin detemir
IGlar	Insulin glargine
INR	International normalised ratio
ISS	Integrated Summary of Safety
IV	Intravenous
MAA	Marketing authorisation application
MACE	Major Adverse Cardiovascular Event
MACE (ISA)	Major Adverse Cardiovascular Event (Integrated safety analysis)
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
OAD	Oral antidiabetic drug
OD	Once daily
PBRER	Periodic benefit–risk evaluation report
PD	Pharmacodynamic
PK	Pharmacokinetic
PSUR	Periodic safety update report

Abbreviation	Meaning
PYE	Patient years of exposure
Ref	Reference
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SU	Sulphonylurea
SUSAR	Suspected unexpected adverse drug reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TIA	Transient ischaemic attack
U	Units
UAP	Unstable angina pectoris
US	United States
α-GI	Alpha-glucosidase inhibitor

1. Introduction

This was a resubmission to register a new biological substance, insulin degludec (rys) (also referred to as IDeg).

1.1. Drug class and therapeutic indication

Insulin degludec (rys) is an ultra-long acting form of insulin.

The proposed indication is:

'to improve glycaemic control in adult patients with diabetes mellitus'.

1.2. Dosage forms and strengths

The proposed dosage forms/strengths are shown below in Table 1.

Table 1: Proposed dosage forms/strengths

Active ingredients	Trade name	Dosage forms/strengths
Insulin degludec (rys)	Tresiba FlexTouch	FlexTouch100 U/mL, 3 mL solution for injection in prefilled pen FlexTouch 200 U/mL, 3 mL solution for injection in prefilled pen
	Tresiba Penfill	Penfill 100 U/mL, 3 mL solution for injection in cartridge

2. Clinical rationale

2.1. Background

2.1.1. Information on the condition being treated

Diabetes mellitus is associated with chronic hyperglycaemia due to either inadequate insulin production, insulin resistance or a combination of the two. Long term ocular, peripheral nervous system, renal and arterial damage can result.

There are predominantly 2 types of diabetes:

- Type 1: immune mediated pancreatic cell destruction results in insulin deficiency. Type 1 diabetes mellitus (T1DM) most commonly develops in childhood.
- Type 2: a combination of gradual insulin resistance and failure of the pancreas to produce sufficient insulin. Type 2 diabetes mellitus (T2DM) most commonly develops in adulthood.

In Australia, the estimated prevalence of adults with diabetes (both type 1 and 2) in 2011 to 2012 was 5.4% and in 2013, over 6000 children (aged 0 to 14 years) were estimated to have T1DM.[1] T2DM is by far the most common type of diabetes; an estimated 849 000 adults (4.7%)

[1] Australian Institute of Health and Welfare (AIHW) webpage

reported that they have type 2 diabetes in 2011 to 2012, although this is thought to be an underestimate. It is estimated that in 2011, 36,263 Australians started using insulin to treat type 2 diabetes (164 people per 100 000 population) and the incidence of insulin use for type 2 diabetes increases with age; it is estimated that there is a five fold increase in the use of insulin between the ages of 40 to 44 and 70 to 74 years.[2]

2.1.2. Current treatment options

2.1.2.1. Type 1 diabetes mellitus

Insulin is the cornerstone of treatment.[3] Insulin needs may be considered in terms of:

- Basal insulin, which is the background requirement of insulin and is independent of carbohydrate needs. This is usually administered via long or intermediate acting insulin once or twice a day; and
- Bolus insulin, which includes prandial insulin to cover oral carbohydrate intake and correction doses which are used to manage very high blood glucose levels. This is usually administered with short or very short acting insulin formations.

2.1.2.2. Type 2 diabetes mellitus

Initial treatment usually starts with addressing lifestyle factors. As per current Therapeutic Guidelines, if glycaemic targets are not met with addressing lifestyle factors, metformin is recommended as first line therapy.[3] If glycaemic targets are still not met, current options include a sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon like peptide-1 (GLP-1) agonist, SGLT-2 inhibitor, thiazolidinedione, acarbose or insulin. For patients with type 2 diabetes, insulin therapy is generally started as a once daily basal insulin injection however some patients may require more intensive treatment. Insulin is usually started in combination to an oral hypoglycaemic therapy.

The following insulin formulations are available in Australia, as shown below in Table 2.

Table 2: Australian Register of Therapeutic Goods (ARTG) registered insulin formulations in Australia

Type	(Relative) Duration of action	Active ingredient	Brand name
Basal	Long acting	detemir	Levemir
		glargine	Lantus, Toujeo, Optisulin
	Intermediate acting	Isophane (protamine suspension)	Humulin NPH, Protaphane, Hypurin Isophane

Adapted from Table 5.4 in 'Diabetes: management', Endocrinology, eTG Complete. Additional information from ARTG website (current as of 6 October 2016).

[2] Incidence of insulin treated diabetes in Australia 2000 to 2011, Australian Institute of Health and Welfare Diabetes series number 22, AIHW webpage.

[3] Diabetes: management; published November 2013. Melbourne: Therapeutic Guidelines Limited; 2016 July.

2.2. Clinical rationale

The sponsor's clinical rationale for the use of insulin degludec, (as stated in the cover letter dated 20 September 2016) is that there is: '*a need for an ultra long acting basal insulin, with a more consistent and predictable absorption profile to reduce the risk of hypoglycaemia and allow greater flexibility in the timing of the injection. Furthermore, a product with a higher insulin concentration will ensure the basal insulin needs of all insulin treated diabetic patients can be met with a single daily dose*'.

2.3. Regulatory history

2.3.1. Australian regulatory history

Tresiba Penfill/FlexTouch (insulin degludec) was previously submitted as an application for registration of new chemical entity for indication of '*treatment of diabetes mellitus*' in Australia in 2012.

In the second round RMP advice, a new safety concern was identified: an independent advisory committee for the FDA was convened on 8 November 2012 after a meta-analysis estimated that the use of insulin degludec products may increase the composite risk of cardiovascular death, non-fatal myocardial infarct, non-fatal stroke and unstable angina by 10% relative to active comparators.

On 11 September 2013, a meeting was held between the sponsor and the TGA to discuss the cardiovascular data.

The application for insulin degludec was formally withdrawn on 25 October 2013 by the sponsor and was not reviewed by the ACPM.

2.3.2. Additional information relating to initial USA FDA submission/assessment of CV risk

An analysis of cardiovascular safety was submitted to the FDA with the original New Drug Application. The following was noted by the Division of Metabolism and Endocrinology Product Office of Drug Evaluation II at the Endocrinologic and Metabolic Drugs Advisory Committee Meeting on 8 November 2012.[4]

- *'Cardiovascular safety analyses submitted with the NDA were based on 5444 patient years of exposure.*
- *A signal suggesting degludec was associated with cardiovascular harm was observed in analyses performed by FDA on the original dataset.*
- *Data for most of the planned long-term controlled extensions of Phase III trials were not available in the original dataset.*
- *The applicant was asked to update the original cardiovascular analysis with these additional data in April 2012.*
- *An analysis based 7716 patient-years of exposure was repeated on updated data received in May 2012.*
- *The signal of harm suggesting degludec could increase the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and unstable angina relative to comparators was again seen in this analysis.*

[4] FDA slides (pages 11 to 12) for the November 8, 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

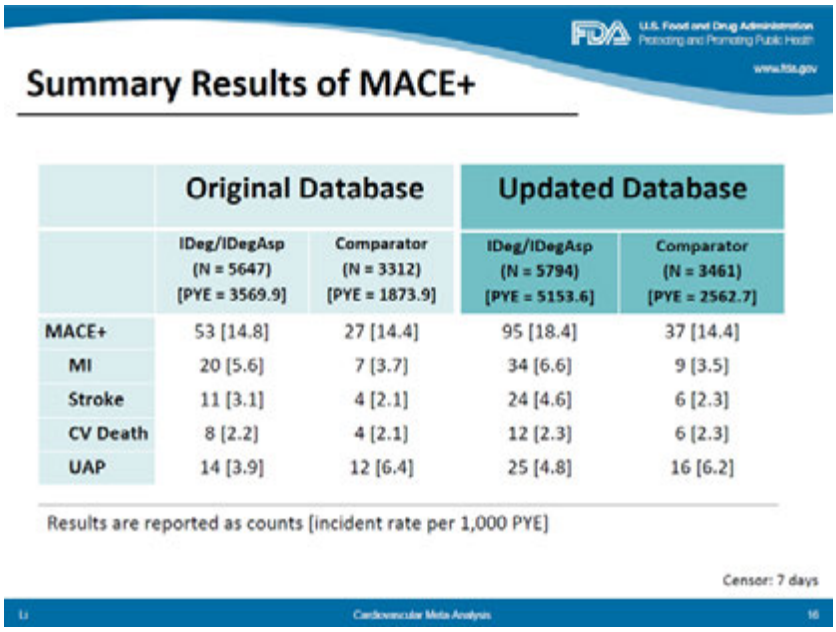
- *The uncertainty around the risk estimate suggested the risk could be as high as 93% or alternatively that degludec could reduce the risk by 12%'.*

The following endpoints were explored:

- MACE+ (pre-specified by sponsor): Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina pectoris
- MACE (requested by the FDA): Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. Excludes unstable angina pectoris.

The following are results from the primary analysis presented at the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on the 8 November 2012 by the FDA.[5]

Figure 1: Summary results of MACE+ (US FDA)



[5] FDA slides (pages 62 to 68) for the 8 November 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

Figure 2: Primary analysis result (US FDA)

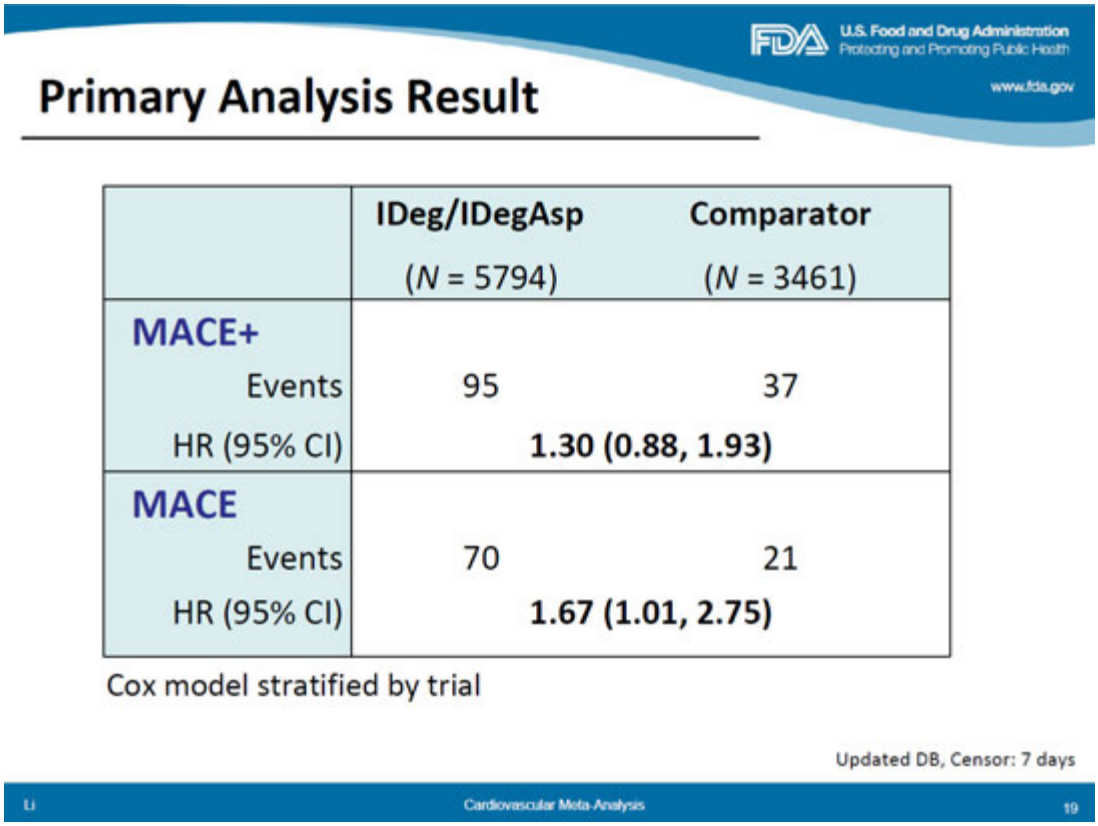


Figure 3: K-M plot of MACE (US FDA)

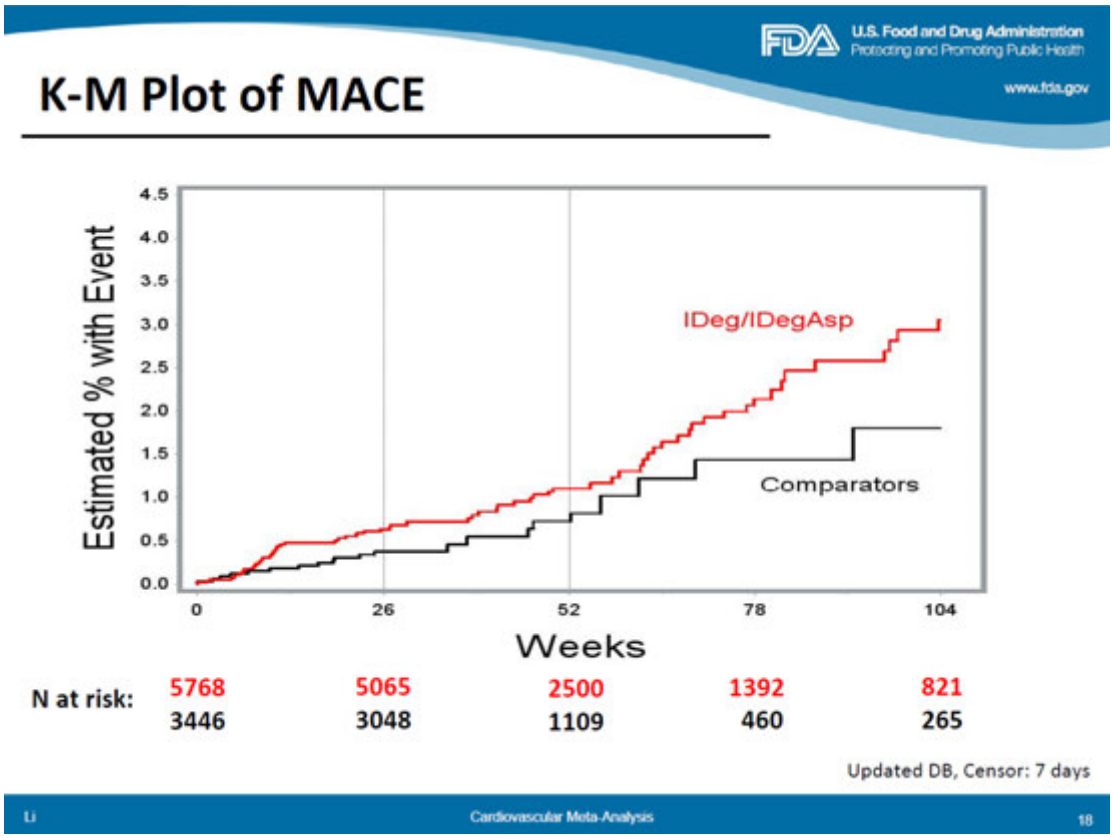


Figure 4: Time-to-event forest plot of MACE (US FDA)

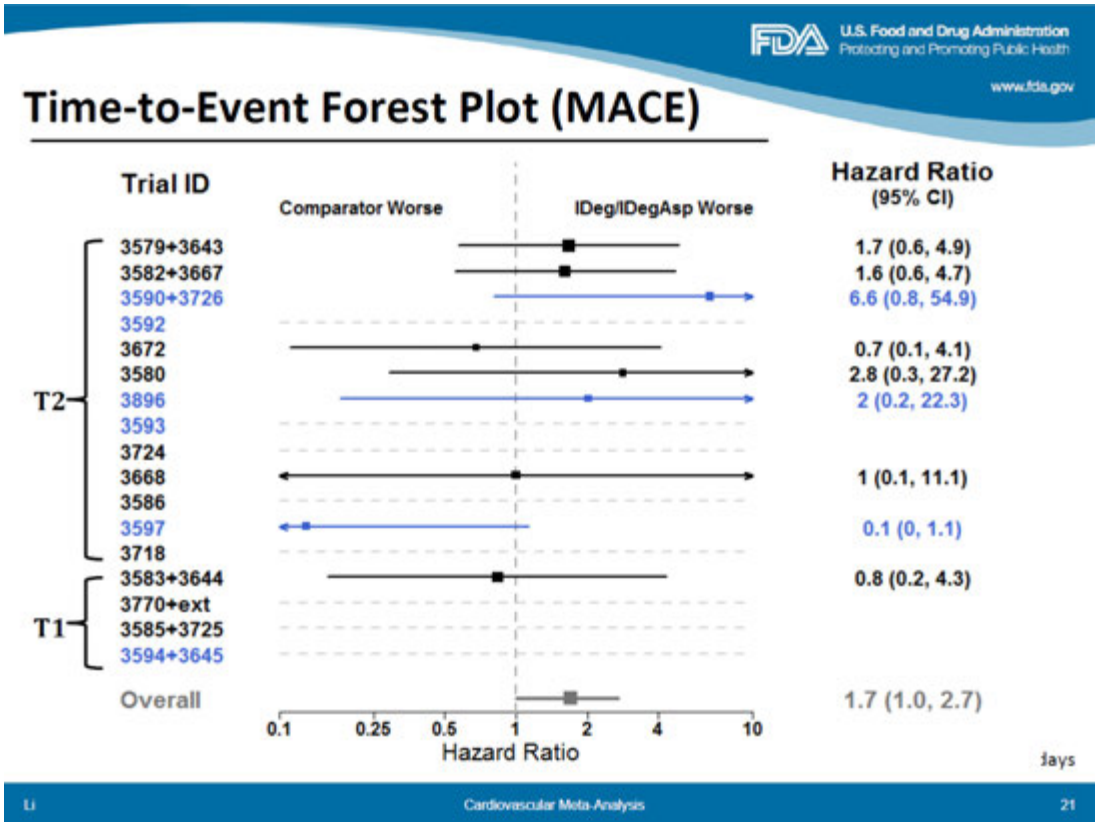


Figure 5: K-M plot of MACE+ (US FDA)

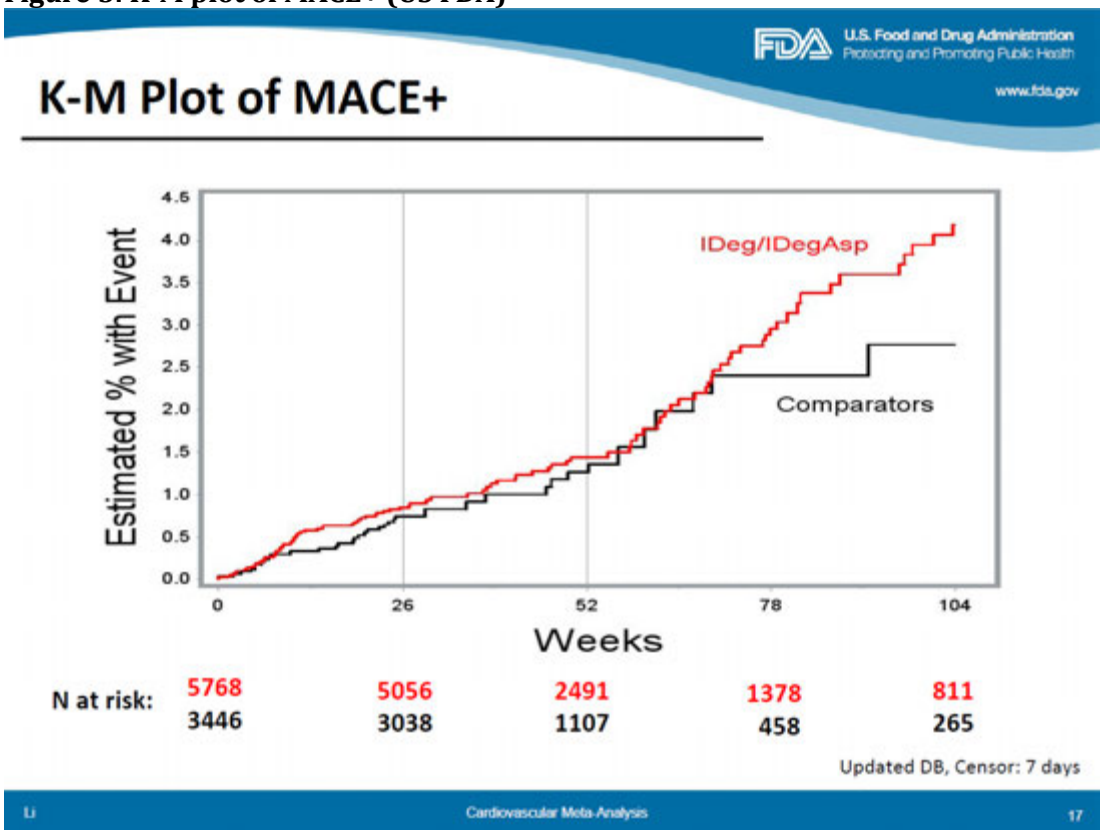
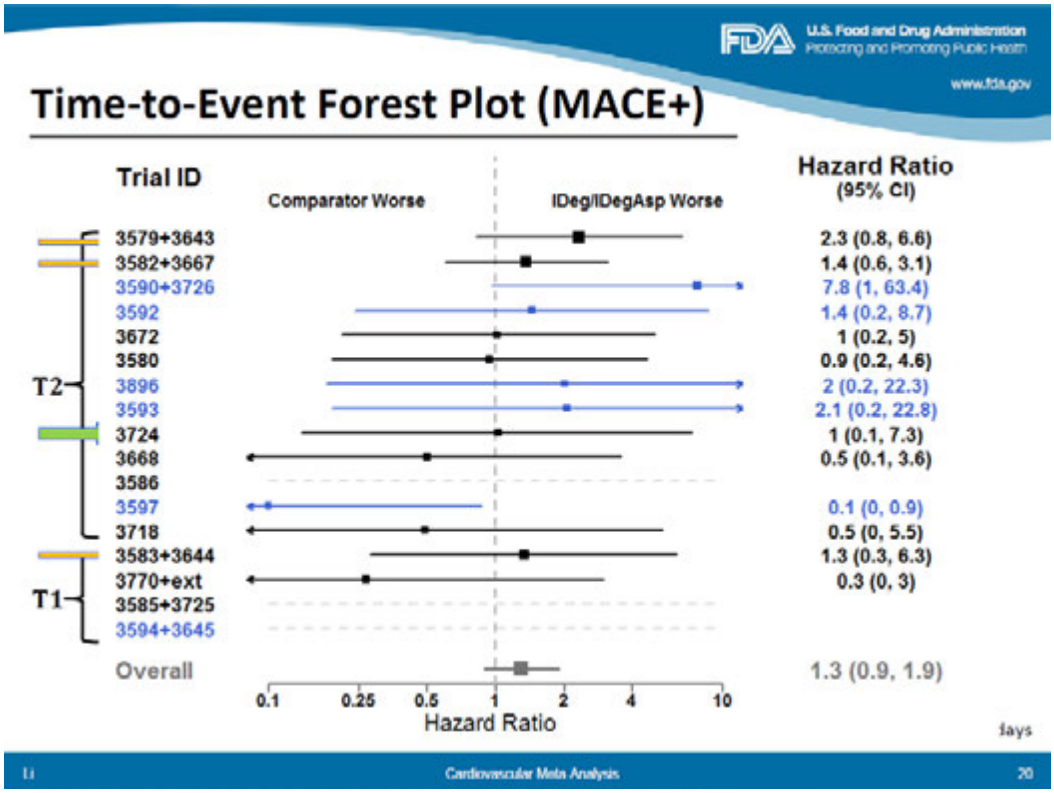


Figure 6: Time-to-event forest plot of MACE+ (US FDA)



As shown in the minutes of the meeting, the committee unanimously supported a follow up cardiovascular outcomes trial '*since there are potential signals for CV risk and a CV trial would need to be conducted to confirm*'.[6] Further, 8 of the 12 committee members agreed that the applicant had provided sufficient efficacy and safety data (which included other data not included in this report) supporting marketing of IDeg and IDegAsp; 4 did not.

On 8 February 2013, the FDA issued a Complete Response Letter and indicated 2 requirements before further consideration of insulin degludec and insulin degludec (rys)/insulin aspart (rys) for registration:

1. A dedicated Cardiovascular Outcomes Trial (CVOT) powered to exclude excess cardiovascular risk from MACE.
2. A clinically meaningful reduction in hypoglycaemic risk compared to other available once-daily basal insulin preparations attributable to insulin degludec PK/PD characteristics.

Resubmission for both IDeg and IDegAsp to the FDA occurred on 26 March 2015 and insulin degludec (Tresiba) and insulin degludec/insulin aspart (Ryzodeg) was approved on 25 September 2015, in the USA.

2.3.2.1. Additional information relating to EU assessment of CV risk

With regards to cardiovascular safety, the Committee for Medicinal Products for Human Use (CHMP)[7] stated the following (page 130 to 131):

- Risks; unfavourable effects: 'Cardiovascular safety was assessed, initially based on meta-analysis of independently confirmed, blindly adjudicated MACE events among the

[6] Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting November 8, 2012. FDA Center for Drug Evaluation and Research.
[7] Committee for Medicinal Products for Human Use (CHMP) assessment report for Tresiba (insulin degludec) EMA/CHMP/557821/2012; 20 September 2012

16 therapeutic confirmatory IDeg + IDegAsp trials (HR 1.10, 95% CI: (0.68; 1.77)). In addition, updated MACE analyses were submitted including a further 3 Phase III trials (cut off 1 May 2012); HR 1.13, 95% CI: 0.705; 1.797'.

- And stated as part of the benefit-risk balance: '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'.

Insulin degludec (Tresiba) was approved on 21 January 2013, in the European Union.

2.4. Guidance

Relevant TGA adopted EMA guidelines are the following:

- Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (14 May 2012 CPMP/EWP/1080/00 Rev. 1)
- Reflection paper on assessment of cardiovascular safety profile of medicinal products (25 February 2016; EMA/CHMP/50549/2015).

2.5. Evaluator's commentary on the background information

The events that lead to the withdrawal of the original dossier for insulin degludec (Tresiba) are noted. As agreed at the pre-submission meeting on 20 October 2016, the focus of the evaluation of the resubmitted dossier will be on new and updated data; especially the cardiovascular outcomes trial.

3. Contents of the clinical dossier

In a pre-submission meeting on the 20 June 2016, it was agreed that the dossier for resubmission would not include the original clinical studies that had been previously evaluated in the original withdrawn submission. The dossier would be limited to data from the DEVOTE study, synopses of new studies completed since the original submission, and other material to address outstanding issues from the previous submission.

3.1. Scope of the clinical dossier

3.1.1. New studies

34 new studies were submitted (compared with the original submission) as synopses.

These include 19 IDeg specific (denoted with trial number starting with NN1250) trials as follows:

- 12 Phase III trials (5 extension trials, 6 new Phase III trials and 1 paediatric trial)
- 5 clinical pharmacology trials
- 2 'other therapeutic' trials: Trial NN1250-3874 was defined as a Phase IIIb trial but has a Phase I like design and Trial NN1250-3943 is of short duration.

Additional information was submitted in December 2016; this was the interim data from the cardiovascular outcomes DEVOTE trial (Study EX1250-4080).

3.1.2. Other documents

Other key documents included:

- Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report IDeg 1 October 2014 to 30 September 2015

In addition, the following were provided:

- Introduction
- Quality Overall Summaries
- Non-clinical overview for IDeg
- Clinical overview for IDeg
- Non-clinical summaries for IDeg
- Clinical summaries for IDeg (including Summary of clinical safety addendum, IDeg).

3.2. Paediatric data

One synopsis has been submitted to support use in a paediatric population (Study NN1250-3561 evaluating use of IDeg in paediatric subjects with T1DM), however a paediatric indication is not being sought in Australia. As diabetes is not uncommon in children, paediatric data can be submitted in a separate submission to support the use of IDeg in the paediatric population.

3.3. Good clinical practice

The newly submitted study synopses state the studies were conducted in accordance with the principles of Good Clinical Practice.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier is consistent with the agreement at the pre-submission meeting.

The clinical safety section (see Section 7, below), refers to updated integrated safety data (with cut-off of 30 September 2014). This integrated data was presented in the submitted document 'Summary of Clinical Safety Addendum, IDeg' which compared the updated data (with cut-off of 30 September 2014) to a dataset with cut-off of January 2011 contained within the document entitled 'Integrated Safety Summary' (31 August 2011). However, the Integrated Safety Summary was not submitted to the TGA with the original IDeg submission; please see Section 7 for further discussion.

4. Pharmacokinetics

Table 4 (below) is a summary of the pharmacokinetics of insulin degludec as previously evaluated and described in the PI.

Table 4: Summary of pharmacokinetics

Absorption	Following subcutaneous injection, stable multi-hexamers are formed, resulting in a depot of insulin. IDeg monomers gradually separate, resulting in a slow and continual release into the circulation. Steady state concentrations are reached after 2 to 3 days of daily IDeg administration.
Distribution	Plasma protein binding of > 99% in human plasma
Metabolism	Degradation of IDeg is similar to that of human insulin.
Excretion	Half-life: 25 hours • independent of dose • determined by rate of absorption from subcutaneous tissue.
Linearity	Dose proportionality demonstrated
Special populations	No differences in hepatic and renal impairment compared to normal subjects and between elderly and younger patients.

Comment: It is noted that there is no difference in PK with renal impairment for this product. This is inconsistent with other insulins where half-life increases with renal impairment. The sponsor will be asked to comment; see Clinical Questions, below.

4.1. New studies providing pharmacokinetic information

Pharmacokinetic data for IDeg has been evaluated in the previously withdrawn submission. There were no unresolved PK issues identified in this submission. The current dossier included synopses for 3 additional PK studies below shown in Table 5 and discussed in Section 4.2.

Table 5: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK (Single dose)	NN1250-4000
PK in special populations	Other special population	NN1250-1999 NN1250-3763

The evaluator notes that Study NN1250-3769 has been submitted as a new study as per the cover letter, however this study was evaluated in the previously withdrawn submission for IDegAsp.

4.2. Summary of pharmacokinetics

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absolute bioavailability

Study NN1250-4000

This was a randomised single centre, open label, 2 period, cross over study to assess the PK and PD properties of IDeg after subcutaneous (SC) versus intravenous (IV) administration in 18 healthy adult subjects.

The primary objective was to estimate the absolute bioavailability of IDeg following SC administration. Subjects were randomly assigned to a single SC dose (0.4 U/kg bodyweight administered in the thigh) and a single IV dose (0.04 U/kg bodyweight) at 2 separate dosing visits (separated by 13 to 21 days).

The absolute bioavailability of IDeg (ratio $AUC_{IDeg,0-\infty,SD,IDeg,s.c.}/AUC_{IDeg,0-\infty,SD,IDeg,i.v.}$) was 0.91 (95% CI: 0.82, 1.01). The sensitivity analysis (excluding unphysiological values) demonstrated an absolute bioavailability of IDeg of 0.88 (95% CI: 0.81, 0.95). The mean serum clearance was 33 mL/h/kg and mean volume of distribution was 242.9 mL/kg. The terminal half-life following IV administration was 5.1 hours.

4.2.1.2. Pharmacokinetics in other special population/with other population characteristics/ethnic differences

Study NN1250-1999

This was a Phase I, open label, uncontrolled, single dose, and single centre study to investigate the PK properties of IDeg in 24 healthy adult Chinese subjects. All subjects received a single SC dose of IDeg (0.4 U/kg body weight) with PK sampling for serum IDeg concentration conducted over 120 hours. Following a single dose of 0.4 U/kg IDeg, total exposure ($AUC_{IDeg;0-120h}$) was estimated to 78192 pmol.h/L (95% CI: 74686, 81864), $C_{max,IDeg}$ estimated to 3489 pmol/L (95% CI: 3115, 3908) and median T_{max} was 11.0 hours.

Study NN1250-3763

This was a single centre, open label multiple dose study to assess the PD response and PK properties at steady state in Japanese subjects with T2DM however was terminated prematurely due to major recruitment challenges. No investigational medicinal product was administered.

Comment: Uncontrolled data are of limited value. Of note, clearance was not documented in the synopsis; it is unclear whether this parameter was assessed in Study 1999.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic characteristics of IDeg have been established in the previously withdrawn submission. In summary, there do not appear to be any outstanding PK issues from the original evaluation. The new data do not add any new information. The PK profile is adequately described in the proposed PI with data from the previously withdrawn submission.

5. Pharmacodynamics

5.1. New studies providing pharmacodynamic information

The pharmacodynamic profile of IDeg has been described in the previously withdrawn submission with no outstanding concerns regarding pharmacodynamics identified. The current

submission included the synopsis of 1 additional PD study for IDeg (Study NN1250-3999) as discussed below.

5.2. Summary of pharmacodynamics

5.2.1. Pharmacodynamic effects

5.2.1.1. Study NN1250-3999

Study NN1250-3999 was a randomised, single centre, open label, 2 period, multiple dose, cross over study comparing the changes in blood glucose and risk of hypoglycaemia during and after exercise in 40 adult subjects with T1DM treated with IDeg or IGlar (in combination with mealtime IAsp).

In each treatment period subjects were randomised to once daily IDeg or IGlar dosing pre-breakfast together with IAsp as bolus insulin. Following a 14 to 28 day run in period with individual dose titration there was a 6 day steady state period with constant individual IDeg/IGlar dose levels. 30 minutes ergometer bicycling was performed 3 hours after lunch on Day 5 of the steady-state period.

The difference between blood glucose concentration before exercise and minimum blood glucose concentration observed during exercise was similar for IDeg and IGlar with an estimated treatment difference of 0.14 mmol/L (95% CI: -0.15, 0.42). The estimated mean and minimum blood glucose concentrations 30 to 180 minutes following exercise were comparable between the IDeg and IGlar groups, as was the mean blood glucose concentration for 24 hours after start of exercise. There were no hypoglycaemic events during exercise. After exercise, the number of confirmed and nocturnal confirmed hypoglycaemic episodes was similar between the two groups; the estimated rate ratios (IDeg/IGlar) for confirmed and nocturnal confirmed hypoglycaemic episodes were 0.76 (95% CI: 0.40; 1.45) and 1.00 (95% CI: 0.40; 2.47) respectively.

Comment: From these limited data there does not appear to be any difference between the 2 groups in terms of confirmed hypoglycaemic episodes. In the real world setting hypoglycaemic episodes are dependent on a number of factors including the degree of physical activity and carbohydrate intake with adjustment of insulin required in accordance with these variables.

5.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic profile of IDeg is well described in the previously withdrawn submission and there were no outstanding issues. The sponsor is not proposing any amendments to the PI based on data from Study NN1250-3999.

6. Clinical efficacy

The current dossier includes synopses for studies completed since 2013, as agreed with the TGA in the pre-submission meeting held on 20 June 2016. See Section 6.2 (below) for discussion of these new data.

There were 9 confirmatory therapeutic trials with IDeg evaluated in the original withdrawn submission (n = 3 in subjects with T1DM and n = 6 in subjects with T2DM). These studies are discussed briefly below in Section 6.1).

6.1. Summary of previously submitted studies

6.1.1. Type 1 diabetes mellitus

The 3 pivotal trials in subjects with T1DM are summarised below in Table 6. All trials were of a similar design; randomised, controlled, open label, multicentre, multinational, parallel, treat-to-target studies comparing IDeg to an active comparator (insulin glargine (IGlar) or insulin detemir (IDet)) administered in a basal-bolus regimen with insulin aspart (IAsp) as mealtime insulin. Study 3770 included a third treatment arm (IDeg Flex) to investigate a variable dosing interval of IDeg. The studies were of 52 week (Study 3583) or 26 week (Studies 3585 and 3770) duration.

The primary objective was to demonstrate non-inferiority in the efficacy of IDeg in controlling glycaemia by comparing change from Baseline in HbA1c at the end of treatment (26 or 52 weeks) between IDeg and active comparator to a predefined non-inferiority limit of 0.4%. Secondary efficacy endpoints included change in FPG from Baseline to end of treatment and percent responders for HbA1c targets. Key safety endpoints included the rate of nocturnal confirmed hypoglycaemic episodes and confirmed hypoglycaemic episodes.

Basal insulin doses were titrated on an individual basis to achieve optimal glycaemic control; thus, similar efficacy for all treatments would be expected. Comparator insulin products were administered as per approved local labelling at the same time every day. Bolus mealtime IAsp was used in all trials with no other concomitant anti-diabetic treatment permitted for subjects with T1DM. It is noted that patients were not blinded to their treatment allocation due to the different pen devices used for IDeg and comparators. This is unlikely to have affected efficacy endpoints as these were objective, however may have created some bias in the reporting of safety endpoints.

Table 6: Summary of therapeutic confirmatory trials (T1DM)

Parameter	Study 3583	Study 3585	Study 3770
Design	52 week efficacy and safety study comparing IDeg OD and IGlar OD in a basal bolus regimen with IAsp in adult subjects with T1DM.	26 week efficacy and safety study comparing IDeg OD versus IDet in a basal-bolus regimen with IAsp in adult subjects with T1DM.	26 week efficacy and safety study comparing IDeg once daily in flexible dosing schedule with IDeg OD with main evening meal and IGlar OD in adult subjects with T1DM.
Treatments	Randomised 3:1 to: IDeg OD + IAsp (n = 472); or IGlar OD + IAsp (n = 157)	Randomised 2:1 to IDeg + IAsp (n = 303); or IDet* + IAsp (n = 153)	Randomised 1:1:1 to IDegFF+ IAsp (n = 164); IDeg OD + IAsp (n = 165); or IGlar + IAsp (n = 164)
Treatment administration	IDeg OD 100 U/mL with main evening meal or IGlar OD according to local label IAsp as bolus mealtime insulin	IDeg 100 U/mL OD or IDet OD with main evening meal IAsp as bolus mealtime insulin	IDeg 100 U/mL OD in flexible dosing schedule with 8 to 40h between doses** or IDeg OD with main evening meal or IGlar OD according to local labelling IAsp as bolus mealtime insulin

Parameter	Study 3583		Study 3585		Study 3770		
Primary efficacy	**Mean change from Baseline in HbA1c after 52 weeks of treatment (%)**		**Mean change from Baseline in HbA1c after 26 weeks of treatment (%)**		**Mean change from Baseline in HbA1c after 26 weeks of treatment (%)**		
	IDeg	IGlar	IDeg	IDet	IDeg Flex	IDeg OD	IGlar OD
	- 0.36	-0.34	-0.71	-0.61	-0.40	-0.41	-0.57
	Mean treatment difference (IDeg - IGlar) = -0.01% (95% CI: -0.14, 0.11). Non-inferiority confirmed.		Mean treatment difference (IDeg – IDet) = -0.09% (95% CI: -0.23, 0.05). Non-inferiority confirmed.		Mean treatment difference (IDeg Flex – IGlar OD) = 0.17% (95% CI: 0.04, 0.30) Non-inferiority confirmed. Mean treatment difference (IDeg Flex – IDeg OD) = 0.01% (95% CI: -0.13, 0.14). Non-inferiority confirmed.		
Secondary efficacy	**Mean change from Baseline in FPG after 52 weeks of treatment (mmol/L)**		**Mean change from Baseline in FPG after 26 weeks of treatment (mmol/L)**		**Mean change from Baseline in FPG after 26 weeks of treatment (mmol/L)**		
	IDeg	IGlar	IDeg	IDet	IDeg Flex	IDeg OD	IGlar OD
	-1.53	- 1.20	-2.40	-0.75	-1.37	-2.32	-1.33
	Mean treatment difference (IDeg – IGlar) = -0.33 mmol/L (95% CI: -1.03, 0.36)		Mean treatment difference (IDeg – IDet) = -1.66 mmol/L (95% CI: -2.37, -0.95)		Mean treatment difference (IDeg Flex – IGlarOD) = -0.05 mmol/L (95% CI: -0.85, 0.76) Mean treatment difference (IDeg Flex – IDeg OD) = 0.95 mmol/L (95% CI: 0.15, 1.75)		
Secondary efficacy	**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		
	IDeg	IGlar	IDeg	IDet	IDeg Flex	IDeg OD	IGlar OD
	7.3	5.4	6.2	6.9	2.8	5.2	3.2

Parameter	Study 3583		Study 3585		Study 3770		
	Estimated odds ratio (IDeg/IGlar) = 1.40 (95% CI: 0.61, 3.20)		Estimated odds ratio (IDeg/IDet) = 0.82 (95% CI: 0.32, 2.08)		Estimated odds ratio (IDeg Flex/IGlar OD) = 0.72 (95% CI: 0.18, 2.84) Estimated odds ratio (IDeg Flex/IDeg OD) = 0.47 (95% CI: 0.13, 1.64)		
Safety endpoint	**Rate of nocturnal confirmed hypoglycaemic episodes# per 100 PYE**		**Rate of nocturnal confirmed hypoglycaemic episodes# per 100 PYE**		**Rate of nocturnal confirmed hypoglycaemic episodes# per 100 PYE**		
	IDeg	IGlar	IDeg	IDet	IDeg Flex	IDeg OD	IGlar OD
	441	586	414	593	623	961	996
	Estimated rate ratio (IDeg/IGlar) = 0.75 (95% CI: 0.59, 0.96)		Estimated rate ratio (IDeg/IDet) = 0.66 (95% CI: 0.49, 0.88)		Estimated rate ratio (IDeg Flex/IGlar) = 0.60 (95% CI: 0.44, 0.82) Estimated rate ratio (IDeg Flex/IDeg OD) = 0.63 (95% CI: 0.46, 0.86)		
Safety endpoint	**Rate of confirmed hypoglycaemic episodes† per 100 PYE**		**Rate of confirmed hypoglycaemic episodes† per 100 PYE**		**Rate of confirmed hypoglycaemic episodes† per 100 PYE**		
	IDeg	IGlar	IDeg	IDet	IDeg Flex	IDeg OD	IGlar OD
	4254	4018	4583	4569	8238	8825	7973
	Estimated rate ratio (IDeg/IGlar) = 1.07 (95% CI: 0.89, 1.28)		Estimated rate ratio (IDeg/IDet) = 0.98 (95% CI: 0.80, 1.20)		Estimated rate ratio (IDeg Flex/IGlar OD) = 1.03 (95% CI: 0.85, 1.26) Estimated rate ratio (IDeg Flex/IDeg OD) = 0.92 (95% CI: 0.76, 1.12)		

* A second IDet dose could be added after 8 weeks in the case of inadequate glycaemic control; ** IDeg administered in the morning on Monday, Wednesday, Friday and in the evening on Tuesday, Thursday, Saturday and Sunday; † Confirmed hypoglycaemic episodes consisted of episodes of severe hypoglycaemia as well as minor hypoglycaemic episodes with confirmed PG value of < 3.1 mmol/L. Minor hypoglycaemic episodes were to be used for the statistical analysis of the confirmatory endpoint; # Nocturnal hypoglycaemia defined as confirmed hypoglycaemic episodes (severe or plasma glucose < 3.1 mmol/L) with an onset between 00:01 and 05:59 inclusive.

6.1.2. Type 2 diabetes mellitus

There were 6 confirmatory therapeutics trials involving subjects with T2DM, including insulin treated subjects (n = 1 study), insulin naïve subjects on oral antidiabetic drugs (OADs) eligible for treatment intensification (n = 4 studies), and one study including both insulin-treated and insulin-naïve subjects to investigate flexible dosing of IDeg.

All trials were of a similar design to the studies conducted in subjects with T1DM; randomised, controlled, open label, multicentre, multinational, parallel, treat-to-target studies comparing IDeg to an active comparator (IGlar or sitagliptin). The primary objective was to confirm efficacy of IDeg in long term control of glycaemia in subjects with T2DM, with change from Baseline in HbA1c at the end of treatment (26 or 52 weeks) the primary efficacy parameter. All studies were non-inferiority trials except for Study 3580 in T2DM subjects, which was a superiority trial with sitagliptin the active comparator. FPG and percent responders for HbA1c targets were secondary efficacy endpoints, with key safety endpoints including hypoglycaemic parameters as shown below in Table 7.

The IDeg 100 U/mL was formulation was used in all studies except Study 3672 which investigated the 200 U/mL formulation. For insulin naïve subjects IDeg was commenced at a starting dose of 10 U/day and for insulin treated subjects a unit-to unit transfer was applied, subject to the discretion of the Investigator. Insulin (IDeg and comparator) was titrated as per pre-specified titration algorithms in accordance with treat-to-target principle. IDeg was used in combination with metformin in all studies, and various other OADs including insulin secretogogues (sulphonylurea (SU) or glinide), DPP-4 inhibitors (DPP-4I), pioglitazone and α-glucosidase inhibitors (α-GI) as shown in Table 7, below. All T2DM trials required subjects to have been treated with unchanged OAD regimens and doses for at least 3 months prior to screening.

Table 7: Studies in subjects with T2DM

Parameter	Study 3582	Study 3579	Study 3672	Study 3586	Study 3668	Study 3580
Design	52 week efficacy and safety study comparing IDeg OD and IGlar OD in a basal-bolus regimen with IAsp in insulin - treated adult subjects ± OADs (±metformin ± pioglitazone)	52 week efficacy and safety study comparing IDeg OD and IGlar OD in insulin-naïve subjects with T2DM treated with OADs (metformin ±DDP-4I)	26 week efficacy and safety study comparing IDeg OD (200 U/mL) and IGlar OD in insulin-naïve subjects with T2DM treated with OADs (metformin ±DDP-4I)	26 week Pan Asian efficacy and safety study comparing IDeg OD and IGlar OD in insulin-naïve subjects with T2DM treated with OADs (± metformin ± insulin secretogogue ± α-GI)	26 week efficacy and safety study comparing IDeg flexible dosing vs. IGlar and IDeg OD vs. IGlar OD in subjects with T2DM treated with OADs alone or basal insulin ± OADs (± metformin ± insulin secretogogue ± pioglitazone)	26 week efficacy and safety study comparing IDeg OD with sitagliptin in insulin-naïve subjects with T2DM treated with 1-2 OADs (metformin, SU/ glinide or pioglitazone) qualifying for intensified treatment.
Treatment	Randomised 3: 1 to: • IDeg OD + IAsp (n = 755) or • IGlar OD + IAsp (n = 251)	Randomised 3:1 to •IDeg OD (n = 773) or • IGlar OD (n = 257)	Randomised 1:1 to • IDeg (n = 230) or • IGlar (n = 230)	Randomised 2:1 to • IDeg (n = 289) or • IGlar (n = 146)	Randomised 1:1:1 to • IDeg Flex (n = 229) or • IDeg OD (n = 228) • IGlar (n = 230)	Randomised 1:1 to • IDeg (n = 229) or • Sita (n = 229)
Treatment administration	• IDeg 100 U/mL OD with main evening meal or IGlar OD according to local label • IAsp as bolus mealtime insulin. • ± metformin • ± pioglitazone	• IDeg 100 U/mL OD with main evening meal or IGlar OD according to local label • metformin • ± DDP-4I	• IDeg 200 U/mL OD with main evening meal or IGlar OD according to local label at the same time each day. • metformin • ± DDP-4I	• IDeg 100 U/mL OD in the evening (start of main evening meal to bedtime) or IGlar OD according to local label • ± metformin • ± SU/glinide • ± α-GI	• IDeg 100 U/mL OD with alternating morning and evening doses* or IDeg 100 U/mL OD with the evening meal or IGlar OD according to local label • ± metformin • ± SU/glinide • ± pioglitazone	• IDeg OD flexible dosing schedule (8-40 hours between injections) or Sitagliptin 100 mg PO daily • + 1-2 OADs (metformin, SU/glinide, pioglitazone)

* IDeg was administered OD in a rotating schedule with 8 to 40 hours between doses; morning dose on Monday, Wednesday and Friday and evening doses on Tuesday, Thursday, Saturday and Sunday.

Table 7: Studies in subjects with T2DM (continued)

Parameter	Study 3582		Study 3579		Study 3672		Study 3586		Study 3668			Study 3580	
Primary efficacy	**Mean change from baseline in HbA1c after 52 weeks of treatment (%)**		**Mean change from baseline in HbA1c after 52 weeks of treatment (%)**		**Mean change from baseline in HbA1c after 26 weeks of treatment (%)**		**Mean change from baseline in HbA1c after 26 weeks of treatment (%)**		**Mean change from baseline in HbA1c after 26 weeks of treatment (%)**			**Mean change from baseline in HbA1c after 26 weeks of treatment (%)**	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg OD	IGlar	IDeg	Sita
	-1.10	-1.18	-1.06	-1.15	- 1.18	- 1.22	-1.42	-1.52	-1.17	-1.03	-1.21	-1.52	-1.09
	Mean treatment difference (IDeg – IGlar) = 0.08% (95% CI: -0.05, 0.21) Non-inferiority confirmed		Mean treatment difference (IDeg – IGlar) = 0.09% (95% CI: -0.04, 0.22) Non-inferiority confirmed		Mean treatment difference (IDeg– IGlar) = 0.04 % (95% CI: -0.11, 0.19) Non-inferiority confirmed		Mean treatment difference (IDeg– IGlar) = 0.11% (95% CI: -0.03, 0.24) Non-inferiority confirmed		Mean treatment difference (IDeg Flex – IGlar) = 0.04% (95% CI: -0.12, 0.20) Non-inferiority confirmed Mean treatment difference (IDeg Flex – IDeg OD) = -0.13% (95% CI: -0.29, 0.03) Non-inferiority confirmed			Mean treatment difference (IDeg – Sita) = -0.43% (95% CI: -0.61, -0.24) Superiority confirmed	
Secondary efficacy	**Mean change from baseline in FPG after 52 weeks of treatment (mmol/L)**		**Mean change from baseline in FPG after 52 weeks of treatment (mmol/L)**		**Mean change from baseline in FPG after 26 weeks of treatment (mmol/L)**		**Mean change from baseline in FPG after 26 weeks of treatment (mmol/L)**		**Mean change from baseline in FPG after 26 weeks of treatment (mmol/L)**			**Mean change from baseline in FPG after 26 weeks of treatment (mmol/L)**	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg OD	IGlar	IDeg	Sita
	-2.25	-1.96	-3.76	-3.30	-3.94	-3.52	-3.03	-2.94	-3.05	-3.01	-2.64	-3.41	-1.24
	Mean treatment difference (IDeg – IGlar) = -0.29 mmol/L (95% CI: -0.65, 0.06)		Mean treatment difference (IDeg – IGlar) = -0.43 mmol/L (95% CI: -0.74, -0.13)		Mean treatment difference (IDeg – IGlar) = -0.42 mmol/L (95% CI: -0.78, -0.06)		Mean treatment difference (IDeg – IGlar) = -0.09 mmol/L (95% CI: -0.41, 0.23)		Mean treatment difference (IDeg Flex – IGlar) = -0.42 mmol/L (95% CI: -0.82, -0.02) Mean treatment difference (IDeg Flex – IDeg OD) = -0.05 mmol/L (95% CI: -0.45, 0.35)			Mean treatment difference (IDeg – Sita) = --2.17 mmol/L (95% CI: -2.59, -1.74)	

* IDeg was administered OD in a rotating schedule with 8 to 40 hours between doses; morning dose on Monday, Wednesday and Friday and evening doses on Tuesday, Thursday, Saturday and Sunday.

Table 7: Studies in subjects with T2DM (continued)

Parameter	Study 3582		Study 3579		Study 3672		Study 3586		Study 3668			Study 3580	
Secondary efficacy	**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**		**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**			**Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)**	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg OD	IGlar	IDeg	Sita
	24.4	23.2	42.1	45.7	45.2	44.7	29.1	31.5	26.5	30.0	32.2	24.9	22.9
	Estimated odds ratio (IDeg/IGlar) = 1.02 (95% CI: 0.72, 1.47)		Estimated odds ratio (IDeg/IGlar) = 0.86 (95% CI: 0.63, 1.17)		Estimated odds ratio (IDeg/IGlar) = 1.05 (95% CI: 0.69, 1.61)		Estimated odds ratio (IDeg/IGlar) = 0.89 (95% CI: 0.56, 1.42)		Estimated odds ratio (IDeg Flex/IGlar) = 0.80 (95% CI: 0.51, 1.26) Estimated odds ratio (IDeg Flex/IDeg OD) = 0.96 (95% CI: 0.61, 1.53)			Estimated odds ratio (IDeg Flex/IGlar) = 0.92 (95% CI: 0.55, 1.53)	
Safety endpoint	**Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE**		**Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE**		**Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE**		**Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE**		**Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE**			**Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE**	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg OD	IGlar OD	IDeg	Sita
	139	184	25	39	18	28	78	124	63	56	75	52	30
	Estimated rate ratio (IDeg/IGlar) = 0.75 (95% CI: 0.58, 0.99)		Estimated rate ratio (IDeg/IGlar) = 0.64 (95% CI: 0.42, 0.98)		Estimated rate ratio (IDeg/IGlar) = 0.64 (95% CI: 0.30, 1.37)		Estimated rate ratio (IDeg/IGlar) = 0.62 (95% CI: 0.38, 1.04)		Estimated rate ratio (IDeg Flex/IGlar OD) = 0.77 (95% CI: 0.44, 1.35) Estimated rate ratio (IDeg Flex/IDeg OD) = 1.18 (95% CI: 0.66, 2.12).			Estimated rate ratio (IDeg/Sita) = 1.93 (95% CI: 0.90, 4.10)	

* IDeg was administered OD in a rotating schedule with 8 to 40 hours between doses; morning dose on Monday, Wednesday and Friday and evening doses on Tuesday, Thursday, Saturday and Sunday.

Table 7: Studies in subjects with T2DM (continued)

Parameter	Study 3582		Study 3579		Study 3672		Study 3586		Study 3668			Study 3580	
Safety endpoint	Rate of confirmed hypoglycaemic episodes per 100 PYE		Rate of confirmed hypoglycaemic episodes per 100 PYE		Rate of confirmed hypoglycaemic episodes per 100 PYE		Rate of confirmed hypoglycaemic episodes per 100 PYE		Rate of confirmed hypoglycaemic episodes per 100 PYE			Rate of confirmed hypoglycaemic episodes per 100 PYE	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg OD	IGlar	IDeg	Sita
	1109	1363	2	185	122	142	298	370	364	363	348	307	126
	Estimated rate ratio (IDeg/IGlar) = 0.82 (95% CI: 0.69, 0.99)		Estimated rate ratio (IDeg/IGlar) = 0.82 (95% CI: 0.64, 1.04)		Estimated rate ratio (IDeg/IGlar) = 0.86 (95% CI: 0.58, 1.28)		Estimated rate ratio (IDeg/IGlar) = 0.82 (95% CI: 0.60, 1.11)		Estimated rate ratio (IDeg Flex/IGlar) = 1.03 (95% CI: 0.75, 1.40) Estimated rate ratio (IDeg Flex/IDeg OD) = 1.10 (95% CI: 0.79, 1.52)			Estimated rate ratio (IDeg/Sita) = 3.81 (95% CI: 2.40, 6.05)	

* IDeg was administered OD in a rotating schedule with 8 to 40 hours between doses; morning dose on Monday, Wednesday and Friday and evening doses on Tuesday, Thursday, Saturday and Sunday.

Comment: The flexible dosing regimen of IDeg was compared to glargine in two trials, one each in subjects with T1DM and T2DM. In addition, Study 3580 compared the IDeg flexible dosing regimen to the DPP4i sitagliptin in T2DM subjects, however as this study employed a treat-to-target approach for IDeg versus a fixed dose of sitagliptin, the greater reduction in HbA1c observed in the IDeg group after 26 weeks is not unexpected.

The design of these studies allowed for flexibility of IDeg dosing from 8 to 40 hours between doses in a clinical trial setting. Whilst similarities in glycaemic control were demonstrated between the IDeg flexible dosing and IGlar groups, in real world clinical practice such extremes of dosing are not ideal for diabetes management.

The studies submitted in the original submission support efficacy as measured by non-inferiority to other basal insulins in T1DM and T2DM for HbA1c, with similar (or lower) risk of hypoglycaemia. There were no outstanding efficacy issues.

Hypoglycaemia is discussed below in Section 7.

6.2. Studies providing new efficacy data

Efficacy data for IDeg provided in synopses for additional Phase III studies submitted as new data in the current dossier as per the cover letter are discussed below. Of note, synopses for studies involving the combination product IDeg/liraglutide were not relevant to the current submission and as such not evaluated.

The dossier included synopses for extension studies for the 3 T1DM pivotal trials, Studies 3583, 3585, and 3770; and 2 of the pivotal trials in T2DM subjects (Studies 3582 and 3579), in addition to 6 new studies (n = 1 in T1DM subjects and n = 5 in T2DM subjects). Some of the hypoglycaemic safety endpoints (nocturnal confirmed hypoglycaemic episodes and confirmed hypoglycaemic episodes) will be included in the following discussion for ease of comparison

with previously evaluated data provided in Tables 6 and 7, above. Safety data from these synopses are otherwise discussed in Section 7.

6.2.1. Studies in subjects with T1DM

6.2.1.1. Study NN1250-3644

Study NN1250-3644 is an extension of Study NN1250-3583 comparing the safety and efficacy of IDeg and IGlar, both with IAsp as mealtime insulin, in subjects with T1DM. The primary objective was to assess long-term safety and tolerability of IDeg, with efficacy endpoints secondary outcomes. Subjects participating in the 52 week extension study continued treatment as previously randomly allocated in Study NN1250-3579. There were 469 subjects (IDeg = 351, IGlar = 118) included in the extension study. The baseline demographics and characteristics were considered similar between the two treatment groups.

The estimated mean reduction from Baseline in HbA1c after 104 weeks of treatment was -0.30% for IDeg and -0.26% for IGlar, with an estimated mean treatment difference (IDeg - IGlar) of -0.04% (95% CI: -0.17, 0.09). A reduction in FPG was observed in both groups (estimated mean treatment difference (IDeg – IGlar) = -0.29 mmol/L (95% CI: -0.97, 0.40)).

There were 34.3% subjects in the IDeg group and 31.2% subjects in the IGlar group achieving HbA1c < 7.0% (estimated odds ratio (IDeg/IGlar) = 1.31 (95% CI: 0.79, 2.16)), with 6.6% and 5.4% subjects in the IDeg and IGlar groups respectively achieving an HbA1c of < 7.0% without confirmed hypoglycaemia (estimated odds ratio (IDeg/IGlar) = 1.27 (95% CI: 0.55, 2.94)).

The rate of confirmed hypoglycaemic episodes was similar between the 2 groups (3750 and 3743 episodes per 100 PYE for IDeg and IGlar respectively, estimated rate ratio (IDeg/IGlar) = 1.02 (95% CI: 0.85, 1.24)). The rate of nocturnal confirmed hypoglycaemic episodes was lower for IDeg (390 per 100 PYE) than IGlar (532 per 100 PYE), estimated rate ratio (IDeg/IGlar) = 0.75 (95% CI: 0.59, 0.95)).

6.2.1.2. Study NN1250-3725

Study NN1250-3725 is a 26 week extension of the 26 week Study NN1250-3585 investigating the safety and efficacy of IDeg compared to IDet in subjects with T1DM in a basal bolus treatment regimen. The primary objective was to assess long term safety and tolerability of IDeg in combination with IAsp, with the secondary objective to compare the efficacy between IDeg and IDet after 52 weeks of treatment in combination with IAsp.

There were 370 subjects who entered the extension study (IDeg = 248, IDet = 122). After 52 weeks of treatment, the estimated mean reduction in HbA1c was 0.48% for IDeg and 0.47% for IDet (estimated mean treatment difference (IDeg-IDet) = -0.01% (95% CI: -0.17, 0.14)).

For FPG, a greater mean reduction from Baseline was observed for IDeg (2.51 mmol/L) than IDet (1.40 mmol/L), with an estimated mean treatment difference (IDeg - IDet) of -1.11 mmol/L (95% CI: -1.83, -0.40)).

A similar proportion of subjects achieved an HbA1c of < 7.0% (IDeg = 31.5%, IDet = 32.0%, estimated odds ratio (IDeg/IDet) = 1.01 (95% CI: 0.61, 1.65)). The estimated odds of achieving an HbA1c of < 7.0% without confirmed hypoglycaemia was 6.5% with IDeg and 11.7% with IDet although the sponsor states there was no statistically significant difference between the 2 groups regarding the proportion of subjects achieving an HbA1c of < 7.0% without confirmed hypoglycaemia.

The estimated rate for confirmed hypoglycaemic episodes was similar between the 2 groups (estimated rate ratio (IDeg/IDet) = 0.95 (95% CI: 0.78, 1.17)), whilst the estimated rate of nocturnal confirmed hypoglycaemic episodes was lower for IDeg than IDet (estimated rate ratio (IDeg/IDet) = 0.67 (95% CI: 0.51, 0.88)).

6.2.1.3. Study NN1250-3770-ext

Study NN1250-3770-ext is a 26 week extension of Study NN1250-3770 to investigate the long term efficacy of IDeg administered once daily in a flexible dosing regimen with meal time IAsp, compared with IGlar administered once daily. There were 2 treatment arms in the extension period (both with meal-time IAsp):

- IDeg OD Free Flex: IDeg administered once daily at any time of the day with 8-40 hours between injections. This treatment arm included subjects allocated to IDeg Flex or IDeg OD during the main trial period.
- IGlar OD: IGlar administered OD as per local label. Subjects allocated to IGlar during the main trial period continued in this treatment arm.

There were a total of 372 subjects included in the extension trial (IDeg OD Free Flex = 239, IGlar OD = 133).

After 52 weeks of treatment, the estimated mean change in HbA1c was -0.13% and -0.20% for IDeg OD Free Flex and IGlar OD respectively. The estimated mean treatment difference (IDeg OD Free Flex – IGlar OD) was 0.07% (95% CI: -0.05, 0.19). The mean HbA1c values increased slightly in both groups during the extension phase, but remained below baseline levels.

A statistically significantly lower mean FPG was observed in the IDeg OD Free Flex (8.0 mmol/L) group compared with the IGlar OD group (9.1 mmol/L) with an estimated treatment difference (IDeg OD Free Flex – IGlar OD) of -1.07 mmol/L (95% CI: -1.82, -0.32).

The proportion of subjects achieving HbA1c < 7% without confirmed hypoglycaemia during the last 12 weeks of treatment was 3.4% with IDeg OD Free Flex and 1.9% with IGlar OD (estimated treatment odds ratio (IDeg OD Free Flex/IGlar OD) = 1.50 (95% CI: 0.39, 5.70)). A numerically greater proportion of subjects in the IDeg OD Free Flex group achieved an HbA1c of < 7.0% (27.7%) compared with IGlar OD (25.6%).

The rate of confirmed hypoglycaemic episodes was numerically higher in the IDeg OD Free Flex group than the IGlar OD group (6811 versus 6341 episodes per 100 PYE; estimated rate ratio (IDeg OD Free Flex/IGlar) = 1.09 (95% CI: 0.91, 1.29)). The rate of nocturnal confirmed hypoglycaemic episodes was lower for IDeg OD Free Flex (640 per 100 PYE) than IGlar (848 per 100 PYE), estimated rate ratio (IDeg OD Free Flex /IGlar) = 0.75 (95% CI: 0.58, 0.97)).

6.2.1.4. Study NN1250-3874

Study NN1250-3874 was a Phase IIIb, randomised, open label, single centre, 2 period cross over trial to compare the efficacy of IDeg and IGlar administered once daily in the morning in a basal-bolus regimen with IAsp as meal-time insulin using Continuous Glucose Monitoring in subjects with T1DM. The study population comprised subjects aged 18 to 75 inclusive with T1DM ≥ 12 months with HbA1c ≤ 8.5%, currently treated with IGlar in a basal bolus regimen. There were 24 subjects randomised 1:1 to one of two treatment sequences (IDeg/IGlar and IGlar/IDeg). The study population had a mean age of 45.3 years, mean duration of T1DM of 18.6 years and mean HbA1c of 7.1%. The study included a 4 week run-in period, and 2 x 6 week treatment periods.

The primary endpoint was the average time within glycaemic target range (> 3.9 mmol/L and < 7.2 mmol/L) in the last 4 hours of each dosing interval during the last 2 weeks of the 6 week treatment period. The observed average duration within the glycaemic target range was 1.39 and 1.09 hours for subjects whilst taking IDeg and IGlar respectively (estimated treatment difference (IDeg - IGlar) = 0.29 hours (95% CI: -0.01, 0.60)). The findings were similar between the two groups for secondary pharmacodynamic endpoints including FPG and glucose exposure.

The estimated treatment ratios (IDeg/IGlar) for confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were 1.214 (95% CI: 0.932, 1.581) and 1.265 (95% CI: 0.611, 2.620) respectively.

6.2.1.5. Study NN1250-3561

Study NN1250-3561 is a Phase III, 26 week, open label, randomised, 2 arm parallel group efficacy and safety study comparing IDeg with IDet as basal insulin in combination with IAsp as bolus insulin in paediatric subjects (aged 1 ≤ 18 years of age) with T1DM, followed by a 26 week extension to investigate long term safety and immunogenicity.

The primary objective was to confirm the efficacy of IDeg administered once daily plus mealtime insulin aspart in controlling glycaemia with respect to change in HbA1c after 26 weeks of treatment to a non-inferiority limit of 0.4%.

Subjects with T1DM aged 1 ≤ 18 years treated for at least 3 months on any insulin regime with a daily insulin requirement of < 2.0 U/kg and HbA1c at screening of ≤ 11% were eligible to participate.

There were 350 subjects randomised in a 1:1 ratio to IDeg OD (n = 174) or IDet (n = 176). The study population were mostly White (75%), male (55.4%) with mean duration of diabetes of 4.0 years and mean HbA1c of 8.1%. There were 24.3% subjects aged 1 to 5 years, 39.4% aged 6 to 11 years and 36.3% aged 12 to 17 years.

The majority of subjects completed the study; IDeg = 170 (97.7%), IDet = 165 (93.8%). After 26 weeks of treatment, the mean (SD) HbA1c was 8.0 (1.1) % in the IDeg OD group and 7.7 (1.0) in the IDet group. IDeg OD was non-inferior to IDet with an estimated treatment difference (IDeg-IDet) of 0.15% (95% CI: -0.03, 0.32). The estimated treatment difference (IDeg - IDet) in change from Baseline in FPG was -0.42 mmol/L (95% CI: -1.65, 0.81).

There was no statistically significant difference between treatment arms in the observed rate of nocturnal confirmed hypoglycaemia episodes (estimated rate ratio (IDeg/IDet) = 0.96 (95% CI: 0.70, 1.34)) or confirmed hypoglycaemia episodes (estimated rate ratio (IDeg/IDet) = 1.13 (95% CI: 0.90, 1.41)).

Comment: The proposed indication for IDeg is '*to improve glycaemic control in adult patients with diabetes mellitus*'. This study is therefore not relevant to the current application. However, if the sponsor wishes to extend the indication to include paediatric subjects, the full clinical study report should be submitted as part of another application, subject to approval of IDeg.

6.2.2. Studies in subjects with T2DM

6.2.2.1. Study NN1250-3667

Study NN1250-3667 is a 26-week extension of the 52 week Study NN1250-3582 to compare the safety and efficacy of IDeg and IGlar plus IAsp in T2DM subjects with or without OADs. The synopsis provided results after 78 weeks of treatment. The primary objective was to assess long-term safety and tolerability of IDeg in combination with IAsp, with efficacy after 78 weeks of treatment a secondary objective. The extension study included 757 subjects (IDeg = 566, IGlar = 191).

After 78 weeks of treatment the mean reduction in HbA1c was -1.03% and -1.19% for IDeg and IGlar groups respectively, with an estimated treatment difference (IDeg-IGlar) of 0.16% (95% CI: 0.02, 0.30). FPG decreased by 2.18 mmol/L in the IDeg group and 2.05 mmol/L in the IGlar group after 78 weeks of treatment (estimated mean treatment difference (IDeg - IGlar) = -0.13 mmol/L (95% CI: -0.50, 0.24)). The proportion of subjects achieving HbA1c < 7% without confirmed hypoglycaemia was 20.7% for both IDeg and IGlar.

The observed rate of confirmed hypoglycaemic episodes was 1039 and 1271 per 100 PYE respectively for IDeg and IGlar (estimated rate ratio (IDeg/IGlar) = 0.85 (95% CI: 0.70, 1.02)). The rate of nocturnal confirmed hypoglycaemic episodes was lower for IDeg (134 per 100 PYE) than IGlar (176 per 100 PYE), estimated rate ratio (IDeg/IGlar) = 0.76 (95% CI: 0.58, 1.00)).

6.2.2.2. Study NN1250-3643

Study NN1250-3643 is a 52 week extension of Study NN1250-3579 comparing the safety and efficacy of IDeg and IGlar in insulin naïve T2DM subjects treated with OADs. The synopsis provided results after 104 weeks of treatment. The primary objective was to assess long term safety and tolerability of IDeg. Efficacy measures were secondary outcomes. Subjects completing the 52 week Study 3579 were eligible to participate in the extension study and restarted treatment as previously randomly allocated in Study 3579. There were 725 subjects (IDeg = 551, IGlar = 174) included in the extension study.

After 104 weeks of treatment, the estimated mean reduction from baseline in HbA1c was 0.96% and 1.08% for IDeg and IGlar respectively, with an estimated mean treatment difference (IDeg - IGlar) of 0.12% (95% CI: -0.01, 0.25). FPG decreased during the trial in both groups, with a statistically significantly greater reduction from baseline in mean FPG observed for IDeg (estimated mean treatment difference (IDeg - IGlar) = -0.38 mmol/L (95% CI: -0.70, -0.06)).

The observed proportion of subjects achieving HbA1c < 7% without confirmed hypoglycaemia during the last 12 weeks of treatment was 37.4% and 45.3% with IDeg and IGlar respectively, with the odds of achieving this target statistically significantly greater with IGlar than IDeg (estimated odds ratio (IDeg/IGlar) = 0.72 (95% CI: 0.53, 0.98)).

The observed rate of confirmed hypoglycaemic episodes was 172 and 205 episodes per 100 PYE for IDeg and IGlar respectively (estimated rate ratio (IDeg/IGlar) = 0.84 (95% CI: 0.68, 1.04)). The rate of nocturnal confirmed hypoglycaemic episodes was lower for IDeg (27 per 100 PYE) than IGlar (46 per 100 PYE), estimated rate ratio (IDeg/IGlar) = 0.57 (95% CI: 0.40, 0.81)).

6.2.2.3. Study NN1250-3587

Study NN1250-3587 is a 26 week, randomised, open label, multinational, 2 arm, parallel group efficacy and safety study comparing IDeg with IGlar in combination with metformin in insulin naïve subjects with T2DM inadequately controlled on OADs. The study population included adults with T2DM ≥ 6 months treated with metformin ± other OADs (insulin secretogogue, DPP-4I, α-glucosidase inhibitor) with HbA1c 7.0 to 10.0% inclusive. The study population comprised 833 subjects randomised 2:1 to IDeg (n = 555) or IGlar (n = 278).

The primary objective was to compare the difference between IDeg and IGlar in change from baseline in HbA1c after 26 weeks of treatment to a non-inferiority limit of 0.4%. The estimated mean treatment difference (IDeg-IGlar) for the change from Baseline in HbA1c after 26 weeks of treatment was -0.05% (95% CI: -0.18, 0.08) with non-inferiority confirmed. A reduction in FPG was observed in both groups (estimated mean treatment difference (IDeg-IGlar) = -0.26 mmol/L (95% CI: -0.53, 0.02)). The observed proportion of subjects achieving HbA1c < 7% without confirmed hypoglycaemia was 46.8% with IDeg and 42.4% with IGlar.

The estimated rate of confirmed hypoglycaemic episodes was numerically lower with IDeg (estimated rate ratio (IDeg/IGlar) = 0.80 (95% CI: 0.59, 1.10)), as was the estimated rate of nocturnal confirmed hypoglycaemic episodes (estimated rate ratio (IDeg/IGlar) = 0.77 (95% CI: 0.43, 1.37)).

Comment: The efficacy of IDeg compared to IGlar in insulin naïve subjects with T2DM has been determined previously in the pivotal Study 3579 evaluated in the previously withdrawn submission.

6.2.2.4. Study NN1250-3923

Study NN1250-3923 was a confirmatory 22 week, randomised, open label, multicentre, 2 arm, parallel group treat-to-target study to evaluate the efficacy and safety of IDeg 200 U/mL with IDeg 100 U /mL in adult subjects with T2DM treated with OADs. There were 373 subjects randomised 1:1 to IDeg 200 U/mL OD (n = 186) or to IDeg 100 U/mL OD (n = 187). Subjects

continued their current OAD treatment regimen (metformin, insulin secretogogue, α-glucosidase inhibitor, pioglitazone or DPP-4I). The pre-trial OAD treatment regimens were evenly distributed between the two groups. The primary objective was to compare the difference in change from Baseline in HbA1c between IDeg 200 U/mL and IDeg 100 U/mL in combination with OADs at the end of treatment to a non-inferiority limit of 0.4%.

At the end of treatment, the dose ratio (IDeg 200 U/mL / IDeg 100 U/mL) of the mean daily insulin dose (U) was 1.01. The estimated mean change in HbA1c was -0.81% for IDeg 200 U/mL and -0.70% for IDeg 100 U/mL. The estimated treatment difference (IDeg 200 U/mL – IDeg 100 U/mL was -0.11% (95% CI: -0.28, 0.05)), confirming non-inferiority. A comparable reduction in FPG was observed in both groups with an estimated treatment difference (IDeg 200 U/mL – IDeg 100 U/ mL) of 0.11 mmol/L (95% CI: -0.34, 0.55). The observed proportion of subjects achieving HbA1c < 7% without confirmed hypoglycaemia was 19.5% with IDeg 200 U/mL and 13.9% with IDeg 100 U/mL. The difference between the two groups in terms of the odds of achieving this target was not statistically significant (estimated odds ratio (IDeg 200 U/mL/IDeg 100 U/mL) = 1.52 (95% CI: 0.83, 2.80)).

There were no differences between the two groups with respect to confirmed hypoglycaemic episodes or nocturnal hypoglycaemic episodes (estimated rate ratios 0.96 (95% CI: 0.67, 1.36) and 0.93 (95% CI: 0.56, 1.55) respectively).

6.2.2.5. Study NN1250-3943

Study NN1250-3943 was a confirmatory, randomised, controlled, open label, multicentre, cross over, treat-to-target study to evaluate the efficacy, patient reported outcomes and safety of IDeg 200 U/mL compared with IGlar in adult subjects with T2DM requiring high dose insulin. The study included a 16 week run-in period during which subjects discontinued their OAD except for metformin, and commenced IGlar. At the end of the run-in period, those subjects requiring IGlar ≥ 81 U were randomised (1:1) to one of two treatment sequences (IDeg/IGlar (n = 73) and IGlar/IDeg (n = 72)). There were 2 x 16 week treatment periods.

The primary endpoint was comparing the change from baseline in HbA1c between IDeg and IGlar at the end of 16 weeks treatment to a non-inferiority limit of 0.4%. IDeg was non-inferior to IGlar in terms of lowering HbA1c, with an estimated treatment difference of -0.06% (95% CI: -0.21, 0.09).

The observed mean change in FPG from Baseline to Week 16 was greater for subjects with IDeg compared with IGlar (-0.8 mmol/L versus -0.0 mmol/L, estimated treatment difference (IDeg-IGlar) = -0.77 mmol/L (95% CI: -1.39, -0.15)). The proportion of subjects achieving HbA1c < 7.0% without confirmed hypoglycaemia was higher in the IDeg group (18.1%) than the IGlar group (10.1%).

The rate of confirmed hypoglycaemia was statistically significantly lower for IDeg than IGlar (192 versus 288 events per 100 PYE; estimated treatment ratio = 0.594 (95% CI: 0.391, 0.901)) and the rate of nocturnal confirmed hypoglycaemia numerically lower for IDeg (38 events per 100 PYE versus 63 events per 100 PYE for IGlar; estimated treatment ratio (IDeg/IGlar) = 0.655 (95% CI: 0.290, 1.480)).

Comment: Non-inferiority of IDeg 200 U/mL to IGlar with respect to change from Baseline in HbA1c at the end of treatment was confirmed in the pivotal Study 3672.

6.2.2.6. Study NN1250-3846

Study NN1250-3846 was a 26 week, randomised, open label, uncontrolled, multicentre, 2 armed parallel groups, and treat-to target study to assess the safety and efficacy of 2 different self-titration algorithms for IDeg OD in combination with metformin in insulin naïve adult subjects with T2DM inadequately treated on OADs. Subjects were randomised (1:1) to 1 of 2 parallel IDeg treatment arms: simple titration algorithm (IDeg simple = 111) or step wise titration algorithm (IDeg step wise = 111). IDeg was administered once daily, with a variable injection

time allowed with 8 to 40 hours inclusive between injections. For subjects in the simple titration treatment arm, self-titration was performed once weekly based on a single pre-breakfast SMPG value measured on the day of insulin titration. For subjects in the step wise titration treatment arm, self- titration was performed once weekly based on the lowest value of 3 pre-breakfast SMPG values measured on 3 consecutive days (2 days prior and day of insulin titration).

At the end of treatment, the estimated mean reduction in HbA1c was -1.13% in the IDeg simple arm and -0.97% in the IDeg step wise arm. Non-inferiority of IDeg simple to IDeg step wise was confirmed, with an estimated mean treatment difference (IDeg simple – IDeg step wise) of -0.16% (95% CI: -0.39, 0.07). The estimated mean treatment difference (IDeg simple – IDeg step wise) in change from Baseline in mean FPG was -0.57 mmol/L (95% CI: -1.30, 0.17). There were a greater number of subjects in the IDeg simple treatment group who achieved HbA1c < 7% without confirmed hypoglycaemia (40.6%) compared to the IDeg step wise group (34.6%), although the difference was not statistically significant.

The rate of confirmed hypoglycaemic episodes was 160 per 100 PYE versus 117 per 100 PYE for the IDeg simple and IDeg step wise treatment arms respectively (estimated treatment ratio (IDeg simple/IDeg step wise) = 1.25 (95% CI: 0.72, 2.14)). The rate of nocturnal confirmed hypoglycaemic episodes was low for both groups (21 and 10 events per 100 PYE for IDeg simple and IDeg step wise respectively).

Comment: This study is evaluating a dosing algorithm rather than medicine. Less improvement in the groups that used the lowest of 3 blood glucose levels would be expected.

6.2.2.7. Study NN1250-4060

Study NN1250-4060 was a 26 week, randomised, open label, multicentre, 2 x 2 factorial design, treat-to-target efficacy and safety study comparing 2 dosing schedules and 2 titration algorithms for IDeg OD in adult Japanese subjects with T2DM inadequately controlled on IGlar ± OADs. The primary objective was to confirm the efficacy of IDeg OD ± OADs in controlling glycaemia by comparing the difference in change from Baseline in HbA1c after 26 weeks of treatment between IDeg OD flexible dosing and IDeg OD fixed dosing, both in combination with OADs, to a non-inferiority limit of 0.4%. The efficacy of IDeg OD simple versus stepwise titration in terms of glycaemic control (change from Baseline in HbA1c) was a secondary objective. Subjects were allowed to continue a maximum of 3 OADs (metformin, SU/glinide, α-GI, DPP-4I or pioglitazone).

The trial was conducted as a 2 x 2 factorial design, with subjects randomised 1:1:1:1 to 1 of 4 treatment arms: IDeg OD (flexible dosing and stepwise titration), IDeg OD (fixed dosing and stepwise titration), IDeg OD (flexible dosing and simple titration), IDeg OD (fixed dosing and simple titration). There were 458 subjects randomised, n = 229 each in the IDeg simple and IDeg stepwise titration groups, and n = 229 each in the fixed and flexible dosing arms.

IDeg was administered once daily as per dosing and titration algorithm in a treat-to-target approach. Subjects in the fixed dosing arm administered IDeg at an agreed time with the Investigator which was to preferably remain unchanged during the trial. Subjects in the flexible dosing group also established an agreed dosing time which was preferably kept unchanged during the trial, however flexibility of dosing time (within ± 8 hours) was allowed for these subjects when convenient.

For subjects in the simple titration treatment arm, titration was performed once weekly based on a single pre-breakfast SMPG value measured on the morning of study visit. The dose of IDeg was increased by 2 units if pre-breakfast SMPG was above target (4.0 to 5.0 mmol/L) or reduced by 2 units if below target. For subjects in the step wise titration treatment arm titration was performed once weekly based on the mean of 3 pre-breakfast SMPG values measured on 3 consecutive days (2 days prior and day of insulin titration). The dose of IDeg could be increased in multiples of 2 units (to a maximum of 8 units) based on mean SMPG value. A

reduction of IDeg dose occurred if there was symptomatic hypoglycaemia or documented low SMPG (≤ 3.9 mmol/L) occurred without explanation.

The primary endpoint was analysed using an ANOVA model with dosing scheme, titration scheme, interaction between dosing and titration scheme, anti-diabetic therapy at screening and sex as fixed factors and age and baseline HbA1c as covariates.

After 26 weeks of treatment, non-inferiority of IDeg flexible dosing to IDeg fixed dosing was demonstrated (estimated mean treatment difference (IDeg flexible-IDeg fixed) = 0.08% (95% CI: -0.05, 0.22)), with the mean HbA1c reducing from 7.8% to 7.3% in the flexible dosing group and from 7.8% to 7.2% in the fixed dosing group. Similar reductions in observed mean FPG from Baseline were reported for both groups); 7.4 mmol/L to 5.8 mmol/L in IDeg flexible group and 7.4mmol/L to 6.0 mmol/L in the IDeg fixed group). There was no statistically significant difference between the groups in terms of mean FPG reduction from Baseline (estimated mean treatment difference not provided in SI units).

Non-inferiority of IDeg simple titration to IDeg stepwise titration in terms of HbA1c reduction was confirmed with estimated mean treatment difference (IDeg simple – IDeg step wise) of 0.03% (95% CI: -0.10, 0.17). Reductions from Baseline FPG were observed in both groups (7.3 mmol/L to 5.8 mmol/L and 7.5 mmol/L to 6.0 mmol/L for IDeg simple and IDeg step wise respectively) , with no statistically significant difference observed between the groups (estimated mean treatment difference not provided in SI units).

The rate of confirmed hypoglycaemia was numerically higher with IDeg flexible dosing (425 events per 100 PYE) versus IDeg fixed dosing (327 events per 100 PYE), with an estimated treatment ratio of 1.33 (95% CI: 0.95, 1.86). A numerically higher rate of nocturnal confirmed hypoglycaemic episodes was also observed with IDeg flexible dosing compared with IDeg fixed dosing (69 versus 51 events per 100 PYE respectively).

The rate of confirmed hypoglycaemic episodes was numerically higher for the IDeg simple titration versus stepwise titration arms (414 and 337 events per 100 PYE respectively), with the difference in the rate of confirmed hypoglycaemic episodes not statistically significant (estimated treatment ratio (IDeg simple/IDeg stepwise) = 1.28 (95% CI: 0.92, 1.80)). Similarly, the rate of nocturnal confirmed hypoglycaemic episodes was numerically higher in the IDeg simple titration arm (71 events per 1200 PYE) than the IDeg stepwise titration arm (49 events per 100 PYE). The rate of nocturnal confirmed hypoglycaemic episodes was stated to be statistically significantly higher in the simple titration group from 16 weeks (maintenance period) to the end of study.

Comment: This study also addressed a dosing algorithm rather than the medicine. The evaluator notes subjects in the flexible dosing group were to administer IDeg at an agreed dosing time which was to preferably remain unchanged; it is not clear from the synopsis how often these subjects utilised flexible dosing. This approach differed from that of pivotal Studies 3770 (T1DM subjects) and 3668 (T2DM subjects) investigating flexible dosing where IDeg was administered in a pre-specified rotating schedule.

6.3. Evaluator's conclusions on clinical efficacy

The efficacy of IDeg was considered demonstrated in the pivotal studies evaluated in the original withdrawn submission. A tabular summary of these data is included in this report (see Tables 6 and 7 above). There were no outstanding issues with regard to efficacy identified by the clinical evaluator for previously withdrawn submission at the second round. The study synopses submitted in the current dossier are considered supportive of the established efficacy.

Acknowledging the limitations of data provided in synopses, the extension studies suggest long term glycaemic control (up to 104 weeks) in terms of sustained reduction in HbA1c in

subjects with T1DM and T2DM. This needs to be considered in conjunction with the long term safety profile (see Section 8, below).

It is noted the proposed PI contains information from the pivotal studies evaluated in the previously withdrawn submission. There are no long term data in the proposed PI. Whilst at face value the long term extension data provided in the synopses are reassuring in terms of HbA1c reduction, data from synopses are not suitable for inclusion in the PI. If the sponsor wishes to include these studies in the PI, a new submission with the full study reports would be required.

The evaluator would recommend the sponsor submit the data from the paediatric study in a separate submission to support the use in children.

7. Clinical safety

The second round evaluation report (dated 6 February 2013) of the withdrawn submission states that '*the evaluation of safety is based on all 41 clinical trials completed with IDeg as of 31 January 2011, with the main focus on the pooled safety data from the eleven IDeg therapeutic confirmatory trials (3 T1DM and 8 T2DM studies)'.* Since the original submission, a number of trials have been completed and this updated data has been submitted in the current submission. In the current submission, updated integrated data was submitted in 2 documents: Summary of Clinical Safety Addendum and the Safety update IDeg, which contain data up until 30 September 2014. These two documents provide integrated safety data from the updated data set (cut off 30 September 2011); although the Safety Update IDeg appears to contain additional details compared to the Summary of Clinical Safety Addendum. The safety section of this CER references data presented in these two documents. However, these two documents compare the updated data to data contained within the Integrated Safety Summary (ISS) which was not submitted in the original Australian submission of IDeg but considered by the sponsor to be similar to the safety data evaluated by the original evaluator.

The following is noted with respect to the data submitted in the original Australian submission and that within the ISS:

- The original Integrated Safety Summary contained data from 41 completed clinical trials and 5624 subjects, with data up to 31 January 2011; the original TGA submission also contained 41 clinical trials and 5624 subjects were exposed to IDeg that had been completed as of 31 January 2011.
- 'All subject' safety analysis dataset presented in the original Australian clinical evaluation for the IDeg group and the comparator group (in a table of the second round clinical evaluation report) for all therapeutic confirmatory trials contains the same number of patients as that contained within the US FDA ISS dataset (in a table from the Summary of Clinical Safety Addendum).
- Adverse event summary table for both the original Australian evaluation and the ISS are identical (from a table in the second round CER and a table in Summary of Clinical Safety Addendum respectively).
- Serious adverse event summary table for both the original Australian evaluation and the ISS are identical (from a table in the second round CER and a table in Summary of Clinical Safety Addendum respectively)

As the data submitted to the TGA originally was very similar, if not identical, to that contained within the ISS, the current evaluator has made reference to the ISS as this is what is described in the dossier.

7.1. Studies providing evaluable safety data

7.1.1. Pivotal studies that assessed safety as the sole primary outcome

Of the new studies which have been submitted, several have safety as the sole primary outcome:

- Study EX 1250-4080 (or the DEVOTE trial), a dedicated cardiovascular outcomes study submitted as full interim report. This study randomised subjects to either IDeg or IGlar. See Section 7.2 below for further details.
- A number of extension studies (submitted as synopses):
  - Study NN1250-3644: an extension trial of IDeg compared to IGlar, both in combination with IAsp as mealtime insulin in T1DM contains results after 104 weeks of treatment (52 weeks of treatment in Study NN1250-3583 plus 52 weeks of treatment in extension trial).
  - Study NN1250-3725: an extension trial of IDeg compared to IDet in T1DM in a basal bolus regimen; contains results after 52 weeks treatment (26 weeks in the main Study NN1250-3585 and 26 weeks in extension trial)
  - Study NN1250-3643: extension trial of IDeg plus oral anti diabetic with IGlar plus oral anti diabetic in T2DM; contains results after 104 weeks of treatment (52 weeks in the main Study NN1250-3579 and 52 weeks in extension trial)
  - Study NN1250-3667: extension trial comparing IDeg with IGlar plus IAsp +/-metformin and +/- pioglitazone in T2DM; contains the results after 78 weeks treatment (52 weeks in the main Study NN1250-3582 and 26 weeks in extension trial).

See Section 6 (Clinical Efficacy, above) for details of studies.

7.1.2. Pivotal and/or main efficacy studies

In the original withdrawn submission, the evaluation of safety was based on all 41 clinical trials completed with IDeg as of 31 January 2011 however the main focus was on the pooled data from the 11 therapeutic confirmatory studies as listed in Table 8, below.

Table 8: Pivotal studies from the original submission, indicating whether additional data contained within current submission

Study number	Disease state	Description	Additional data contained in current submission?[1]
NN1250-3583	Type 1 diabetes mellitus	52 week randomised, controlled, open label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of IDeg and IGlar both administered once daily in a basal bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes	Yes, extension trial (Study NN1250-3644)

Study number	Disease state	Description	Additional data contained in current submission?[1]
NN1250-3585	Type 1 diabetes mellitus	A Phase IIIa, 26 week confirmatory, randomised, controlled, open label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of IDeg and IDet in a basal bolus regimen with IAsp as mealtime insulin in subjects with T1DM	Yes, extension trial (Study NN1250-3725)
NN1250-3770	Type 1 diabetes mellitus	26 week, multinational, multicentre, open label, randomised, 3 arm, parallel, treat-to-target trial comparing the efficacy and safety of IDeg injected once daily (OD) at intervals of approximately 8 to 40 h between doses (IDegFlex) versus IGlar injected OD according to local labelling at approximately the same time in subjects with T1DM	Yes, extension trial (Study NN1250-3770) (all subjects changed to an IDeg Free Flex regimen)
NN1250-3579	Type 2 diabetes mellitus	Phase IIIa, 52 week, randomised, controlled, open label, active comparator, multicentre, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and IGlar, both injected once daily (OD) in combination with OAD in subjects with type 2 diabetes mellitus currently treated with OAD(s) and who qualified for more intensified treatment	Yes, extension trial (Study NN1250-3643)

Study number	Disease state	Description	Additional data contained in current submission?[1]
NN1250-3580	Type 2 diabetes mellitus	Phase IIIa, confirmatory 26 week, randomised, open label, multicentre, multinational, controlled trial comparing the efficacy and safety of IDeg and sitagliptin each dosed once daily in a population of insulin naïve subjects with T2DM qualifying for intensified treatment and currently treated with 1 or 2 OADs (metformin, sulphonylurea (SU), glinides or pioglitazone) in any combination at an unchanged dosing for at least 3 months prior to screening.	No
NN1250-3582	Type 2 diabetes mellitus	Phase IIIa, 52 week, multicentre, multinational, open label, randomised, active controlled, treat-to-target, parallel group trial comparing the efficacy and safety of IDeg and IGlar in a basal bolus regimen with IAsp as mealtime insulin ± metformin ± pioglitazone in subjects with type 2 diabetes mellitus.	Yes, extension trial (Study NN1250-3667)
NN1250-3586	Type 2 diabetes mellitus	Phase IIIa, 26 week randomised, confirmatory, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of IDeg and IGlar, both injected once daily in combination with OAD(s) in a population of insulin naïve subjects with T2DM currently treated with OADs qualifying for intensified treatment.	No

Study number	Disease state	Description	Additional data contained in current submission?[1]
NN1250-3668	Type 2 diabetes mellitus	Phase IIIa, 26 week randomised, controlled, open label, multicentre, multinational, 3 arm, treat-to-target trial comparing efficacy and safety of 3 different dosing regimens of either NN1250 (IDeg) or IGlar with or without combination with OAD treatment, in subjects with type 2 diabetes mellitus.	No
NN1250-3672	Type 2 diabetes mellitus	Phase IIIa, confirmatory 26 week randomised, controlled, open labelled, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of IDeg 200 U/mL and IGlar both administered OD in combination with metformin and DPP-4 inhibitor in insulin-naïve subjects diagnosed with type 2 diabetes mellitus currently treated with OADs qualifying for intensified treatment.	No
NN1250-3718	Type 2 diabetes mellitus	Multicentre, multinational randomised (1:1), controlled, open-label, treat-to- target trial. Active control (IGlar).	No
NN1250-3724	Type 2 diabetes mellitus	Multicentre, multinational randomised (1:1), controlled, open label, treat-to-target trial. Active control (IGlar).	No

1) Clinical development program as of 30 September 2014.

The original CER noted that Studies NN1250-3718 and NN1250-3724 were not considered to be pivotal as these used a 3 weekly dosing schedule which is inconsistent with proposed dosing schedule. However, it should be noted that the Summary of Clinical Safety addendum included these studies in the Phase III patient pool and thus are included in the updated integrated safety data contained within this report.

It is also noted that the new extension trials had the same design and trial set up as the main trials, in general, except for Study NN1250-3770-EXT. In this trial, the subjects receiving IDeg Flex or IDeg OD regimens in the main trial, all changed to an IDeg Free Flex regimen (subjects

allowed to inject IDeg at any time of the day with a minimum time interval of 8 hours and a maximum time interval of 40 hours between IDeg doses).

7.1.3. Other studies

According to the cover letter outlining new information submitted in this dossier, 34 additional clinical trials have been included. These include 19 IDeg specific (denoted with trial number starting with NN1250) trials as follows:

- 12 Phase III studies/trials (5 extension trials, as above, considered to be pivotal and/or main efficacy studies; 6 new Phase III trials and 1 paediatric trial).
- 5 clinical pharmacology studies/trials.
- 2 'other therapeutic' studies/trials as designated within the Summary of Clinical Safety Addendum; Study NN1250-3874 was defined as a Phase IIIb trial but has a Phase I-like design and Study NN1250-3943 is of short duration.

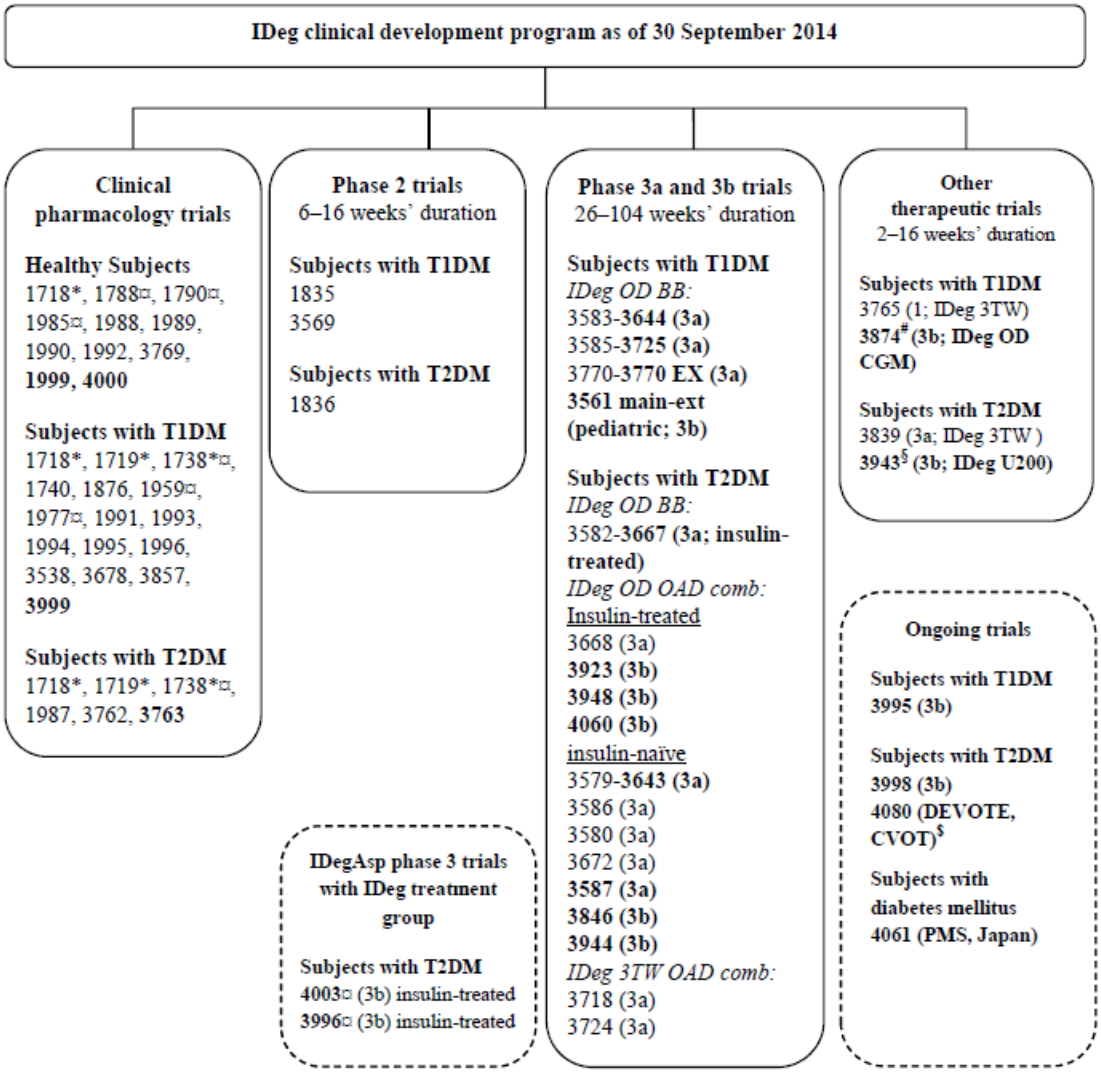
This is somewhat consistent with the studies listed in the Summary of Clinical Summary Addendum (IDeg) as new since the previous US FDA submission (completed between 31 January 2011 and 30 September 2014) except for the one pharmacology study which appears to have been included in error in the cover letter included in the current Australian submission. According to the cover letter, 5 new trials have been submitted: Studies NN1250-1999, NN1250-3769, NN1250-4000 (3 studies in healthy subjects), NN1250-3999 (in subjects with T1DM) and NN1250-3763 (in subjects with T2DM), however it appears that Study NN1250-3769 was assessed in the original CER (6 August 2013) and therefore is not considered to be new.

As there is consistency between these 2 lists of new studies, summary data as presented in Summary of Clinical Safety Addendum IDeg will be referenced in this CER.

No new Phase II trials have been completed since the original submission.

The following figure (Figure 7) is a summary of all completed and ongoing clinical trials with IDeg as of 30 September 2014 (from Summary of Clinical Safety Addendum)

Figure 7: Completed and ongoing trials with IDeg as of 30 September 2011



Bold text: Trials not included in the original NDA. Trials marked with * included both subjects with T1DM and subjects with T2DM. Trials marked with ¤ included both IDeg and IDegAsp. #Trial 3874 was defined as a phase 3b trial but is included in the 'Other' category due to its phase 1-like design. §Trial 3943 is in the 'Other trial' category due to short duration of the trial. $Data from Trial 4080 (DEVOTE) will not be included in the safety update, but presented in a separate report. BB: basal bolus, CGM: continuous glucose monitoring, EX: extension, IDeg: insulin degludec, IDegAsp: insulin degludec/insulin aspart; OAD: oral antidiabetic agents, OD: once daily, PMS: post-marketing study, 3TW: three times weekly, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus

It should be noted that Study EX 1250-4080 (the DEVOTE trial), is not included in the above figure as it was ongoing as of 30 September 2014 and is reported separately in Section 7.2.1 below.

7.2. Studies that assessed safety as the sole primary outcome

7.2.1. Study EX1250-4080 'DEVOTE', a cardiovascular outcomes study

7.2.1.1. Study design, objectives, locations and dates

The trial is a randomised, double blind, parallel group, controlled Phase IIIb trial. The control arm was IGlar, a long acting insulin preparation and the comparator was IDeg; both added to standard of care treatment in patients with T2DM. The patient population was enriched for

higher CV risk and included subjects with established T2DM and existing, or at high risk of, CV disease.

The primary objective was to confirm the cardiovascular safety of IDeg in comparison to IGlar.

The secondary objectives were to assess the efficacy of IDeg on markers of glycaemic control and assess other safety parameters in the study population.

The data described in this CER is from the interim analysis. The objective of the interim analysis is to assess the non-inferiority of IDeg to IGlar for the primary endpoint of the trial (time from randomisation to first major adverse cardiovascular event (MACE)). MACE is a 3 component endpoint composed of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. An interim analysis was pre-specified after at least 150 confirmed first MACEs had occurred.

The trial was conducted at 435 sites in the following countries: Algeria, Argentina, Brazil, Canada, Croatia, Greece, India, Italy, Japan, Republic of Korea, Malaysia, Mexico, Poland, Romania, Russian Federations, South Africa, Spain, Thailand, United Kingdom and United States. The trial was not conducted in Australia.

Assumptions regarding recruitment in the sample size calculations have been realised – the original intent was for all subjects to be recruited within 18 months; first patient, first visit occurred on 28 October 2013 and the total number of subjects planned to be enrolled had been recruited at the time of the interim analysis cut-off date of 19 January 2015. There was no defined follow up time for the interim analysis; rather it was determined by the number of first MACE that occurred and it is noted that those who had a first-MACE could continue in the study and will continue to be followed. The trial is event driven and will continue until a pre-specified number (633) of first MACEs occur.

As stated by the sponsor, the trial design was influenced by input from the FDA regarding key trial design factors (such as double blinded trial and IGlar as comparator), specific glycaemic control targets, hypoglycaemia definitions, target population demographics (such as population with established T2DM and cardiovascular risk factors), other safety parameters (such as population are followed for the duration of the trial, even if study drug is discontinued) and some operational matters.

7.2.1.2. Inclusion and exclusion criteria

As part of the trial design, subjects with T2DM at high risk of experiencing CV events were eligible for inclusion.

Key inclusion criteria included: T2DM; HbA1c ≥ 7.0 % OR HbA1c < 7.0 % and current insulin treatment corresponding to ≥ 20 U/day of basal insulin; current treatment with one or more oral or injectable anti-diabetic agent(s); age > 50 years with a history of at least 1 pre-specified CV condition; or age > 60 years with at least 1 pre-specified CV risk factor.

Key exclusion criteria included: An acute coronary or cerebrovascular event in the previous 60 days; planned coronary, carotid or peripheral artery revascularisation; chronic heart failure NYHA class IV; current haemodialysis or peritoneal dialysis or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 per CKD-Epi; end stage liver disease; current or past (within the last 5 years) malignant neoplasms except basal cell and squamous cell skin carcinoma.

7.2.1.3. Study treatments

Subjects were randomised to either IGlar or IDeg in a 1:1 ratio. The trial was double blinded. Current anti-diabetic therapy was to be continued except for the basal insulin component (if any) which was replaced by the randomised treatment, IDeg or IGlar. Both treatments were provided in 100 U/mL 10 mL vials (not pens) and were to be administered daily between dinner and bedtime subcutaneously.

No maximum dose was specified for either treatment; dose was titrated according to individual patient plasma glucose values. The protocol recommended adjustment of insulin dose on a weekly basis and blood glucose measurements should be made 3 days prior to titration.

For those patients receiving rapid-acting insulin (bolus) prior to the trial, the investigator could decide to replace this with IAsp, which was provided free of charge to the subject; pens were provided for IAsp if required.

Intensification or treatment with bolus insulin and other anti-diabetic treatments was allowed during the trial. The protocol provided detailed recommendations regarding the use of insulin.

Following randomisation, the subjects had two weekly site visits and thereafter, the subjects were had contact with the site on a monthly basis, either by phone or at a site visit (every 3 months). For each subject's site visit or phone contact, the most recent data from the prior week was recorded in the eCRF.

There were no restrictions in concomitant medication permitted in the trial except that no investigational medicine product was allowed. Cardiovascular disease and risk factors were to be treated at the investigator's discretion at the local standard of care. If a subject became pregnant or intended to become pregnant, the trial product was discontinued but could be restarted after pregnancy and lactation.

7.2.1.4. Safety variables and outcomes

The primary endpoint was defined as the time from randomisation to first occurrence of Event Adjudication Committee (EAC) confirmed Major Adverse Cardiovascular Events (MACE). MACE included events confirmed as CV death (of which unknown/undetermined causes of death were also included for the statistical analysis), non-fatal myocardial infarction and non-fatal stroke.

The EAC consisted of members external to the sponsor and therefore considered independent; they were blinded to treatment allocation. The EAC adjudicated on predefined cardiovascular events and episodes of severe hypoglycaemia. The EAC consisted of 10 permanent members who are 'board certified' in cardiology (4 members), neurology (3), endocrinology (3) and clinical experts in the diagnosis and treatment of the following endpoints and medical aspects of clinical trials: acute coronary syndrome (ACS), cerebrovascular events, fatal events and episodes of severe hypoglycaemia.

Table 9, shown below, is an overview of the adjudication of CV endpoints from the interim analysis study report.

Table 9: Adjudication of CV endpoints

Event type	Description	Adjudication outcome
Death	All deaths irrespectively of cause	• **CV death** • Non CV death • **Undetermined***
Acute coronary syndrome (ACS)	Symptoms of myocardial ischaemia requiring hospitalisation or peri-procedural myocardial ischaemia or silent myocardial infarction.	**Acute myocardial infarction (AMI)** • **STEMI** • **Non-STEMI** **Silent MI** Unstable angina pectoris requiring hospitalisation
Cerebrovascular events	Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction	**Stroke:** • **ischaemic** • **haemorrhagic** • **undetermined**

* regarded as CV-death in statistical analyses. 3-component MACE consists of CV deaths, including undetermined death, non-fatal MI and non-fatal stroke (events marked in **bold**).
ACS, acute coronary syndrome; AMI, acute myocardial infarction; CV, cardiovascular; MI, myocardial infarction; STEMI, ST elevation myocardial infarction.

Note: Table taken from interim study report

All events potentially related to death, acute coronary syndrome, cerebrovascular events and hypoglycaemia were pre-defined as applicable for adjudication. Potential events were identified by a number of different methods: investigator identified, EAC identified, from centrally read ECGs and a pre-defined search of preferred terms for all reported adverse events. Subjects who withdrew early were followed up with respect to MACE-related outcomes until the termination of the trial, if agreed to by the subject.

Safety data collection was limited to Serious Adverse Events (SAEs), events associated with drug discontinuation and medication errors leading to an SAE, except in Japan where non-serious AEs and non-severe hypoglycaemic episodes were required by the Japanese authorities. The sponsor states in the interim analysis report that this limited safety data collection is consistent with FDA guidance.

Severe hypoglycaemia was defined as 'an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions' as defined by the American Diabetes Association.[8] Episodes of hypoglycaemia where the subject was not able to self-treat were reported on a specific hypoglycaemic episode CRF.

Interim analysis safety related secondary endpoints included:

- Number of EAC-confirmed MACE and unstable angina pectoris requiring hospitalisation
- Time from randomisation to all-cause deaths
- Number of SAEs
- Number of EAC confirmed events of severe hypoglycaemia
- Number of medications errors leading to an SAEs
- Number of AEs leading to discontinuation of investigational product
- Number of technical complaints related to AEs

It is noted that outcomes specifically related to neoplasms are also reported in the interim study report. Outcomes related to laboratory parameters, vital signs and physical examination findings during the trial period were not specifically reported in the interim analysis study report; only if reported as an SAE.

The following secondary endpoints were reported from pooled data:

- Glycosylated haemoglobin (HbA1c)
- Fasting plasma glucose (FPG)
- Investigational product dose, that is, basal insulin dose

Further elaboration of HbA1c, investigational product dose and FPG will not be made in this clinical evaluation report as they were not part of the pre-defined interim safety analysis; drug exposure is discussed later in Section 7.2.1.13 (Results for other outcomes).

7.2.1.5. Randomisation and blinding methods

Subjects were randomised to either IDeg or IGlar by use of a central web based interactive voice/web response system in a 1:1 ratio. The randomisation was generated by the sponsor, however the method used to generate the random allocation sequence is not reported.

[8] Seaquist E, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. J Clin Endocrinol Metab 2013; 98(5):1845-1859.

This study was carried out in a double blinded manner. The EAC was also blinded to the treatment received. To conceal treatment allocation, dispensing unit numbers were allocated by the interactive voice/web response system and visually, the IDeg and IGlar were indistinguishable. Unblinding of individual patients was only to occur in a medical emergency, if necessary.

7.2.1.6. Analysis populations

The full analysis set (FAS) was used as the only analysis set for the interim analysis. The full analysis set includes all randomised subjects and subjects are analysed 'as randomised'.

7.2.1.7. Sample size

The sample size for the interim analysis was determined by the number of EAC confirmed first MACEs in the FAS; it was calculated that 150 EAC confirmed first MACEs will provide 95% power to rule out a hazard ratio exceeding 1.8, assuming a true hazard ratio of 1.0.

The total number of patients enrolled in the trial was based on the final primary evaluation, that is, calculation that 633 EAC confirmed first MACEs will provide a 91% power to rule out hazard ratios exceeding 1.3 (assuming a true hazard ratio of 1.0). The assumptions included were that the EAC confirmed first MACE would occur at a rate of 2.1 per 100 patient years of exposure, recruitment occurs over 18 months and the 'lost to follow up' rate is 1%. Therefore, it was calculated that a total of 7500 subjects (3750 per arm) are required for a 5 year study.

7.2.1.8. Statistical methods

As stated above, the interim analysis was performed when at least 150 EAC-confirmed first major adverse cardiovascular events (MACEs) had been accumulated. It is noted that the sponsor has stated in the study report that the interim analysis is performed solely for regulatory purposes and no changes to the trial design or conduct has been or will be made based on the results.

The primary endpoint of the interim analysis was analysed using a Cox proportional hazard approach with treatment group as factor using the FAS. The data was planned to be presented descriptively in a Kaplan-Meier plot according to treatment group (IDeg versus IGlar) and the hazard ratio and two-sided 95% confidence interval will be estimated.

Non-inferiority of IDeg to IGlar will be considered confirmed if the upper limit of the 2 sided 95% confidence interval for the hazard ratio is < 1.8 or equivalent if the p-value for the 1 sided test of H_0: HR ≥ 1.8 against H_a: HR < 1.8, is less than 2.5%. Per the interim study report, the FDA recommended that there be enough MACE to definitively exclude an increased hazard of 80%; this study had a power of 95%.

Subjects were censored at last direct contact, if there had been no prior MACE. Time to censoring date was calculated from the date of randomisation. If a subject was 'lost to follow up' or withdrew consent, the subject was censored at the date for the subject's last direct contact (on site visit or phone contact with subject). The exposure period was defined as the time period from the date of randomisation to date of last direct contact. Following a first (non-fatal) MACE, subjects continued in the trial. In a case where the date of the EAC confirmed event differed from the date provided by the investigator, the EAC determined date was used. It is also noted that at the time of the database lock date, some events that had occurred would not yet have been adjudicated by the EAC. These events were not included in the primary analysis.

The statistical analysis plan states that no adjustment of the alpha level was made since the primary endpoint of the interim analysis is different to that of the final evaluation (rule out hazard ratio of 1.3 and 1.8 respectively) and the interim analysis outcome does not impact on the ongoing trial design, conduct or analysis.

Sensitivity analyses were carried out, using the same Cox regression model as the primary analysis and on the FAS. A pre-specified supportive analysis was also done; this included all EAC-confirmed MACE as well as identified MACE events yet to be adjudicated by the EAC.

All secondary endpoints were also analysed using the FAS.

The statistical analysis plan for the interim analysis was finalised prior to the database lock for the interim analysis; the interim study report notes that there are some additional data presented that were not stipulated in the interim analysis statistical analysis plan, however these do not appear to relate to the primary endpoint.

7.2.1.9. Participant flow

Table 10: Summary of the subjects who participated in the interim analysis

Subjects	IDeg	IGlar	Total
Number of subjects screened			8203
Number of subjects randomised	3818	3820	7638
Number of subjects exposed to study drug	3807 (99.7%)	3802 (99.5%)	7609 (99.6%)
Proportion of days on treatment (of the total time in trial)	98.1%	97.9%	
Number of subjects on a treatment pause (temporary or permanent) at time of interim analysis database lock	116 (3.0%)	136 (3.6%)	252 (3.3%)
Number of subjects on treatment at time of interim analysis database lock	3655 (95.7%)	3618 (94.7%)	7273 (95.2%)
Number of deaths	30 (0.8%)	45 (1.2%)	75 (1.0)
Number of subjects withdrawn from the trial at time of interim analysis database lock (not including deaths)	6 (0.2%)	3 (0.1%)	9 (0.1%)
Total patient years on trial treatment at interim analysis database lock (Patient years of exposure)	1830.9	1824.5	3655.4

7.2.1.10. Major protocol violations/deviations

The study report for the interim analysis includes only 'important protocol deviations' with a status of closed as of the 23 January 2015 (4 days after the cut-off date for the interim analysis). A total of 122 important protocol deviations were reported at a site level and 565 at a subject level. None of the subjects with important protocol deviations withdrew from the trial although investigational product was discontinued in some cases.

The study report identified 2 subsets of protocol deviations which potentially impact the outcomes of the interim analysis:

- 6 'duplicate subjects' were identified; these subjects were randomised at 2 different trial sites with 2 different subject numbers. Data from these subjects collected at the site where

they were first randomised were used and the subjects were withdrawn at the second site. This resulted in 4 subjects included in the IDeg group and 2 subjects included in the IGlar group. It is unclear from the report which study drug these patients actually received. None of the six subjects had an EAC confirmed MACE prior to the database lock; however, one subject who had been randomised to both IDeg and IGlar had an adjudication outcome pending for an investigator reported myocardial infarction. Thus, for the purposes of the primary endpoint for this interim analysis, it is not expected that these deviations will impact the outcome.

- Thirteen protocol deviations, affecting 11 subjects, related to the concurrent participation of subjects in other trials in addition to Study EX1250-4080. Subjects were asked to discontinue Study EX1250-4080 treatment and no subject had a MACE or SAE reported prior to the interim analysis. This is unlikely to affect the outcome of this trial.

7.2.1.11. Baseline data

At the time of cut off for the interim analysis (19 January 2015), subjects had participated in the trial for a minimum of 12 weeks and at most 59.5 weeks. Mean time on trial was 6.6 months for IDeg and 6.7 months for IGlar. Assessment of treatment compliance was not formally done.

Table 11: Baseline data for the subjects at the interim analysis database lock

	IDeg	IGlar	Total
Total number of subjects in FAS data set[1]	3818	3820	7638
Age in years (mean)	64.9	65.0	65.0
Age group (% of total) • 50 to 60 years • > 60 to 65 years • > 65 to 75 years • > 75 years	100% • 27.8 • 25.7 • 28.4 • 8.1	100% • 28.2 • 25.8 • 37.0 • 9.0	100% • 28.0 • 25.7 • 37.7 • 8.6
Female (% of total)	37.2	37.6	37.4
Male (% of total)	62.8	62.4	62.6
BMI (kg/m^2) mean	33.6	33.6	33.6
Renal function (mean eGFR; mL/min/SSA)	68.0	67.7	67.8
Smoking status (% of total): Current/ Never/Previous	11.3/44.3/44.5	11.0/45.6/43.4	11.1/44.9/43.9
Duration of diabetes (years) mean	16.2	15.8	16.0
HbA1c ≥ 7.0% at Baseline (% of total, where total is 7600)	Not stated	Not stated	83.3
Mean HbA1c at Baseline (%)	Not stated	Not stated	8.1

	IDeg	IGlar	Total
Mean fasting blood glucose (mmol/L)	Not stated	Not stated	9.5

1) Note: some data missing for individual subject parameters and therefore the number of subjects for an individual parameter is not always the same as total number of subjects in the FAS; difference is indicated if measurement presented is a percentage of total dataset subjects.

In general, the arms were relatively well balanced for the characteristics and parameters measured (mean stated in this evaluation report, where relevant). Many subjects have had long standing diabetes, with a mean duration of 16.0 years across both arms although it is also noted that there was a range of subjects enrolled, from newly diagnosed to those with advanced disease (duration of diabetes at baseline ranged up to 64.3 years). The mean HbA1c at Baseline was high at 8.1% (pooled data for both arms).

The intent of the trial was to enrol subjects at high risk of experiencing a cardiovascular event and this is reflected in the number of subjects with established cardiovascular disease and risk factors for cardiovascular disease.

Table 12: Pre-existing cardiovascular risk factors for the study subjects

	IDeg N	IDeg (%)	IGlar N	IGlar (%)	Total N	Total (%)
Number of subjects	3818		3820		7638	
Established CV disease						
a) prior myocardial infarction	1292	(33.8)	1295	(33.9)	2587	(33.9)
b) prior stroke or prior transient ischaemic attack	589	(15.4)	646	(16.9)	1235	(16.2)
c) prior arterial revascularisation	1704	(44.6)	1660	(43.5)	3364	(44.0)
d) >50% stenosis on angiography	958	(25.1)	960	(25.1)	1918	(25.1)
e) history of symptomatic coronary heart disease	649	(17.0)	639	(16.7)	1288	(16.9)
f) asymptomatic cardiac ischemia	166	(4.3)	162	(4.2)	328	(4.3)
g) chronic heart failure NYHA II-III	456	(11.9)	480	(12.6)	936	(12.3)
h) chronic kidney disease	1187	(31.1)	1183	(31.0)	2370	(31.0)
Risk factors for CV disease						
i) microalbuminuria or proteinuria	1234	(32.3)	1247	(32.6)	2481	(32.5)
j) hypertension and left ventricular hypertrophy	742	(19.4)	775	(20.3)	1517	(19.9)
k) left ventricular systolic and diastolic dysfunction	250	(6.5)	250	(6.5)	500	(6.5)
l) ankle/brachial index <0.9	136	(3.6)	145	(3.8)	281	(3.7)

N, Number of subjects; %, percentages are based on N; CV; cardiovascular; NYHA, New York Heart Association; IDeg, insulin degludec; IGlar, insulin glargine (Lantus®); TIA, transient ischaemic attack.
Please note that a given subject might have several criteria fulfilled, including criteria belonging to different age groups. Chronic kidney disease corresponding to glomerular filtration rate 30-59 mL/min/1.73 m^2 per CKD-Epi.

Note: From Interim study report for Study EX1250-4080

Baseline cardiovascular characteristics were relatively well balanced, with a slight preponderance (> 1% difference) towards prior stroke or transient ischaemic attack on the IGlar arm and vice versa for prior arterial revascularisation on the IDeg arm.

Current treatment with more than one oral or injectable anti-diabetic agent(s) was required for inclusion on this study. Treatments are summarised in Table 13, below.

Table 13: Pre-trial antidiabetic treatment (FAS)

	IDeg N	(%)	IGlar N	(%)	Total N	(%)
Number of subjects	3818		3820		7638	
Blood glucose lowering drugs at baseline						
Metformin	2284	(59.8)	2259	(59.1)	4543	(59.5)
SU	1112	(29.1)	1105	(28.9)	2217	(29.0)
Alpha glucosidase inhibitors	63	(1.7)	67	(1.8)	130	(1.7)
TZD	146	(3.8)	123	(3.2)	269	(3.5)
DPP4 inhibitors	461	(12.1)	474	(12.4)	935	(12.2)
GLP1 receptor agonist	296	(7.8)	298	(7.8)	594	(7.8)
SGLT2 inhibitors	79	(2.1)	84	(2.2)	163	(2.1)
Other	47	(1.2)	61	(1.6)	108	(1.4)
Not registered with any of the above	997	(26.1)	1017	(26.6)	2014	(26.4)
Insulin treatment at baseline						
Premix	382	(10.0)	349	(9.1)	731	(9.6)
Short acting	1385	(36.3)	1405	(36.8)	2790	(36.5)
Intermediate acting¤	552	(14.5)	551	(14.4)	1103	(14.4)
Long acting	2283	(59.8)	2283	(59.8)	4566	(59.8)
Insulin naive	607	(15.9)	620	(16.2)	1227	(16.1)

IDeg, insulin degludec; IGlar, insulin glargine (Lantus®); N, number of subjects; %, proportion of subjects based on N; SU, sulphonylurea; TZD, thiazolidinedione; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide-1; SGLT-2, sodium-Dependent Glucose Transporter Two; Other, A10BX drugs not categorised as GLP1-RA or SGLT2-2; Intermediate acting insulin products covers human insulin products, NPH and unknown type of insulin products; Pre-trial refers to the active antidiabetic treatment at baseline.

Original table from Interim study report for Study EX1250-4080

Approximately 75% of subjects were treated with oral anti-diabetic medications/blood glucose lowering drugs prior to enrolment and more than 25% were receiving only insulin at baseline. This is a relatively large proportion of patients receiving insulin only; comment will be sought from the sponsor regarding the relevance to Australian practice. Australian guidelines recommend insulin as part of treatment intensification. It is usually not used as sole agent unless there are contraindications to other oral therapy or the patient has T1DM.[9] The most common blood glucose lowering drugs were metformin, DPP4 inhibitors and GLP1 receptor agonists. It is noted that the types of anti-diabetic medication received during the trial was not provided in the study report in a clear summary; the sponsor will be asked to provide this.

Table 14: Pre-trial cardiovascular medication

	IDeg N = 3818	IGlar N = 3820	Total N = 7638
Antihypertensive therapy (% of total)	93.7	93.6	93.6
Statins (% of total)	78.5	77.1	77.8
Platelet aggregation inhibitors (% of total)	68.5	68.4	68.4

The common use of cardiovascular medication is a reflection of the study population with pre-existing cardiovascular disease and/or risk factors. Use of individual medications/subgroups within the antihypertensive and platelet aggregation inhibitor groups was well balanced across each arm; however, it is noted that the use of statin medication is

[9] The Royal Australian College of General Practitioners. General practice management of type 2 diabetes: 2016-18. East Melbourne, Vic: RACGP, 2016.

relatively low compared to what may be expected in standard Australian clinical practice in this cardiovascular high risk population. For high risk patients, routine treatment with lipid lowering therapy is recommended.[10] The sponsor will be asked to comment on this in the clinical questions, below.

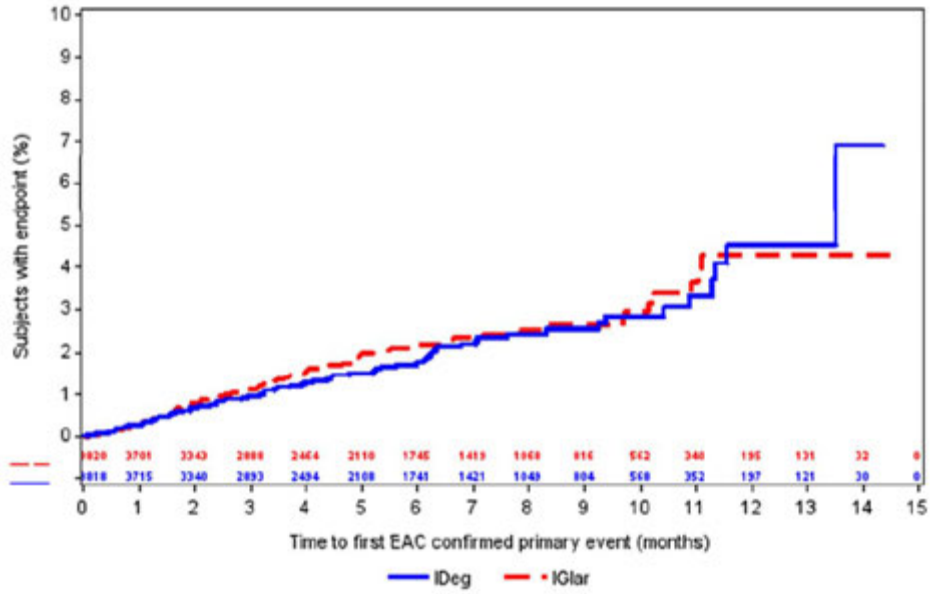
7.2.1.12. Results for the primary safety outcome

The primary endpoint for the interim analysis was the time from randomisation to the first EAC-confirmed MACE. MACE was defined as CV death, an unknown cause of death, a non-fatal myocardial infarction or a non-fatal stroke. The full analysis set (FAS) was used and subjects were analysed as randomised.

72 EAC confirmed first MACE occurred on the IDeg arm and 78 on the IGlar arm. The estimated hazard ratio was 0.920 with a 95% confidence interval of 0.668 to 1.267. Non-inferiority is claimed since the upper bound of the confidence interval is below 1.8 and the actual point estimate is less than 1.0.

Figure 8, below, is a plot of the time to first EAC confirmed MACE.

Figure 8: Time to first EAC confirmed MACE



Numbers represents number of subjects at risk.
EAC, event adjudication committee; IDeg, insulin degludec; IGlar, insulin glargine (Lantus®).

The study report notes that '*after 12 months of observation fewer than 200 subjects are at risk in each treatment arm, and the Kaplan-Meier curves become unreliable at this point as illustrated by the flatness of the curves, followed by large 'jumps' caused by single events*.

[10] The Royal Australian College of General Practitioners. General practice management of type 2 diabetes: 2016-18. East Melbourne, Vic: RACGP, 2016.

Table 15: Summary of the EAC confirmed first MACE events

	IDeg N	(%)	E	R	IGlar N	(%)	E	R	Total N	(%)	E	R
Number of subjects	3818				3820				7638			
PYO	1870				1869				3739			
First MACE	72	(1.89)	72	3.85	78	(2.04)	78	4.17	150	(1.96)	150	4.01
Cardiovascular death	21	(0.55)	21	1.12	20	(0.52)	20	1.07	41	(0.54)	41	1.10
MI (non-fatal)	32	(0.84)	32	1.71	37	(0.97)	37	1.98	69	(0.90)	69	1.85
Stroke (non-fatal)	19	(0.50)	19	1.02	21	(0.55)	21	1.12	40	(0.52)	40	1.07

IDeg, insulin degludec; IGlar, insulin glargine (Lantus®); EAC, event adjudication committee; MACE, major cardiovascular event; N, number of subjects; %, percentage of subjects; E, number of events; R, event rate per 100 patient years of observation (PYO); PYO, patient years of observation; CV, cardiovascular; MI, myocardial infarction. Undetermined causes of deaths are classified as cardiovascular deaths.

From interim study report

As seen in the Table 15 (above), non-fatal myocardial infarctions were the most common first MACE event on each arm, followed by cardiovascular death and then non-fatal stroke.

The interim report states that given the observed result at the interim analysis, it is estimated that there is a 97% probability of excluding the margin of 1.3 with the assumption of hazard ratio = 1.0 at final analysis.

Results from the pre-specified sensitivity analyses were consistent with the primary analysis. A pre-specified supportive analysis included all potential first MACE events that had yet to be EAC adjudicated; the hazard ratio for this analysis was 0.764 (95% confidence interval 0.573, 1.019) reflecting the higher number of events from the IGlar arm awaiting adjudication compared to that of IDeg (29 on IGlar arm compared to 10 events on IDeg arm; total of 39 events). This is supportive of the primary analysis however should be interpreted cautiously.

Subgroup analyses showed that the incidence of EAC confirmed MACE was higher in the subgroup with established CV disease compared to risk factors only and that in those subjects with an EAC confirmed first MACE, the use of CV medication at Baseline was slightly more common. Subgroup analysis needs to be interpreted with caution in this interim analysis as the study was not powered for this.

7.2.1.13. Results for other safety outcomes

Other results related to EAC-confirmed cardiovascular outcomes

- Overall, 201 cardiovascular events were confirmed by the EAC; this includes 13 events which were subsequent MACE and 38 events of unstable angina requiring hospitalisation. All MACE events that occurred more than once were non-fatal myocardial infarcts, as can be seen in the table below. At the time of the interim analysis database lock, slightly more EAC confirmed MACE events (all events, not just first time) had occurred on the IGlar arm (85 compared to 78 events).

Table 16: EAC confirmed cardiovascular events

	IDeg N	(%)	E	R	IGlar N	(%)	E	R	Total N	(%)	E	R
Number of subjects	3818				3820				7638			
PYO	1870				1869				3739			
CV events incl. CV death	93	(2.44)	101	5.40	92	(2.41)	100	5.35	185	(2.42)	201	5.38
MACE	72	(1.89)	78	4.17	78	(2.04)	85	4.55	150	(1.96)	163	4.36
MI (non fatal)	32	(0.84)	38	2.03	38	(0.99)	40	2.14	70	(0.92)	78	2.09
Stroke (non fatal)	19	(0.50)	19	1.02	22	(0.58)	22	1.18	41	(0.54)	41	1.10
Cardiovascular death	18	(0.47)	18	0.96	20	(0.52)	20	1.07	38	(0.50)	38	1.02
Undetermined causes of death	3	(0.08)	3	0.16	3	(0.08)	3	0.16	6	(0.08)	6	0.16
UAP requiring hospitalisation	22	(0.58)	23	1.23	15	(0.39)	15	0.80	37	(0.48)	38	1.02

IDeg, insulin degludec; IGlar, insulin glargine (Lantus®);N, number of subjects; %, percentage of subjects; E, number of events; MACE, major adverse cardiovascular event; R, event rate per 100 patient years of observation (PYO); PYO, patient years of observation; EAC, event adjudication committee; CV, cardiovascular; MI, myocardial infarction; UAP, unstable angina pectoris.

Table from Interim study report

- Of the EAC confirmed deaths, the majority were determined to be cardiovascular related (18 on the IDeg arm, 20 on the IGlar arm) and 6 subjects had an undetermined cause of death (3 on each arm).
  - Of these deaths, sudden cardiac death occurred most commonly (14 on IDeg arm, 12 on IGlar arm), followed by death due to acute myocardial infarction (2 on IDeg arm, 6 on IGlar arm). The other causes of EAC confirmed cardiovascular death were secondary to heart failure (IDeg: 0; IGlar: 1) and stroke (IDeg: 2; IGlar:1)
  - Of the non-cardiovascular deaths (6 on the IDeg arm and 10 on the IGlar arm), a pulmonary cause was the most common (IDeg: 2; IGlar: 3) followed by malignancy (IDeg: 2; IGlar: 2); no other causes of death had more than one event in its category.
- Seven cardiovascular events occurring in 6 subjects (3 subjects in each group) were not adjudicated due to lack of information. They were reported by the investigator as 3 fatal myocardial infarctions, 2 cerebrovascular events (1 fatal) and one unstable angina.
- At database lock for the interim analysis, there were 39 subjects with a potential MACE (including unstable angina) for which the adjudication outcome was still pending, 10 on the IDeg arm and 29 on the IGlar arm.
- With regards to EAC-confirmed unstable angina requiring hospitalisation, the rate per 100 patient years of observation was slightly higher on the IDeg arm (1.23) compared to the IGlar arm (0.80).

Safety related secondary endpoints

A number of safety related endpoints were specified as secondary endpoints. It is noted that the interim study report states that 'Number of EAC confirmed MACE and unstable angina pectoris requiring hospitalisation events' is a secondary endpoint, however this was not specified in the interim analysis Statistical Analysis Plan (SAP) and therefore not included in this clinical evaluation report. However, the SAP did specify a safety secondary endpoint of 'Number of positively adjudicated unstable angina pectoris requiring hospitalisation' and this is noted below.

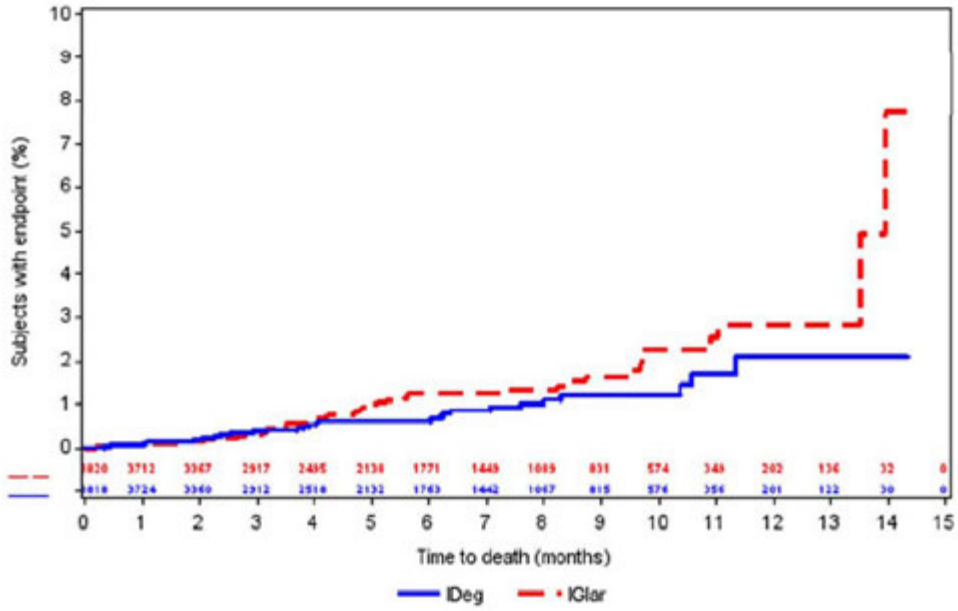
Table 17: Secondary safety related endpoints (interim analysis)

	IDeg		IGlar		Total	
Number of subjects	3818		3820		7638	
Patient years of observation	1870		1869		3937	
	Number	Rate[1]	Number	Rate[1]	Number	Rate[1]
Number of positively adjudicated unstable angina pectoris requiring hospitalisation	23	1.23	15	0.80	38	1.02
Time from randomisation to all-cause deaths	See graph below				Data not provided	
Number of SAEs	717 (number of subjects: 483)	38.34	804 (subjects: 509)	43.01	1521 (subjects: 992)	40.68
Number of EAC-confirmed events of severe hypoglycaemia[2]	90 (number of subjects: 72)	4.81	146 (subjects: 84)	7.81	236 (subjects: 156)	6.31
Number of medication errors leading to an SAEs	1	0.05	2	0.11	Data not provided	
Number of AEs leading to discontinuation of investigational product[3]	211 (number of subjects: 154)	11.3	227 (subjects: 173)	12.1	438 (subjects: 327)	11.7
Number of technical complaints related to AEs	0	0	0	0	0	0

1) Rate: event rate per 100 patient years of observation; 2) individual events included sweating, trembling, hunger, palpitations, confusions, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance, incoordination, headache, malaise, seizure, none of the above; 3) for the purposes of the interim analysis, this was defined as those subjects who interrupted trial treatment due to an AE and had not restarted at the time of the interim analysis database lock. Some may restart after the database lock.

The secondary endpoint of time from randomisation to all cause death is represented graphically as follows in Figure 9 (note that after 12 months of observation, less than 200 subjects are at risk).

Figure 9: Time from randomisation to all cause death



Numbers represents number of subjects at risk; IDeg, insulin degludec; IGlar, insulin glargine (Lantus®).

Overall, there were 30 deaths (0.79% of randomised subjects) on the IDeg arm and 45 (1.18% of randomised subjects) on the IGlar arm.

There are some small imbalances for some safety related secondary endpoints; for example, it is noted that the rate of hospitalisations due to unstable angina was slightly higher on the IDeg arm, however, given that this is an interim analysis and some of the events have occurred with low numbers, definitive conclusions cannot be made at this stage.

7.2.1.14. Other safety results

Drug Exposure (pooled data only)

- Mean duration in trial and proportion of days on treatment (of the total time in trial) at interim analysis was similar for both arms: 6.6 months and 98.1% respectively on the IDeg arm and 6.7 months and 97.9% on the IGlar arm.
- Basal insulin and IAsp (bolus insulin; note: it was the investigator's choice whether to use IAsp as the bolus insulin) (*pooled data only)*: For all subjects, mean daily dose at Baseline was 40.8 U for basal insulin and 41.1 U for IAsp (number of subjects = 3387). The mean dose of both basal and IAsp insulin increased during the first 6 months of treatment: to 59 U and 56.2 U respectively.

SAEs

- Rates for SAEs in terms of severity, action taken, causality and outcome across the two groups were similar.
- Commonly (> 0.2% of subjects) reported SAEs were similar in type and frequency between the two groups. Cardiac failure congestive was the most common SAE. Hypoglycaemia, as a preferred term, was reported on the IDeg arm at a rate twice that of IGlar (1.87 events per 100 patient years of exposure compared to 0.96), however the rates are both relatively low.

Neoplasms

- 38 SAEs relating to neoplasms were reported: 0.5% of subjects reported a neoplasm (rate: 1.02 events per patient years of observation) on each arm.

- At the time of the interim analysis database lock, 18 neoplasm SAEs had been evaluated by blinded, external classifiers. 10 events (in 8 subjects) were classified as malignant neoplasms; 4 events on the IDeg arm and 6 events on the IGlar arm.

Hypoglycaemia

- SAEs of hypoglycaemia were reported numerically more frequently on the IDeg arm compared to the IGlar arm (2.46 events per 100 observation years compared to 1.44, respectively).
- Adverse events (by preferred term) which were potentially related to hypoglycaemia (as determined by sponsor) lead to a higher rate of discontinuation on the IDeg arm (rate 0.32 events per 100 patient years of observation compared to 0.11).

EAC confirmed severe hypoglycaemia

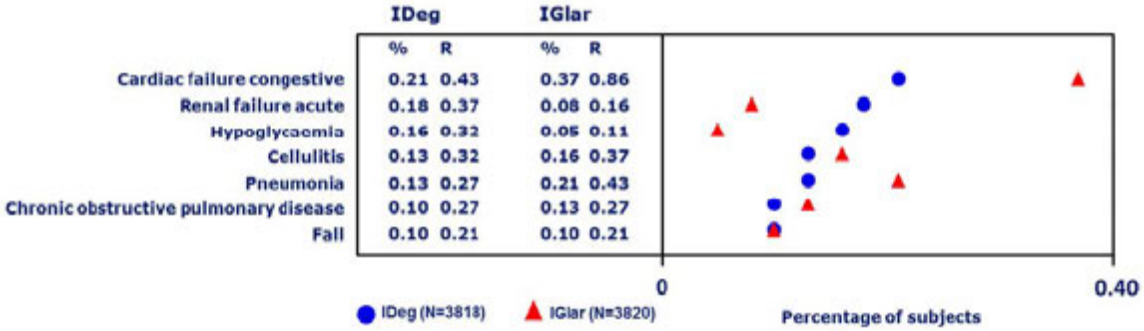
At the time of the cut off for the interim analysis, 373 events had been identified for hypoglycaemia adjudication and 177 had adjudication completed, therefore the results are only preliminary. The EAC confirmed fewer severe hypoglycaemic events with IDeg - 90 events (72 subjects; rate 4.81 events per patient year of observation) on the IDeg arm and 146 events (84 subjects; rate 7.18 events per patient year of observation) on the IGlar arm, although it is noted that the actual proportion of subjects affected were similar (1.9% on IDeg and 2.2% on IGlar) suggesting that some subjects particularly on the IGlar arm may have had multiple episodes.

In terms of baseline characteristics, subjects who were initially insulin naïve had a lower proportion of subjects and rate of EAC confirmed hypoglycaemia. In terms of bolus insulin received, the rate of EAC-confirmed severe hypoglycaemia was higher for those receiving IAsp, compared to those who did not. Overall, it is noted that there are some discrepancies between the two arms with respect to the rates of hypoglycaemia for some parameters. However, it is acknowledged that the aetiology of hypoglycaemia is multifactorial, some numbers are low and the source of these results are from an interim analysis therefore the significance of these discrepancies with relation to the study drug is difficult to determine.

Adverse events leading to discontinuation of investigational product

- 154 of subjects (211 events) on the IDeg arm and 173 subjects (227 events) on the IGlar discontinued due to an adverse event (not including fatal events). The rate of SAEs, severity, causality, outcome and action were relatively similar for both arms. The rate of AEs leading to discontinuation which were considered to be probably or possibly related to study drug or were an SAE were similar on both arms.

Figure 10: AEs which lead to > 0.1% subjects discontinuing study drug



%, percentage of subjects with events; R, event rate per 100 patient years of observation; IDeg, insulin degludec; IGlar, insulin glargine (Lantus®).

Of the AEs which lead to discontinuation in > 0.1% subjects, the rates were numerically higher in the IDeg arm for renal failure acute and hypoglycaemia compared to IGlar, but rates overall were low.

7.2.1.15. Evaluator commentary

This cardiovascular outcomes trial was initiated following the detection of a signal indicating cardiovascular risk associated with IDeg and IDegAsp in the Phase III development programs (See Section 2.4.4 above). The primary endpoint of time from randomisation to the first EAC confirmed MACE was similar for both arms and estimated hazard ratio was 0.920 (95% CI 0.668 to 1.267). The upper limit of the confidence interval was within the bounds of the pre-determined limit of 1.8 and therefore the condition for non-inferiority was met.

Insulin glargine was the comparator product; this product is registered on the ARTG. The cardiovascular safety profile of insulin glargine has been studied in a trial of 12,537 subjects with impaired fasting glucose, impaired glucose tolerance or T2DM.[11] Dosages for both IDeg and IGlar in the study were titrated to individual glucose levels, consistent with recommendations in Australia.[12] Specifically relating to T2DM, the Australian Therapeutic Guidelines suggest a starting dose for T2DM as 0.2 units/kg when added to other anti-hyperglycaemic drugs;[12] the starting dose used in the protocol for those patients who were not currently on insulin was 10 U daily, arguably slightly higher dose than that used in the protocol. This may have implications for the rates of adverse events hypoglycaemia: use at a higher dose in accordance with Australian guidelines may result in higher rates of adverse events than seen in the trial.

This clinical study was well designed; however, a number of limitations are noted:

- The trial population included only those with T2DM. In the original cardiovascular meta-analysis 45% of subjects with the detected cardiac signal had T1DM. The indication being sought by the sponsor for both IDeg and IDegAsp includes patients with T1DM. The external validity of these results with respect to the type 1 diabetic population, especially those younger than 50 years old, is unknown.
- The mean time on study for both arms is just over 6 months. In clinical practice, patients with diabetes will be on treatment with basal insulin for considerably longer than this. This also limits the external validity of these results.

[11] The ORIGIN Trial Investigators 'Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia' N Engl J Med 2012;367:319-28.
[12] Diabetes: management (published November 2013). In eTG complete (Internet). Melbourne: Therapeutic Guidelines Limited; 2016 July

- It is likely that most pre-existing cardiovascular risk factors were more longstanding than either the use of insulin pre study or the use of IDeg or IGlar during the study and is an important factor in the rate of cardiovascular events.
- More than 25% of subjects were on insulin at baseline; if any excess cardiovascular risk was due to insulin, pre-existing treatment may have contributed.
- The outcomes described are derived from an interim analysis; although the primary endpoint result is reassuring with respect to the cardiovascular investigation, final results will be more definitive.

There were several secondary endpoints for this study; however robust conclusions cannot be drawn at this interim analysis stage.

It is noted that the original cardiovascular signal reviewed by ACSOM (see Section 2.4.1 above) included both MACE and MACE+, however according to the sponsor, the FDA specifically requested a definition of MACE that did not include unstable angina. Outcomes for the so called MACE+ (additionally includes angina pectoris; see section 2.4) were not presented in this interim analysis study report, however it is noted that the number of unstable angina requiring hospitalisation (EAC confirmed) was higher on the IDeg arm.

Overall, the study design was robust. The primary endpoint was met for non-inferiority at this interim analysis stage. This study is a better designed study to assess cardiovascular safety than the meta-analysis of clinical trials submitted with the previous evaluation.

7.3. Other Safety studies

7.3.1. Extension studies

For the following studies, primary endpoints included safety outcomes; these studies are also included in the integrated safety analysis. The full study report for these studies were not included in the dossier and therefore not evaluated. Efficacy data for the following studies are described in Section 6.2, above.

7.3.1.1. Study NN1250-3644

This was an extension trial of IDeg compared to IGlar, both in combination with insulin aspart as mealtime insulin in T1DM contains results after 104 weeks of treatment (52 weeks of treatment in Study NN1250-3583 plus 52 weeks of treatment in extension trial).

Relatively similar rates were seen on both arms for adverse events, AEs probably related to study drug, severe AEs, SAEs and AEs leading to withdrawal. However, the rate of AEs that were possibly related to study drug on the IDeg arm was almost double the rate of the IGlar arm (15 events per 100 PYE compared to 8 events respectively). A comment will be sought from the sponsor regarding this.

Outcomes for hypoglycaemia were also relatively similar, except for nocturnal confirmed hypoglycaemic episodes, for which IDeg had a lower rate of 390 episodes per 100 PYE compared to 532 on the IGlar arm.

All other safety parameters noted in the synopsis did not indicate any significant differences except for:

- 6 subjects reporting a change to 'abnormal, clinically significant' fundsocopy findings on the IDeg arm; the number of subjects on the IGlar arm was not reported and is presumed to be zero. Although this difference is noted, it is also noted that randomisation was skewed in a 3:1 manner in favour of IDeg. No rate was reported in the synopsis.
- Statistically significant greater increase from Baseline of HDL cholesterol in the IGlar group compared to IDeg; however, the specific values were not indicated.

A comment will be sought from the sponsor regarding this.

After 104 weeks, mean total daily insulin dose (basal and bolus) was 64 U on the IDeg arm and 68 U on the IDet arm.

7.3.1.2. Study NN1250-3725

This was an extension trial of IDeg compared to IDet in T1DM in a basal bolus regimen and contains results after 52 weeks treatment (26 weeks in the main Study NN1250-3585 and 26 weeks in extension trial).

The IDeg arm reported a higher rate of adverse events compared to the IDet arm: 459 events per 100 PYE compared to 420 events and more subjects reported SAEs on the IDeg arm (12% compared to 7.2%) although the rate was similar (20 events per 100 PYE on the IDeg arm compared to 17 on the IDet arm). A comment will be sought from the sponsor regarding this. Severe AEs were reported at a lower rate on the IDeg arm compared to the IDet arm (23 compared to 35 events per 100 PYE respectively).

In terms of severe hypoglycaemia episodes, outcomes were similar. In terms of confirmed hypoglycaemia, though, the rate was lower on the IDeg arm for both confirmed and nocturnal confirmed hypoglycaemia compared to the IDet arm.

Other safety endpoints did not show any differences, although it is noted that a weight difference of 1.07 kg (95% CI: 0.47 to 1.67) was seen between the arms.

After 52 weeks, mean total daily insulin dose (basal and bolus) was 62 U on the IDeg arm and 72 U on the IDet arm.

7.3.1.3. Study NN1250-3643

This is an extension trial of IDeg plus oral anti diabetic with IGlar plus oral anti diabetic in T2DM and contains results after 104 weeks of treatment (52 weeks in the main Study NN1250-3579 and 52 weeks in extension trial).

The IDeg arm reported a higher rate of adverse events compared to the IGlar arm: 362 events per 100 PYE compared to 339 events; outcomes were relatively similar between the arms for other adverse event endpoints. A comment will be sought from the sponsor regarding the rate difference.

In terms of hypoglycaemia, it is noted that the percentage of IDeg subjects who experienced a confirmed hypoglycaemic episode was higher compared to the IGlar arm (58% compared to 54.9%), however the rate of events was higher on the IGlar arm (172 events per 100 PYE on the IDeg arm compared to 205 on the IGlar arm). A comment from the sponsor will be sought.

After 104 weeks, mean total daily insulin dose (basal and bolus) was the same; 60 U on the IDeg arm and the IGlar arm.

7.3.1.4. Study NN1250 3667

This was an extension trial comparing IDeg with IGlar plus IAsp ± metformin and ± pioglitazone in T2DM, contains the results after 78 weeks treatment (52-weeks in the main Study NN1250-3582 and 26 weeks in the extension trial).

Outcomes were relatively similar for the described adverse events, except for deaths; 3 deaths were reported in the extension trial, all in the IDeg arm, and overall, 11 deaths occurred in the IDeg arm compared to 2 in the IGlar arm. Even considering the skewed randomisation of 3:1 in favour of IDeg, this seems to be a slightly higher proportion on the IDeg arm; a comment will be sought from the sponsor.

In terms of hypoglycaemia, the rates of confirmed and nocturnal hypoglycaemia and severe and nocturnal severe hypoglycaemia were all lower on the IDeg arm compared to the IGlar arm.

After 78 weeks, mean total daily insulin dose (basal and bolus) was the same, 147 U on the IDeg arm and the IGlar arm.

7.3.2. Evaluator commentary

The extension studies provide longer term follow up data for IDeg which is relevant given the use of insulin in clinical practice. A number of discrepancies in some safety parameters reported in the synopses are noted and comment will be sought from the sponsor.

7.4. Integrated safety data

Table 18, below, is from the Summary of Clinical Safety Addendum IDeg and contains data from trials completed as of 30 September 2014. A large number of patients have been exposed to IDeg in clinical trials, the vast majority in Phase III trials. This, however, does not include the DEVOTE trial.

Table 18: Exposure in all completed trials for IDeg and IDegAsp

	IDeg* N	IDegAsp* N	IDeg + IDegAsp* N	Comparator N	Total N
Clinical Pharmacology Trials	1007	487	1295	723	1355
Healthy Subjects	256	76	332	26	358
Subjects with T1DM	608	351	760	549	793
Subjects with T2DM	143	60	203	148	204
Phase 2 trials	330	270	600	306	906
Subjects with T1DM	152	0	152	91	243
Subjects with T2DM	178	270	448	215	663
Phase 3 trials	6206	2382	8568	4098	12666
Subjects with T1DM	1102	362	1464	647	2111
Subjects with T2DM	5104	2020	7104	3451	10555
Insulin-naive Subjects with T2DM	2911	882	3793	2375	6168
Insulin-treated Subjects with T2DM	2193	1138	3311	1076	4387
Other Therapeutic Trials	310	0	310	308	329
Subjects with T1DM	41	0	41	24	42
Subjects with T2DM	269	0	269	284	287
Total	7853	3139	10773	5435	15256

N = Number of subjects, Subjects from clinical pharmacology cross over trials may count in several treatment arms. For clinical pharmacology trials, comparator include placebo.
* Includes all formulations. For Trials 3996 and 4003, exposure to IDeg and IDegAsp was included in the IDeg and IDegAsp columns, respectively, and none was included as 'comparator'. Subjects in main-extension trials only counted once. Similarly, subjects in Trials 4003 (coming from 3941) and 3948 (coming from 3579-3643) only counted once in each column. For Trial 3948, the non-randomized arm was included as IDeg. Trials: 1718 Part 1, 1718 Part 2, 1719, 1738, 1740, 1788, 1790, 1791, 1792, 1835, 1836, 1876, 1959, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1985, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1999, 3538, 3539, 3569, 3570, 3579-3643, 3580, 3582-3667, 3583-3644, 3585-3725, 3586, 3587, 3590-3726, 3592, 3593, 3594-3645, 3597, 3668, 3672, 3678, 3718, 3724, 3762, 3765, 3769, 3770-main-ext, 3834, 3839, 3844, 3846, 3857, 3874, 3896, 3923, 3940, 3941, 3943, 3944, 3948, 3996, 3999, 4000, 4003, 4008, 4060

It is noted that subjects who participated in both main and extension trial parts were counted only once for subject exposure. It is also noted that some trials included only IDeg and IDegAsp and no other comparator. It is also noted that 'other therapeutic trials' included 3 trials which were crossover trials and one that had only a single arm, which presumably accounts for the similar numbers of subjects in the IDeg arm, the comparator arm and total number.

Compared to the data set available in the original Integrated Safety Summary (cut-off date of 31 January 2011), there is now data for 2229 more subjects who received IDeg and 4063 more subjects in total. The majority of the new IDeg subjects participated in Phase III T2DM trials (1931 subjects).

Table 19 (below) shows the exposure time of subjects in all completed Phase III studies.

Table 19: Exposure time of subjects in all completed Phase III studies

	% of patients with any exposure (N)	% of patients with exposure ≥ 6 months (N)	% of patients with exposure ≥ 12 months (N)	% of patients with exposure ≥ 18 months (N)	% of patients with exposure ≥ 24 months (N)	% of patients with exposure ≥ 30 months (N)
All subjects						
IDeg	100 (6206)	84.2 (5224)	33.9 (2102)	(22.9 (1419)	13.6 (841)	6.1 (377))
Comparators	100 (2717)	88.2 (2397)	28.9 (786)	465 (17.1)	9.9 (269)	0
T1DM						
IDeg	100 (1102)	89.9 (991)	79.0 (871)	31.4 (346)	30.0 (331)	0
Comparators	100 (467)	93.4 (436)	80.3 (375)	24.6 (115)	24.2 (113)	0
T2DM						
IDeg	100 (5104)	82.9 (4233)	24.1 (1231)	21.0 (1073)	10.0 (510)	7.4 (377)
Comparators	100 (2250)	87.2 (1961)	18.3 (411)	15.6 (350)	6.9 (156)	0
Insulin naive T2DM						
IDegAsp	100 (2991)	88.9 (2587)	21.0 (611)	18.3 (532)	17.5 (510)	13.0 (377)
Comparators	100 (1770)	86.5 (1531)	11.2 (199)	9.4 (166)	8.8 (156)	0
Insulin treated T2DM						
IDegAsp	100 (2193)	75.1 (1646)	28.3 (620)	24.7 (541)	0	0
Comparators	100 (480)	89.6 (430)	44.2 (212)	38.3 (184)	0	0

N = number of patients. Includes Studies NN- 3579-3643, 3580, 3582-3667, 3583-3644, 3585-3725, 3586, 3587, 3668, 3672, 3718, 3724, 3770-main-ext, 3846, 3923, 3944, 3948, 3996, 4003, 406

As seen in Table 19 above, here has been some follow up in most subgroups for at least 24 months, except the insulin treated T2DM population, for which the longest follow up is less than 24 months.

Comparators in the Phase III trials included a heterogeneous group, IGlar daily + IAsp, IDet daily/twice a day + IAsp, IGlar + oral antidiabetic drugs (some only included metformin), sitagliptin and oral antidiabetic drug, IDeg ± OAD (either fixed or stepwise titration or with IAsp) and placebo/liraglutide/metformin. It is assumed that the comparator arms containing IDeg are not included in the comparator group for the purposes of the integrated safety data

however this is not expressly stated in the Summary of Clinical Safety Addendum document. As previously noted, the Phase III trials were open label; which may result in some reporting bias.

Table 20: Subject disposition for the completed Phase III trials which included IDeg

	IDeg N (%)	Comparator N (%)	Total N (%)
Screened			14064
Screening failures			3900
Run-in failures			624
Withdrawn before randomisation			0
Randomised	6809 (100.0)	2731 (100.0)	9540 (100.0)
Exposed	6769 (99.4)	2717 (99.5)	9486 (99.4)
Completed main trial	5929 (87.1)	2349 (86.0)	8278 (86.8)
Withdrawn at/after randomisation and before extension	880 (12.9)	382 (14.0)	1262 (13.2)
Adverse Events	129 (1.9)	36 (1.3)	165 (1.7)
Fulfilling withdrawal criteria	207 (3.0)	47 (1.7)	254 (2.7)
Ineffective Therapy	23 (0.3)	12 (0.4)	35 (0.4)
Non-Compliance with the protocol	134 (2.0)	77 (2.8)	211 (2.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Other	387 (5.7)	210 (7.7)	597 (6.3)
Completed main trial not screened for extension	231 (3.4)	96 (3.5)	327 (3.4)
Completed main trial screening failure in extension	3 (0.0)	1 (0.0)	4 (0.0)
Included in extension	1955 (100.0)	738 (100.0)	2693 (100.0)
Withdrawn during extension	116 (5.9)	51 (6.9)	167 (6.2)
Adverse Events	20 (1.0)	9 (1.2)	29 (1.1)
Fulfilling withdrawal criteria	21 (1.1)	11 (1.5)	32 (1.2)
Ineffective Therapy	7 (0.4)	2 (0.3)	9 (0.3)
Non-Compliance with the protocol	13 (0.7)	10 (1.4)	23 (0.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Other	55 (2.8)	19 (2.6)	74 (2.7)
Completed extension	1839 (94.1)	687 (93.1)	2526 (93.8)
Full analysis set	6790 (99.7)	2720 (99.6)	9510 (99.7)
Safety analysis set	6769 (99.4)	2717 (99.5)	9486 (99.4)
Extension trial set	1955 (28.7)	738 (27.0)	2693 (28.2)

N= Number of subjects, %= Percentage of subjects.
Percentage of subjects included in extension, withdrawals during extension, reasons for withdrawals during extension and completers in extension are based on number of subject included in extension. All other percentages are based on randomized subjects. For trial 3948, if a subject did not meet one or more of randomisation criteria then subject was not randomized and was considered a screening failure.
Trials: 3579-3643, 3580, 3582-3667, 3583-3644, 3585-3725, 3586, 3587, 3668, 3672, 3718, 3724, 3770-main-ext, 3846, 3923, 3944, 3948, 3996, 4003, 4060

It is noted that more subjects on the IDeg arm withdrew due to 'fulfilling withdrawal criteria' in the main studies (3% compared to 1.7% in the comparator group).

7.4.1. Adverse events

Data in the following section relating to integrated safety analyses are contained within the document entitled Summary of Clinical Safety Addendum IDeg (cut-off date of 30 September 2014) in the current dossier and contains data from studies which were not included in the original submission.

Since the original submission, an additional 18 IDeg trials have been completed; 12 Phase III trials (5 extensions, 6 other Phase III and 1 paediatric trial with a main and extension part), 4 clinical pharmacology studies and 2 'other therapeutic' trials. These trials contribute to the updated data set. In addition, two completed Phase IIIb IDegAsp trials (Studies NN5401-4003 and NN5401-3996) are also included as there was exposure to IDeg in this trial; the subjects on these trials who received IDegAsp are also included in the IDeg group for the purposes of this integrated analysis. This has the potential to bias outcomes although it is acknowledged that the relative number of subjects who received IDegAsp is low (total 156) compared to the total number in the IDeg pool.

The following pools of data have been used for the safety update:

- Phase III trials:
  - All subjects (except for hypoglycaemic episodes)
  - Subjects with T1DM
  - Subjects with T2DM (except for hypoglycaemic episodes)
  - Subjects with T2DM, insulin treated (for exposure, SAEs and hypoglycaemic episodes)
  - Subjects with T2DM, insulin naïve (for exposure, SAEs and hypoglycaemic episodes)
- Phase II, III and other therapeutic trials:
  - All subjects, IDeg trials (for rare AEs)
- Ongoing trials (blinded):
  - All subjects, IDeg trials (for deaths, other SAEs, SAEs leading to withdrawal and pregnancies).

Data specific to 'Other therapeutic trials' (2 to 16 weeks duration; includes 2 new trials; a Phase IIIb trial that is designed like a Phase I trial and a trial with short duration) are not summarised in this CER as the trials are relatively short in duration and the numbers of subjects are relatively small compared to the complete database (310 subjects in total compared to 6206 in IDeg Phase III trials).

In terms of clinical pharmacology trials, although not specifically described in the Summary of Clinical Safety Addendum, data was available for AEs, SAEs, rare events and deaths and presented as pooled data for IDeg and IDegAsp. 7 clinical pharmacology studies have been completed since the 31 January 2011 for both IDeg and IDegAsp, including two conducted with exploratory formulations of IDegAsp, 2 in healthy subjects and 1 terminated early due to poor recruitment, resulting in an additional 167 subjects were included in the IDeg + IDegAsp group and 123 in the comparator group. The exposure in each of these trials was generally relatively short. Updated data specific to clinical pharmacology therapeutic trials are not summarised in this CER.

Descriptive safety data were based on the safety analysis set, defined as the following (from the Summary of Clinical Safety Addendum): *'includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set contribute to the evaluation 'as treated'.*

Data in the ISS and the updated Summary of Clinical Safety Addendum were coded to different versions of Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 and 17.0 respectively which has impacted some of the outcomes. Amongst the changes, some preferred terms have changed from 1 System Organ Class to another between versions including some which relate to hypoglycaemia. Unless noted, data contained within this report has been coded using MedDRA version 17.0.

Adverse events that occurred in individual studies have not been summarised in this CER unless noted.

As of 30 September 2014, 28 Phase III trials with adult subjects have been conducted with IDeg (17 trials) and IDegAsp (11 trials). Pooled data with IDegAsp for all subjects from Phase III trials has also been included for some safety parameters in this clinical evaluation report; deaths, cardiovascular events, immunological events, neoplasms and rare events.

7.4.2. All adverse events (irrespective of relationship to study treatment), Integrated safety analyses (cut-off date of 30 September 2014)

This integrated analysis contains data from the Phase III trials only unless marked.

Table 21 is from the Summary of Clinical Safety Addendum (cut-off date of 30 September 2014) and is a summary of the adverse events occurring in completed Phase III trials.

Table 21: Treatment emergent adverse events occurring in completed Phase III trials

	IDeg				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety analysis set	6769				2717			
All Adverse Events	4658	(68.8)	20784	383.8	1837	(67.6)	7871	383.2
Serious Adverse Events	574	(8.5)	800	14.8	213	(7.8)	290	14.1
Adverse Events leading to Death	26	(0.4)	32	0.6	12	(0.4)	13	0.6
Adverse Events Possibly or Probably Related to IMP	997	(14.7)	1769	32.7	386	(14.2)	632	30.8
Severity								
Mild	4109	(60.7)	14810	273.5	1601	(58.9)	5494	267.5
Moderate	1985	(29.3)	5002	92.4	825	(30.4)	1952	95.0
Severe	630	(9.3)	971	17.9	248	(9.1)	423	20.6
Unknown	1	(0.0)	1	0.0	2	(0.1)	2	0.1
Adverse Events withdrawals	147	(2.2)	193	3.6	45	(1.7)	50	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,

For IDeg, the rates for AE parameters in the updated data are similar compared to the original Integrated Safety Summary (cut-off date 31 January 2011).

With respect to the T1DM population (IDeg = 1102 and comparator = 467), it should be noted that the number of subjects included in this Phase III subset has not changed compared to the Integrated Safety Summary (cut-off date 31 January 2011). It is assumed that this is because the new Phase III trials in T1DM were all extension trials of existing Phase III trials, except for a paediatric trial. Similar to the entire dataset, the rate of events per 100 patient years of exposure in the T1DM IDeg subgroup has generally decreased or remained relatively similar in the new dataset compared to the Integrated Safety Summary (cut off January 31, 2011). The rates are also relatively similar to those seen for the comparator group with only slight variance except for adverse event withdrawals for which the rate in the IDeg group is double that of the comparator group (3.3 events per 100 subject years of exposure compared to 1.5); a discrepancy was also noted in the original evaluation. It is also noted that compared to the overall population, the rate of all adverse events is higher in the T1DM group on both the IDeg group and the comparator arms (IDeg: total population rate 383.8 events per 100 subject years of exposure compared to 411.7 events per 100 subject years of exposure in the T1DM population).

With respect to the T2DM population (IDeg = 5667 and comparator = 2250), the rates of adverse events were generally similar to those in the Integrated Safety Summary (31 January 2011) for further details of updated data. Similarly, these rates of adverse events are generally consistent with (including numerically lower) to the overall population. The IDeg group in the T2DM population was generally not too dissimilar to the comparator group, although there were slightly more mild adverse events on the IDeg arm.

In terms of specific adverse events, nasopharyngitis, upper respiratory tract infections and headaches were the most frequently reported adverse events for both the overall populations as well as the T1DM and T2DM subsets. It is noted that the T1DM subset showed a higher rate of adverse events in the individual categories compared to the overall population or the T2DM subgroup.

7.4.3. Treatment related adverse events (adverse drug reactions), Integrated safety analyses (cut-off date of 30 September 2014)

The most frequently reported related adverse events for all subjects were events relating to hypoglycaemia (multiple preferred terms) and events related to injection site reactions

(multiple preferred terms). Hypoglycaemia was the most commonly reported single preferred term and occurred at a slightly lower rate in the IDeg arm (3.6 events per 100 subject years) compared to the comparator (5.1 events per 100 subject years).

The rate at which adverse events possibly or probably related to the treatment was relatively similar in the IDeg group and comparator group: 32.7 per 100 subject years of exposure; the comparator arm was 30.8 events per 100 subject years of exposure. The rate of possibly/probably related adverse events is slightly lower than that seen in the Integrated Safety Summary (cut-off date 31 January 2011) for both groups.

For T1DM subjects, the rate at which adverse events possibly or probably related to the treatment occurred was 34.6 per 100 subject years of exposure and for T2DM, the rate was 32.0; the comparator arms were 32.4 and 30.2 respectively. The rates for treatment related AE parameters in the updated data (30 September 2014) were lower than that in the Integrated Safety Summary (cut-off date 31 January 2011).

7.4.4. Deaths and other serious adverse events, Integrated safety analyses (cut-off date of 30 September 2014)

38 treatment-emergent deaths were reported in all completed IDeg trials; all occurred in Phase III trials and occurred in similar proportion of subjects in both groups, both for the overall population and T1DM and T2DM subsets. In terms of the types of event leading to death, myocardial infarction was most common (0.1% of subjects for both IDeg (n = 5) and comparator (n = 2)). The only other events that had > 1 incident reported were for the events of 'death' (n = 2), 'road traffic accident' (n = 2) and 'completed suicide' (n = 2), all on the IDeg arm. 17 new deaths have been reported since the ISS (cut off 31 January 2011), including 12 in the IDeg group.

Table 22: Deaths in IDeg clinical trial population

	IDeg, proportion of subjects	Comparator, proportion of subjects
All Deaths in Phase III trials	0.4% (n=26), total n = 6769	0.4% (n=12), total n = 2717
Deaths reported in original Integrated safety summary (completed clinical trials with IDeg; cut-off date 31 January 2011)[1]	0.3% (n = 14)	0.3% (n = 7)
MACE (including UAP) deaths	0.2% (n=13)	0.3% (n = 7)
Deaths in T1DM group	0.5% (n = 5), total N = 1102	0.6% (n = 3), total N = 467
Deaths in T2DM group	0.4% (n = 21), total N = 5667	0.4% (n = 9), total N = 2250

n = number of subjects; 1) As reported in the Summary of Clinical Safety Addendum (IDeg); this data is consistent with the number of deaths reported in the original TGA clinical evaluation, but no percentages were reported.

Frequency of deaths is relatively similar to those reported in the original Integrated Safety Summary.

In terms of causality, 2 deaths were reported to be considered to be possibly related to IDeg by the relevant investigator. The first case was in a 73 year old T2DM subject who developed metastatic small cell lung cancer who was a non-smoker and other risk factors were unknown; the patient was exposed to IDeg for just over 2 years. The sponsor judged the case to be unlikely to be related to IDeg. The second case was the development of metastatic rectal cancer in a 47 year of T2DM patient with a BMI of 29.9 and a history of 'adiposity per magna'. The patient had received IDeg for approximately 14 months prior to diagnosis. The sponsor judged the case to be unlikely to be related to IDeg as there is a known association of colon cancer to both diabetes and obesity. It is noted that both neoplasms and colon cancer are being monitored as requested by the EMA and SwissMedic regulatory agencies respectively (see Section 7.6, Postmarketing experience, for further information).

It is also noted that although the Summary of Clinical Safety Addendum states that 17 deaths have occurred since the ISS, (as referenced in the Summary of Clinical Safety Addendum), 18 case reports are provided. The reason for discrepancy is unclear.

7.4.4.1. Ongoing trials

As of 30 September 2014, three deaths have been reported in ongoing, blinded trials, one event each of cardiac death, myocardial infarction and jaundice cholestatic. One death was reported on a post marketing study, the event reported as 'myocardial infarction'.

7.4.4.2. Insulin degludec and Insulin degludec/aspart (pooled data)

52 deaths have been reported in completed trials with IDeg and IDegAsp, 51 in Phase III trials and a single death in a Phase II trial. In terms of the types of event leading to death in the Phase III trials, myocardial infarction was most common (0.1% of subjects for both IDeg (n = 6) and 0.0% (n = 2) comparator) and the only events that had > 1 incident reported were for the events of 'metastasis to liver' (n = 2) 'death' (n = 3), 'road traffic accident' (n = 2), 'interstitial lung disease' (n = 2) and 'completed suicide' (n = 2), all on the IDeg or IDegAsp arms. A summary of deaths reported in completed trials is given in Table 23, below.

Table 23: Deaths in IDeg + IDegAsp clinical trial population

	IDeg + IDegAsp, proportion of subjects	Comparator, proportion of subjects
All Deaths	Total: 52 deaths	
Deaths reported in Phase III trials	0.4% (n = 36) total N = 9015	0.4% (n = 15) total N = 4098
Deaths reported in Phase III trials in Integrated Safety Summary (cut-off date 31 January 2011)[1]	0.3%	0.2%
MACE (including UAP) deaths in Phase III trials	0.2% (n = 18)	0.2% (n = 9)

n = number of subjects; 1) as reported in the Summary of Clinical Safety Addendum (IDeg)

7.4.5. Other serious adverse events

Information pertaining to SAEs below relates to data from Phase III trials, and is summarised in Table 24, below.

Table 24: Serious adverse events in completed Phase III trials

	IDeg N	(%)	E	R	Comparator N	(%)	E	R
Safety analysis set	6769				2717			
Serious Adverse Events	574	(8.5)	800	14.8	213	(7.8)	290	14.1
Adverse Events leading to Death	26	(0.4)	32	0.6	12	(0.4)	13	0.6
Adverse Events Possibly or Probably Related to IMP	126	(1.9)	158	2.9	36	(1.3)	45	2.2
Severity								
Mild	56	(0.8)	64	1.2	19	(0.7)	20	1.0
Moderate	186	(2.7)	228	4.2	88	(3.2)	96	4.7
Severe	382	(5.6)	508	9.4	130	(4.8)	174	8.5
Adverse Events withdrawals	87	(1.3)	100	1.8	31	(1.1)	33	1.6

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,

In general, the data as presented in the table above does not differ greatly from that presented in the ISS (cut-off date 31 January 2011).

In the Phase III trials, the most frequently reported serious adverse events were related to hypoglycaemia, occurring at a rate of 2.8 events per 100 subject years of exposure for IDeg and 2.4 for the comparators (included multiple preferred terms).

The most commonly reported preferred terms for SAEs (proportion of subjects having adverse event ≥ 0.5%) occurring with IDeg were hypoglycaemia and hypoglycaemic unconsciousness, occurring at similar rate in comparator group.

In terms of the updated data for T1DM, there was little change from the Integrated Safety Summary data (cut off 31 January 2011) for SAE parameters. The rates of SAEs were relatively similar in the IDeg and comparator groups. Hypoglycaemia, hypoglycaemic unconsciousness, hypoglycaemic coma and diabetic ketoacidosis were reported as SAEs (preferred term) in ≥ 0.5% of subjects in the IDeg group.

In terms of subjects with T2DM, frequency of SAE parameters was similar when comparing the Integrated Safety Summary data set (cut off 31 January 2011) and the new data set for IDeg. In terms of differences between the IDeg group and the comparator group, it is noted that SAEs possibly or probably related to the study drug occurred in the IDeg group at double the rate of that of the comparator, however the rates were low overall (1.4 events per 100 subject years of exposure compared to 0.7 respectively). In terms of hypoglycaemia events as a group, SAEs were reported on the IDeg arm at a rate of 1.1 events per 100 PYE (IDeg) compared to 0.5 events per 100 PYE on the comparator arm –the rate for IDeg is double the comparator but also low.

7.4.5.1. Ongoing trials

In the two ongoing IDeg trials, 3.7% of subjects have reported 62 SAEs as of 30 September 2014. SAEs reported by more than 1 subject are as follows: hypoglycaemia, hypoglycaemic unconsciousness, non-cardiac chest pain, chest pain, acute myocardial infarction and coronary artery disease.

7.4.6. Discontinuations due to adverse events, Integrated safety analyses (cut-off date of 30 September 2014)

The following data is for the completed Phase III trials.

Rates of AEs and SAEs leading to withdrawal from a trial in the updated data set are generally similar between the IDeg group and comparator arm, although it is noted that in the T1DM

subset, the percentage of subjects who withdrew from the trial due to an AE occurred at a rate of 3.3 events per 100 subject years of exposure, double that of the comparator group (1.5). These rates are also consistent with those seen in the Integrated Safety Summary (although sometimes numerically less). The most commonly reported preferred terms (≥ 0.1%) that lead to withdrawal in the IDeg group were weight increased, hypoglycaemia, myocardial infarction, cerebrovascular accident, hypoglycaemia unconsciousness and nausea; relatively similar frequencies were seen in the comparator groups. The number of patients who withdrew due to an adverse event that was possibly/probably related to the study treatment was not presented.

7.4.6.1. Ongoing trials

In the 2 ongoing blinded IDeg Phase III trials (Studies NN1250-3995 and NN1250-3998), 5 subjects (0.4%) subjects have discontinued trial product due to six SAEs (as of 30 September 2014):

- Study NN1250-3995: 1 SAE of 'hypoglycaemic unconsciousness' (1 subject) and 2 SAEs of 'hypoglycaemia' (1 subject)
- Study NN1250-3998: 3 SAEs (3 subjects) of 'lung adenocarcinoma', 'pancreatic carcinoma' and 'breast cancer'

7.4.7. Evaluation of issues with possible regulatory impact

7.4.7.1. Liver function and liver toxicity, Integrated safety analyses (cut-off date of 30 September 2014)

Since the original ISS (cut-off date 31 January 2011), one additional subject has recorded an increased in ALT > 3 x upper limit of normal and a total bilirubin twice the upper limit of normal at the withdrawal visit; this subject had a mass in the common bile duct which was diagnosed as a carcinoma.

No subjects across either the IDeg or IDegAsp programs have met the criteria for Hy's law.

7.4.7.2. Renal function and renal toxicity, Integrated safety analyses (cut-off date of 30 September 2014)

No specific information was included in the Summary of Clinical Safety Addendum (IDeg).

7.4.7.3. Other clinical chemistry Integrated safety analyses

No specific information was included in the Summary of Clinical Safety Addendum (IDeg).

7.4.7.4. Haematology and haematological toxicity, Integrated safety analyses (cut-off date of 30 September 2014)

No specific information was included in the Summary of Clinical Safety Addendum (IDeg).

It is noted that 6 adverse events of preferred term 'thrombocytopenia' were reported, including 5 on the IDegAsp group and of these, one event on each arm was considered to be possibly or probably related to the study drug.

7.4.7.5. Other laboratory tests, Integrated safety analyses (cut-off date of 30 September 2014)

No specific information was included in the Summary of Clinical Safety Addendum.

7.4.7.6. Electrocardiograph findings and cardiovascular safety, Integrated safety analyses (cut-off date of 30 September 2014)

Insulin Degludec + IDegAsp

For the integrated analysis presented in the Summary of clinical safety addendum, the definition of Major Adverse Cardiovascular Events (MACE) includes events of acute coronary syndrome (ACS) including unstable angina, stroke or cardiovascular death. This is in comparison to the

dedicated cardiovascular outcomes trial reported in Section 7.2 (the DEVOTE trial) which does not include unstable angina pectoris. Therefore, to distinguish this different definition, the MACE for the integrated safety analysis will be designated as MACE (ISA). A total of 421 cardiovascular events were sent for adjudication by a blinded event committee, 305 for IDeg and IDegAsp and 116 for comparators; the majority were treatment-emergent events.

There was very little difference between the ISS analysis (cut-off date 31 January 2011) and the updated data. The rate of adjudication committee confirmed first MACE (ISA) in updated Phase III trial data was 1.63 events per PYE on the IDeg + IDegAsp arm and 1.36 events per PYE on the comparator arms.

Acute coronary syndrome (including unstable angina) was the most common EAC confirmed MACE (ISA) in both the IDeg + IDegAsp arms and the comparator arms (at a rate of 1.00 event per 100 subject years and 0.87 events per 100 subject years respectively, of which unstable angina was the most common component.

In comparison to the Integrated Safety Summary (cut off 31 January 2011), the rate of cardiovascular death remains similar for both groups. Any differences in the rates of the other individual components of the MACE (ISA) between the Integrated Safety Summary and updated dataset are very small and not likely to be significant.

IDeg only

For IDeg alone data (not pooled with IDegAsp), the rates for adjudicated MACE (ISA) events were 1.8 events per 100 subject years in the IDeg group and 1.5 in the comparator group.

No specific information regarding electrocardiograph findings was included in the Summary of Clinical Safety Addendum.

7.4.7.7. Vital signs and clinical examination findings, Integrated safety analyses (cut-off date of 30 September 2014)

No specific information was included in the Summary of Clinical Safety Addendum.

7.4.7.8. Immunogenicity and immunological events, Integrated safety analyses (cut-off date of 30 September 2014)

Insulin Degludec + IDegAsp

Overall rates of immunogenicity related AEs, including those assessed to be possibly or probably related to study drug, occurred at a similar rate in the IDeg + IDegAsp group and the comparator group.

The 4 most frequent immunogenicity-related AEs in both treatment groups in a narrow scope search were ‘rash’ ‘eczema’ ‘urticaria’) and ‘hypersensitivity’; occurring at a similar rate in both groups. The most frequent immunogenicity-related AEs assessed by the investigator as possibly or probably related to the drug in both treatment groups were ‘rash’ and ‘urticaria’. It is noted that six (0.1%, total n = 9015) IDeg + IDegAsp subjects withdrew from trials due to events assessed possibly or probably related to the trial drug; compared to one from comparator group; 0.0%, total n = 4098, however it is difficult to draw any conclusions based on these low numbers. The three most frequent immunogenicity-related AEs captured by the ‘narrow + broad scope’ search were ‘cough’, ‘oedema peripheral’ and ‘rash’ in the IDeg group.

Per the Summary of Clinical Safety addendum, patterns of immunogenicity AEs are generally consistent with those reported in the ISS (cut-off date 31 January 2011); although it is also noted that the original ISS was analysed with an older MedDRA version. For comparison purposes, it was reanalysed with the same MedDRA version (17.0) as the Summary of Clinical Safety Addendum which resulted in an increase in overall immunogenicity AEs.

The sponsor has stated that the outcomes seen for immunogenicity in patients with T1DM and T2DM and the IDeg trials only was similar to that seen in the pooled data however no data was available to clarify this.

7.4.7.9. Serious skin reactions, Integrated safety analyses (cut-off date of 30 September 2014)

No specific information was included in the Summary of Clinical Safety Addendum (IDeg).

It is noted that 4 adverse events of photosensitivity reaction were reported in the completed Phase III trials for IDeg, 3 in IDeg group and 1 in the comparator group, but none were considered to be possibly or probably related to the study drug.

7.4.7.10. Neoplasms, Integrated safety analyses (cut-off date of 30 September 2014)

In the safety update, a total of 308 events were retrieved by the MedDRA version 17.0 search for neoplasms in the pooled data for IDeg and IDegAsp: rate was 3.5 per 100 PYE for IDeg and IDegAsp and 2.5 events per 100 PYE for comparators in completed Phase III trials. Imbalances were detected for individual preferred terms reported, however the significance is unknown.

Overall rates of neoplasm adverse events reports in subgroups were also presented and further discrepancies were noted (for example, in the T1DM subgroup for the pooled data, the rate in the IDeg + IDegAsp group was 4.0 events per 100 subjects years of exposure compared to 2.7; for IDeg all subjects, the rate in the IDeg group was 3.7events per 100 subjects years of exposure compared to 2.5; for IDeg T1DM, the rate in the IDeg group was 2.3 events per 100 subjects years of exposure compared to 1.1 and for IDeg T2DM, the rate in the IDeg group was 4.2 events per 100 subjects years of exposure compared to 3.0).

Adverse events of neoplasms are identified as medical events of special interest and were sent to an independent and blinded consultant for classification into malignant, benign and unclassifiable neoplasms. Numerically, there is a higher rate of external consultant classified neoplasms in the IDeg + IDegAsp group compared to the comparator groups and this is most pronounced for benign neoplasms (see Table 25, below).

Table 25: External classification of neoplasms in IDeg and IDegAsp trials

	IDeg + IDegAsp				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety update								
Safety Analysis Set	9015				4098			
Total Exposure (yrs)	6685.1				2869.6			
Malignant neoplasms	59	(0.7)	66	1.0	23	(0.6)	23	0.8
Benign neoplasms	186	(2.1)	217	3.2	61	(1.5)	67	2.3
Unclassifiable neoplasms	43	(0.5)	45	0.7	13	(0.3)	13	0.5

N = number of subjects with adverse events; % = proportion of subjects in analysis set having adverse events; E = number of adverse events; R = number of events divided by subject years of exposure multiplied by 100; Total Exposure (yrs) = total exposure in years for safety analysis set

The Summary of Clinical Safety Addendum (updated data) stated that the most common subgroups of malignant neoplasms in the pooled data were gastro-intestinal, skin, bladder, breast, thyroid and pulmonary neoplasms (consistent with the most common cancers).

With respect to IDeg only data, the overall rate of externally classified malignant neoplasms was similar to the pooled data, 1.1 events per 100 subject years of exposure in the IDeg group compared to 0.8 in the comparator group. It is noted that the four most frequently diagnosed malignant carcinomas as assessed by external classification all occur at a higher frequency than the comparator arm (basal cell carcinoma (6 events compared to 0 in the comparator arm),

prostate cancer (5 events compared to 1), adenocarcinoma of colon (4 events compared to 0) and colon cancer (3 events compared to 0) although it is also noted that there are more than twice the number of subjects in the IDeg group compared to the comparator group (6769 and 2717 respectively). Overall, a numerically higher number of benign neoplasms assessed by external classification were reported in the IDeg group (3.3 events per 100 subject years of exposure compared to 2.4 in the comparator group), similar to that seen in the pooled data. Even taking into account the difference in total number of patients enrolled on the IDeg group compared to the comparator group, some numerical discrepancies are noted for some individual benign neoplasms which shown higher rates in the IDeg group compared to the comparators- for example, large intestinal polyp (20 events compared to 2), gastric polyps (14 events compared to 1), renal cyst (18 events compared to 2), hepatic cysts (7 events compared to 0), colon adenoma (8 events for IDeg compared to 0) and lipoma (7 events compared to 1). A comment will be sought from the sponsor regarding the differences seen.

Overall numerical differences between the groups are noted in the neoplasm data, however the rates are relatively low and therefore it is unclear whether this is true difference or has occurred by chance. It is noted that in the PSUR submitted for this evaluation that both neoplasms and colon cancer are being monitored as part of an authority request from the SwissMedic and EMA respectively (see Section 7.6 for further information) and this should continue to be monitored.

7.4.7.11. Hypoglycaemia, Integrated safety analyses (cut-off date of 30 September 2014)

In T1DM, the rate of confirmed and documented symptomatic nocturnal episodes and all confirmed episodes is lower for the IDeg arm compared with the comparator; however, all documented symptomatic episodes occurred at a higher rate on the IDeg arm compared with the comparator.

For insulin naive T2DM subjects (basal insulin only), the rate of all measured hypoglycaemic episodes is either similar or lower for the IDeg arm compared with the comparator.

For insulin treated T2DM subjects (including basal-bolus therapy), the rate of all measured hypoglycaemic episodes is either similar or lower for the IDeg arm compared with the comparator.

Meta-analysis of hypoglycaemic episodes

A meta-analysis was carried out on all hypoglycaemic episodes from all Phase III trials (T1DM and T2DM) with IDeg OD versus IGlar. The meta-analysis was based on the full analysis set, which included all randomised subjects although in exceptional cases, subjects could be excluded from the full analysis set. The analysis was carried out on an intention-to-treat basis and as randomised.

- For Confirmed hypoglycaemic episodes, defined as 'subject unable to treat himself/herself and/or have a recorded plasma glucose < 3.1 mmol/L': there no statistical difference between IDeg once daily versus IGlar once daily for T1DM, T2DM basal bolus, or throughout the maintenance period only (week 16 to end of trial) for all subgroups (T1DM, T2DM basal bolus, T2DM basal only therapy). There were small differences patients with T2DM on basal insulin only.
- Nocturnal confirmed hypoglycaemic episodes defined as 'subject unable to treat himself/herself and/or have recorded plasma glucose < 3.1 mmol/L' between the period of 00:01 and 05:59 am inclusive: was significantly lower with IDeg for T1DM, T2DM basal bolus and T2DM basal only therapy.

7.4.7.12. Other safety parameters, Integrated safety analyses (cut-off date of 30 September 2014)

Other adverse events highlighted in the Summary of Clinical Addendum

- Medication errors: the rate of medication error on IDeg arm was 4.5 events per 100 PYE; on the comparator arms it was 3.0 events respectively; a similar pattern was also seen in the ISS (cut off 31 January 2011). The most common medication error (by preferred term) was wrong dose administered, occurring in 2% of subjects (rate 2.7 per 100 subject years of exposure) for IDeg and 0.9% in the comparator group (rate 1.3). The rates of medication errors assessed to be probably or possibly related to the trial drug were 1.1 events per 100 patient years of exposure for IDegAsp and 0.6 for the comparators.

The majority of medication error AEs was reported in patients using basal bolus regimens and due to mix up between basal and bolus insulin. Mix-up between bolus and basal insulin is identified as an Important identified risk in the PSUR (see section 7.6). The sponsor notes that '*pen injectors used in the clinical Phase IIIa trials were packaged and labelled specifically for use in these trials, whereas the final packaging and labelling for the marketed products has been developed and optimized to minimise the potential for product mix up. IDeg is marketed in the FlexTouch (PDS290) prefilled pen injector, to which differentiation features have been applied*'.

- Injection site reactions: rates of injection site (including related) reactions with IDeg and comparators were similar.
- Lipodystrophy: The same rate of lipodystrophy in both the IDeg and comparator group was seen.
- Peripheral oedema: rate of peripheral oedema and local swelling was similar between the IDeg and the comparator arm. It is noted that the rate of local swelling appears to have increased since the ISS (cut-off date 31 January 2011). However, it is not clear whether this is due to a true increase or due to the recoding of some oedema peripheral events in the original ISS to 'local swelling' due to the MedDRA version updates that have occurred between the safety update and the ISS, as it does not appear that the ISS data has been presented in the updated MedDRA version. In terms of related events or oedema peripheral and local swelling, the rates in the updated data were relatively similar to those seen in the Integrated Safety Summary.

7.5. Other safety issues

7.5.1. Safety in special populations

7.5.1.1. Paediatrics

As of the cut-off date of 30 September 2014, one paediatric trial (Study NN1250-3561) has been completed. The Summary of Clinical Safety Addendum indicates that there were no safety signals; however, this trial has not been evaluated by the TGA. Furthermore, the sponsor is not requesting a paediatric indication so this data is not relevant to the current submission.

7.5.1.2. Use in pregnancy and lactation

Five additional pregnancies in the IDeg trials and 1 additional pregnancy in the IDegAsp trials have been reported in the period between 31 January 2011 (ISS report) and cut-off date for Summary of Clinical Safety Addendum (30 September 2014) in both completed and ongoing trials.

For these additional 5 pregnancies, there was a spontaneous abortion at 19 weeks, 2 healthy babies and 2 unknown outcomes (although an induced abortion was reported for one of these). One case reported that the mother developed post-partum cardiomyopathy but was considered unlikely related to treatment by the investigator; in terms of the child, the baby had jaundice at

birth and between 2 to 5 weeks after birth, the infant had non-serious events of mild jerky movements, digestive issues, abnormal stool colour, and rash of the face, neck and head.

In total 18 pregnancies have been reported for IDeg trials and 6 for the IDegAsp trials. Of the 18 pregnancies reported in IDeg trials, 12 have occurred in subjects receiving IDeg or IDeg/IGlar. Outcomes for these trials include 6 babies delivered, 4 miscarriages/spontaneous abortions/blighted ovum and 2 pregnancy terminations. It is noted that two babies developed jaundice and one was born by emergency caesarean at 35 weeks. 3 of the 4 miscarriages/spontaneous abortions/blighted ovum occurred < 12 weeks gestations; another miscarriage was described as a blighted ovum which is presumed to be an early loss of pregnancy however the gestation period is not stated. As mentioned above, one spontaneous abortion occurred at 19 weeks. In contrast, 5 pregnancies occurred in comparator arms, all IGlar and resulted in 3 health babies and 2 miscarriages before 12 weeks gestation.

The number of pregnancies that have occurred on the IDeg clinical trials are low; conclusions regarding the effects of IDeg on these outcomes cannot be made based on this data.

7.5.1.3. Other

No new information relating to intrinsic factors, overdose, drug abuse, withdrawal and rebound or the effects on ability to drive or operate machinery or impairment of mental ability were reported.

It is noted that trials investigating the combination product of insulin degludec/liraglutide have been completed and some were ongoing as of 30 September 2014. These trials were not part of the clinical development program of IDeg and the safety data is not included in this CER.

7.5.2. Safety related to drug-drug interactions and other interactions

No new information included relating to extrinsic factors or drug interactions were reported.

7.6. Post marketing experience

7.6.1. Periodic safety update report

Title: Insulin degludec periodic safety update report (PSUR)/periodic benefit–risk evaluation report (PBRER) (1 October 2014 to 30 September 2015) version 3.0, dated 3 December 2015.

The start date of the PSUR/PBRER is the day immediately following the cut-off date for the Summary of Clinical Safety Addendum (cut off 30 September 2014) and therefore contains more updated data.

7.6.1.1. Worldwide marketing authorisation status

IDeg is approved in more than 60 countries, and marketed in more than 30 countries.

7.6.1.2. Regulatory actions of note in the PSUR/PBRER period

- Singapore: marketing application for IDeg was withdrawn by sponsor, as the regulatory authority decided to wait for the results of the DEVOTE trial before making a final decision regarding the marketing application.
- Malaysia: rejection (following appeals process) for IDeg; DEVOTE trial results are required to confirm the cardiovascular safety of the products.

7.6.2. Clinical trial data

Safety related clinical trial data has already been summarised in this CER, based on the Summary of Clinical Safety Addendum, thus the only additional clinical trial data to be included in the CER from the PSUR/PBRER are those from clinical trials completed and are ongoing in this reporting period.

7.6.2.1. Completed trials

Table 26: Additional clinical trial data in PSUR/PBRER

Trial ID/Phase	Summary
NN1250-3587 **Phase IIIa**	26 week, multicentre, 2:1 randomised, open label, 2 arm, treat-to-target trial comparing IDeg and IGlar in combination with metformin in T2DM insulin naïve subjects who qualified for treatment intensification. Per PSUR: 'no apparent differences between Tresiba and IGlar with respect to AEs and standard safety parameters'. Confirmed hypoglycaemia episodes: 85 per 100 patient years of exposure for IDeg and 97 for IGlar. Rate of severe hypoglycaemia was 1 episode per 100 patient years of exposure on both arms
NN1250-3944 **Phase IIIb**	26 week, randomised (1:1), double blind, multinational trial comparing IDeg to placebo, both in combination with liraglutide and metformin in T2DM qualifying for treatment intensification. Per PSUR, no specific safety issues identified. Confirmed hypoglycaemia episodes: 57 per 100 patient years of exposure for IDeg and 12 for placebo. No severe hypoglycaemic episodes reported.
NN1250-4060 **Phase IIIb**	26 week, Japanese, multicentre, open labelled, randomised, 2 x 2 factorial design comparing 2 dosing schedules and 2 titration algorithms for IDeg in subjects with T2DM inadequately treated with IGlar +/- oral antidiabetic agents. Per PSUR, no specific safety issues identified. Confirmed hypoglycaemia episodes: 425 per 100 patient years of exposure for IDeg flexible dosing (flexibility with dosing +/- 8 hours was allowed) and 327 for fixed IDeg dosing; 414 per 100 patient years of exposure for IDeg simple titration (performed once weekly and based upon a single pre-breakfast plasma glucose value)and 337 for IDeg stepwise (done weekly based on mean of 3 pre breakfast plasma glucose levels); that is, more hypoglycaemia seen for flexible dosing and also for those on simple titration. One severe hypoglycaemic episode was reported in a patient receiving a fixed dose on simple titration.

7.6.2.2. Ongoing trials

As of 30 September 2015, it is estimated 8869 subjects have been randomised in ongoing clinical trials in which IDeg is the primary investigational drug. Of these, Study EX1250-4080 (DEVOTE trial) is by far the largest trial. In 2 other trials, up to 20% of subjects have withdrawn from the trial however the sponsor notes that 4% in Study NN1250-3995 and 2% in Study NN1250-3998 were withdrawn due to adverse events.

There were 3479 SAEs in 1961 subjects reported in this reporting period and 390 events (in 215 subjects) were classified as serious adverse drug reactions. 62 of these events were classified as suspected unexpected adverse drug reactions (SUSARs) and 55 of these occurred on the cardiovascular outcomes Study EX1250-4080 (DEVOTE trial). As SUSARs that are part of

MACE were not unblinded, only a subset of unblinded SUSARs are available for Study EX1250-4080 and the most frequently reported events were within the cardiac disorders SOC, followed by the renal and urinary disorders SOC. 4 adverse drug reactions (in 3 patients) resulted in a fatal outcome; these related to chronic kidney disease, diabetes or coronary artery disease.

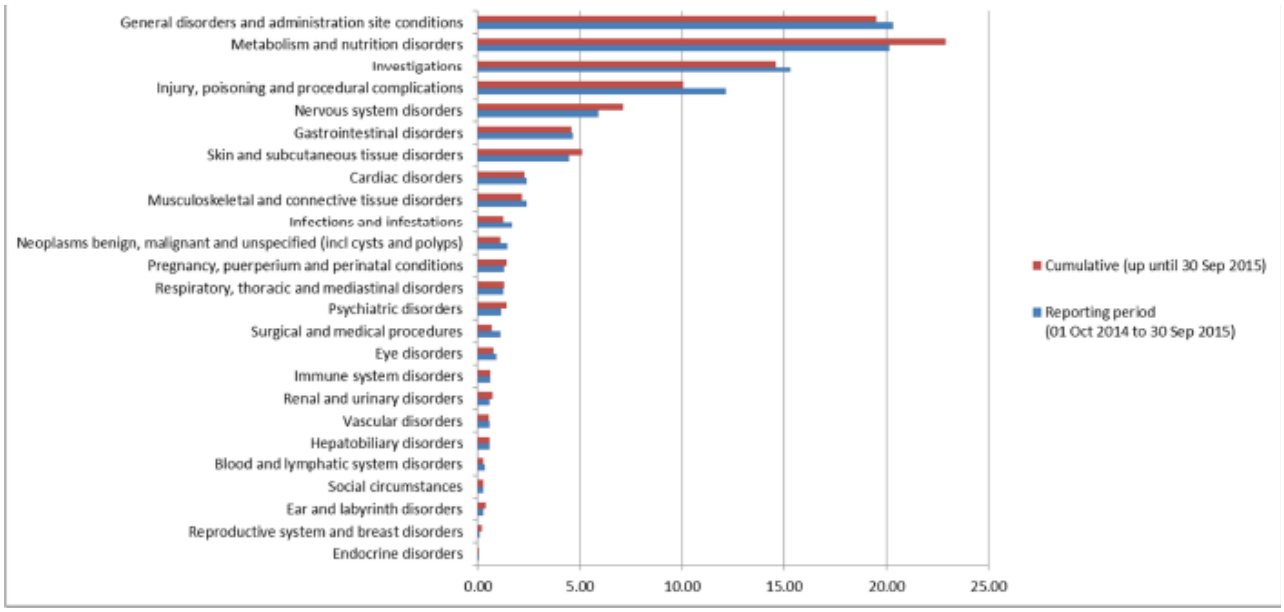
The PSUR states that *'No significant safety findings were reported from ongoing trials in the reporting period of this PSUR'*.

7.6.3. Post marketing exposure

It is estimated that there has been 317,433 patient years of exposure to IDeg up until 30 September 2015 ('cumulative exposure'), and 69% of that exposure occurred during the current PSUR reporting period.

- Cumulatively, 2934 adverse drug reactions have been reported in 1700 spontaneous case reports, of which 16% were serious. 1645 adverse drug reactions, of which 146 were serious, were reported in this PSUR period.
- 281 events in 185 serious case reports were reported for this PSUR period (of a total 300 adverse events in 197 case reports) from non-interventional post-marketing studies and other solicited sources and of these, 57 events were considered to be serious.
- The following Figure 11 shows the distribution of adverse events by SOC from post marketing sources (PSUR).

Figure 11: Distribution of adverse events (% of total) by System Organ Class from postmarketing sources



According to the PSUR, the most frequently reported event was related to hypoglycaemia (SOC of metabolism and nutrition disorders) followed by injection site reactions (SOC general disorders and administration site conditions). Compared to the cumulative reports, there was an increased frequency of reports in the SOC injury, poisoning and procedural complications, which the PSUR suggests *'may have been caused due to the increased reporting of off label use in Brazil …. [these reports] mainly concerned the use of Tresiba in children and adolescents with T1DM, which were reported when trying to identify adult patients with T2DM for a patient support programme (NovoDia) in Brazil.'*

Per the PSUR, *'the overall distribution, pattern and type of post-marketing events received in the reporting interval of this report are consistent with the cumulative experience'*

- 60 fatal cases have been reported; 49 were received in this PSUR period. 35 fatal cases were reported from non-interventional studies and 2 were assessed as possibly related to IDeg.

Per the PSUR, '*based on the available information, the fatal cases are not considered to change the current knowledge related to the safety profile of Tresiba*'.

- Off label reports were received for the use of IDeg pregnant women, lactating women and children/adolescents. The majority did not have associated adverse events.

7.6.3.1. Fixed combination therapies

A combination product of insulin degludec/liraglutide was approved in the European Union on 18 Sept 2014 and the most recent PSUR (April 2015 to September 2015) determined that the overall balance between risk and benefit was unchanged.

For the IDeg/IAsp combination, see Ryzodeg IDegAsp submission.

7.6.3.2. Medication errors

Based on post marketing reports, 97 events (16 serious (included 12 overdose reports); 81 non serious) have been reported in the PSUR period and cumulatively, 137 events have been reports. The reporting rate of human related medication errors remains stable at 0.04 events per 100 patient years of exposure for both the current PSUR reporting period and the cumulative reporting period.

Of note, the *potential risk of mix-up between basal and bolus insulin* was upgraded from an important *potential* risk to an important *identified* risk based on the receipt of a number of well documented post-marketing cases. From the marketed use of IDeg, 12 non-serious events were reported in the PSUR reporting period in which the patient had taken or received bolus insulin instead of IDeg or IDeg instead of bolus insulin. Of these, 5 were AE reports of either hypoglycaemia (3 events) or hyperglycaemia (2 events).

The only reported serious adverse event due to mix up was hypoglycaemia which occurred with a mix up of the strengths of IDeg (200 units/mL with 100 units/mL). Medication errors due to mix up between the different strengths of IDeg are classified as an important potential risk.

During the PSUR reporting period, there were also 15 reports concerning misuse or abuse of IDeg and 20 reports of overdose. The reporting rate for both misuse/abuse and overdose are similar for the PSUR reporting period and the cumulative experience. There is also significant overlap in the reports between overdose and misuse/abuse, of which the majority were either a suicide attempt or deliberate severe overdosing and co-morbidities such as underlying psychiatric disease were present in most of the cases.

Other safety information, the PSUR states that:

- *'No relevant significant safety information that could have the impact on benefit–risk assessment of Tresiba was reported from the non-interventional studies'.*
- *'No new nonclinical safety findings were reported during the period of this PSUR for Tresiba'.*
- *'No new significant safety findings or concerns specifically for Tresiba were identified based on the results of the review of the scientific literature'.*
- *'No indication of an increased risk of inadequate glycaemic control or lack of efficacy with Tresiba was seen in the randomised clinical trials with Tresiba completed in the reporting period of this PSUR'.*

7.6.3.3. Signal review and evaluation of authority request

One signal review of MACE is ongoing; MACE data from the dedicated cardiovascular outcomes trial, other clinical trials and post marketing sources is included.

An Evaluation of Authority Request is ongoing regarding neoplasms and colon cancer as requested by SwissMedic and EMA's Committee for Medicinal Products for Human Use respectively. All potential events of neoplasms from all completed Phase IIIa and IIIb IDeg trials were sent to an external, independent and blinded consultant for classification into malignant, benign and unclassifiable neoplasms and post marketing data was analysed.

7.6.4. Summary of safety concerns per PSUR

No new potential or important risks have been identified in this PSUR period. Table 27, shown below, gives a summary of safety concerns in the PSUR version 3.0 dated 3 December 2015.

Table 27: Summary of safety concerns in the PSUR dated (version 3.0, dated 3 December 2015 covering the period of 1 October 2014 to 30 September 2015)

Category of safety concern	Safety concerns	Comments
Important Identified Risks	Hypoglycaemia	No new safety concerns identified
	Immunogenicity-related events (allergic reactions)	No new safety concerns identified
	Medication errors due to mix-up between basal and bolus insulin	Upgraded from important potential risk
Important Potential Risks	Immunological events, formation of neutralising insulin antibodies	Per PSUR: '*No indication of an increased risk of inadequate glycaemic control or lack of efficacy with Tresiba was seen in the randomised clinical trials with Tresiba completed in the reporting period of this PSUR'.*
	Medication errors due to mix-up between the different strengths of IDeg	One post marketing case was reported; patient received 80 units of IDeg 100 units/mL whilst in hospital, when the patient usually receives 40 units of IDeg 200 units/mL. No change was made to category of safety concern. The PSUR states that risk minimisation measures include packaging details, a 'direct healthcare professional communication, a poster for display in pharmacies and diabetic units and a patient education leaflet.

Category of safety concern	Safety concerns	Comments
Missing Information	Pregnant and lactating women	No new safety concerns identified
	Neonates and infants (< 1 year of age)	Evaluator note: IDeg was approved for the treatment of diabetes mellitus in children and adolescents from the age of 1 year in the EU during the reporting period of this PSUR.
	Hepatic impairment	No new safety concerns identified
	Moderate and severe renal impairment	No new safety concerns identified.
	Elderly patients (> 75 years) with T1DM	No new safety concerns identified.

Comment: It is noted that the safety concern of 'Medication errors due to mix-up between basal and bolus insulin' was upgraded from Important potential risk to Important identified risk. Given this, it is of importance that the RMP is updated appropriately for Australia to mitigate this risk. The ongoing monitoring of neoplasms/colon cancer and MACE events is also noted.

7.7. Evaluator's overall conclusions on clinical safety

The important identified risks of IDeg as noted in the PSUR/PBRER are hypoglycaemia, immunogenicity related events (allergic reactions) and medication errors due to mix-up between basal and bolus insulin. A safety related concern arising from the original submission for IDeg related to cardiovascular outcomes and a core component of the safety data submitted in this resubmission of IDeg was the cardiovascular outcomes DEVOTE trial. This trial was of robust design and the primary endpoint comparing IDeg with IGlar was met for non-inferiority in an interim analysis; therefore, the cardiovascular signal detected in the Phase III development program in the original submission was not supported. Nevertheless, it is noted that only interim results are presented and final results will provide stronger evidence. Further it is noted the DEVOTE trial does not provide data specific to the T1DM population.

New integrated safety data with cut-off date of 30 September 2014 has been presented for IDeg in the current submission. This data has been compared in the submission documents to the Integrated Safety Summary (ISS) with cut-off of 31 January 2011.

The updated safety dataset contained 34 additional trials, of which 19 were IDeg specific. This included 12 Phase III trials (including 5 extension trials), 5 clinical pharmacology trials and two 'other' trials. In total, there were 7853 subjects who have been exposed to IDeg across the completed clinical trials as of 30 September 2011 and data for 2229 more subjects who received IDeg compared to the original Integrated Safety Summary (cut-off date of 31 January 2011).

It is noted that there were a variety of patient types included in this integrated dataset: subjects with T1DM and T2DM, and within the T2DM subset, subjects were either insulin naïve or insulin treated. Similarly, the comparator group was an amalgamation of all comparators across a number of trials and patient populations. Therefore, as with all analyses of integrated data, outcomes should be interpreted with some caution given that the population is a somewhat heterogeneous group. Nevertheless, this integrated data has the benefit of bringing together a large number of subjects who have received IDeg.

Based on the updated data presented, there do not appear to be any new significant safety signals that have emerged since the previous submission in terms of integrated safety data.

From the integrated data, the following is noted regarding hypoglycaemia:

1. Hypoglycaemia, either as a preferred term or as a group of preferred terms, was one of the most common AEs and SAEs reported, events leading to discontinuation and considered to be probably or possibly related to the study drug. This is not surprising given the mechanism of action for IDeg.
2. In terms of AEs possibly or probably related to study drug, hypoglycaemia as a preferred term is reported at a slightly higher rate in the comparator group compared to IDeg in Phase III trials.
3. SAEs that were related to hypoglycaemia (multiple preferred terms) were reported at a similar rate for IDeg and comparators (2.8 events per 100 PYE and 2.4 respectively) overall.
4. In specific analyses for hypoglycaemia, the rate of confirmed, severe and documented symptomatic hypoglycaemia both in terms of all episodes and nocturnal episodes for IDeg occurred at a rate similar or slightly lower than the comparator arm for most parameters. This was the case in all disease subgroups, T1DM, T2DM insulin treated and insulin naïve. The only measurement for which the rate was higher on the IDeg arm was all documented symptomatic episodes in the T1DM subgroup.
5. A meta-analysis of hypoglycaemic episodes from Phase III trials of IDeg daily versus IGlar was done: across all categories, statistically significant differences are seen in favour of IDeg, however these differences are small and the clinical significance of these differences is not clear.

With regards to the hypoglycaemia outcomes, the heterogeneous group of comparators for the integrated data is noted. It is also noted that the aetiology of hypoglycaemia can be multifactorial and medication is only one potential contributing factor. Prescriber and patient education is important to ensure appropriate use of IDeg. The sponsor has included hypoglycaemia in the proposed product information as a precaution, as well as information for the patient in the consumer medicines information.

It is also noted that there are 2 ongoing safety evaluations as detailed in the PSUR:

1. Neoplasms/colon cancer: An Evaluation of Authority Request is ongoing regarding neoplasms and colon cancer.

As described in this CER, numerical imbalances were seen in the rate of adverse events reported related to neoplasms in the IDeg group compared to comparator in the updated integrated data set, showing higher rates for IDeg. Following external classification, the largest discrepancies appear to be in the benign neoplasm subset. The reasons for these discrepancies are difficult to ascertain. Ongoing monitoring should be maintained.

2. Cardiovascular events: as previously described.

It is also noted that medication errors due to mix up between basal and bolus insulin was upgraded from important potential risk to an important identified risk in the PSUR, and that medication errors have been reported as adverse events in the clinical trials.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The first round assessment of benefits is shown in Table 28, below.

Table 28: First round assessment of benefits

Indication – adults with diabetes	
Benefits	**Uncertainties**
Overall, non-inferior efficacy for glycaemic control versus other basal insulins in a treat to target regime for T1DM and T2DM.	The external validity to the real world can be a problem with diabetes trials.
Unique ultra-long acting insulin, half-life 25 hours, with less intra patient variability.	There is the potential that in patients with poor compliance where insulin may not be administered every 24 hours, glycaemic control may be improved. However, this subgroup was not studied. The unique PK and PD profile of IDeg means that education of both prescribers and patients is critical to ensure appropriate use. This is particularly important given the important identified risk of medication errors due to mix up between basal and bolus insulin.
Potential for flexible dosing has been proposed given that IDeg is ultra-long acting. There is a similar efficacy in glycaemic control with this regime (but possibly more hypoglycaemia).	Flexible dosing has potential to be of benefit to patients, particularly if a dose is forgotten. However, in general, patients with diabetes benefit from routine.
Rate of nocturnal hypoglycaemia generally lower for IDeg compared to comparators.	
DEVOTE trial provided supportive evidence for non-inferiority of CV endpoints.	

8.2. First round assessment of risks

The first round assessment of risks is shown in Table 29, below.

Table 29: First round assessment of risks

Risks	Uncertainties
Hypoglycaemia: Hypoglycaemia and events related to hypoglycaemia, commonly occurred with the use of IDeg in the clinical trials. It is recognised that hypoglycaemia is an inherent risk associated with all insulins, however due to the 'ultra long' action of IDeg, the period following a single dose in which hypoglycaemia may occur is longer than other insulins. However, it is also acknowledged that the aetiology of hypoglycaemia is multifactorial and the type of insulin used is only one important component. Thus, education of prescribers and patients again will play an important part in mitigating this risk.	
Flexible dosing: The rate of hypoglycaemia was higher during flexible dosing. The evaluator would not support the extrapolation of the flexible dosing clinical trials to the real world setting due to the differences in patient population and monitoring in a clinical trial setting.	
Medication errors due to mix-up between basal and bolus insulin in both clinical trials and post market setting	
Exclusion of some oral anti-diabetic drugs in Phase III trials	*Use with GLP-1 agonists and SGLT2 inhibitors:* There is uncertainty regarding the use of these drugs in combination with IDeg since these drugs were not studied in the Phase III trials. This should be also noted in the product information. However, drug interactions are unlikely based on known mechanisms of action
	Neoplasms/colon cancer: In the updated integrated data, some numerical discrepancies in the rates of neoplasms were seen in the IDeg group compared to the comparators. Neoplasms and colon cancer are the subject of an ongoing evaluation as requested by the EMA and SwissMedic. Further monitoring should be continued.

Risks	Uncertainties
Cardiovascular events (MACE): Although the outcomes of the interim analysis for the DEVOTE trials are reassuring with respect to the signal detected in the original evaluation, the final results from this study will allow more robust conclusions and provide long term data. Further monitoring should be continued (including the DEVOTE trial and the ongoing signal review).	The DEVOTE trial did not include patients with T1DM and therefore the specific cardiovascular risk in this disease subset is unknown and can only be extrapolated from the T2DM data.
	Use in renal impairment

8.3. First round assessment of benefit-risk balance

The concerns about the cardiovascular safety have been adequately addressed in the interim analysis of the DEVOTE trial. Overall, the benefit-risk balance is positive for IDeg if appropriate steps for education of prescribers and patients are undertaken, as well as active ongoing monitoring for detected signals.

9. First round recommendation regarding authorisation

At this stage, the clinical evaluators have no major concerns for the approval of the registration of insulin degludec for the treatment of diabetes, providing the sponsor provide a suitable response to the questions and comments regarding the PI and RMP.

10. Clinical questions

10.1. Pharmacokinetics

None.

10.2. Pharmacodynamics

None.

10.3. Efficacy

None.

10.4. Safety

1. Section 7.2.1.11: Please provide a concise summary of the anti-diabetic medication received by the subjects during the trial by randomisation group.
2. Section 7.2.1.11: Please comment on the relatively high use of insulin alone > 25% at Baseline in this trial compared to what may be expected in a comparable Australian population.

3. Section 7.2.1.11: Please comment on the relatively low use of statin medications (77.8% overall) at baseline in this trial compared to what may be expected in a comparable Australian population.
4. Section 7.2.1.12: It is noted in the interim study report for the DEVOTE trial that the footnote for [a table] entitled 'Time to first EAC-confirmed MACE, primary analysis' states that '*MACEs linked to cardiovascular /undetermined deaths are excluded (using date of death in calculation of time to risk for this subject if first event)'.* However, CV (including undetermined) deaths is one of the key components of the MACE composite endpoint. Please clarify this footnote and how it impacts the results contained in [this table].
5. Section 7.3.1: Please comment on the following individual discrepancies reported for some safety parameters in the extension studies with safety as primary endpoint:
    a. *Study NN1250-3644:* rate of AEs that were possibly related to study drug; fundoscopy findings, HDL cholesterol
    b. *Study NN1250-3643:* confirmed hypoglycaemic episodes.
6. Section 7.3.1: Can the sponsor please comment on the difference in number of deaths seen in Study NN1250-3667 in the 2 arms?
7. Section 7.4.6.10: Numerical discrepancies were noted for several externally classified individual benign neoplasms as discussed in 7.4.6.10. Please comment.

11. Second round evaluation of clinical data submitted in response to questions

Following a satisfactory first round evaluation of, it was decided that Tresiba could proceed to the Delegate for consideration of approval. See the AusPAR for further details.

12. Second round benefit-risk assessment

Following a satisfactory first round evaluation of, it was decided that Tresiba could proceed to the Delegate for consideration of approval. See the AusPAR for further details.

13. Second round recommendation regarding authorisation

Following a satisfactory first round evaluation of, it was decided that Tresiba could proceed to the Delegate for consideration of approval. See the AusPAR for further details.

14. References

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