Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

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

Proprietary Product Name: Ryzodeg FlexTouch, Ryzodeg Penfill

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

**First round report: March 2017**

**Second round report: July 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 |
| ACSOM | Advisory Committee on the Safety of Medicines |
| AMI | Acute myocardial infarction |
| AUC | Area under the concentration time curve |
| ARTG | Australian Register of Therapeutic Goods |
| BIAsp 30 | Biphasic insulin aspart |
| BID | Twice a day |
| CER | Clinical evaluation report |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| $C_{max}$ | Maximum plasma concentration |
| CVOT | Cardiovascular Outcomes Trial |
| DPP-4I | Dipeptidyl-peptidase 4 inhibitor |
| DSUR | Development safety update report |
| EAC | Event adjudication committee |
| EMA | European Medicines Agency |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FDC | Fixed dose combination |
| GIR | Glucose infusion rate |
| GLP-1 | 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 |
| ISS | Integrated Summary of Safety |
| MACE | Major Adverse Cardiovascular Event |
| MACE (ISA) | Major Adverse Cardiovascular Event (Integrated safety analysis) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OAD | Oral antidiabetic drug |
| OD | Once daily |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |

| Abbreviation | Meaning |
|---|---|
| PSUR | Periodic safety update report |
| PBRER | Periodic benefit–risk evaluation report |
| PYE | Patient years of exposure |
| RMP | Risk management plan |
| SD | Standard deviation |
| Ref | Reference |
| SAE | Serious adverse event |
| SMPG | Self-measured plasma glucose |
| SOC | System organ class |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TID | 3 times daily |
| TZD | Thiazolidinedione |
| U | Units |
| UAP | Unstable angina pectoris |

# 1. Introduction

## 1.1. Submission type

This was a resubmission to register the new fixed dose combination (FDC) product insulin degludec (rys)/insulin aspart (rys) (IDegAsp). Insulin degludec is a new medicine and the subject of a new related submission as a single agent product (Tresiba FlexTouch/Penfill);[1] insulin aspart is listed on the ARTG.

## 1.2. Drug class and therapeutic indication

Insulin degludec (rys)/insulin aspart (rys) combines ultra-long acting insulin with a rapid acting insulin analogue. Insulin aspart (rys) is an active component of products already registered in Australia (NovoMix and NovoRapid).

The proposed indication is '*to improve glycaemic control in adult patients with diabetes mellitus.*'

## 1.3. 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 |
|---|---|---|

[1] See the following AusPAR for this submission: AusPAR for Tresiba FlexTouch/Tresiba Penfill insulin degludec Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-5.

| Active ingredients | Trade name | Dosage forms/strengths |
|---|---|---|
| Insulin degludec (rys)/ insulin aspart (rys) | Ryzodeg FlexTouch | FlexTouch 100 U/mL (70% soluble insulin degludec and 30% soluble insulin aspart), 3 mL solution for injection in prefilled pen |
| | Ryzodeg Penfill | Penfill 100 U/mL (70% soluble insulin degludec and 30% soluble insulin aspart), 3 mL solution for injection in cartridge |

# 2. Clinical rationale

## 2.1. Background

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.[2]

T2DM is by far the most common type of diabetes; an estimated 849,000 adults (4.7%) 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 T2DM (164 people per 100,000 population) and the incidence of insulin use for T2DM increases with age; it is estimated that there is a5 fold increase in the use of insulin between the ages of 40 to 44 and 70 to 74 years.[3]

## 2.2. Current treatment options[4]

### 2.2.1. Type 1 diabetes mellitus

Insulin is the cornerstone of treatment. 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

[2] Australian Institute of Health and Welfare (AIHW) website; aihw.gov.au.
[3] Incidence of insulin treated diabetes in Australia 2000 to 2011, Australian Institute of Health and Welfare (AIHW), Diabetes series number 22. 29 April 2014.
[4] Diabetes: management (published November 2013). In eTG complete (internet) Melbourne: Therapeutic Guidelines Limited; July 2016.

- 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.

### 2.2.2. 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.[4] 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 T2DM, 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: 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 |
| Bolus | Very short acting (rapid) | glulisine | Apidra |
| | | lispro | Humalog |
| | | aspart | NovoRapid |
| | Short acting | Neutral | Actrapid, Humulin R, Hypurin Neutral |
| Combination | Biphasic, pre-mixed | Neutral/isophane | Mixtard 50/50, Mixtard 30/70 |
| | | Lispro/lispro protamine | Humalog Mix25, Humalog Mix50 |
| | | Aspart/aspart protamine | NovoMix 30 |
| | | Neutral/isophane | Humulin 30/70 |

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

## 2.3. Clinical rationale

The sponsor's rationale for this new FDC is that there is '*a need for an ultra long acting basal insulin which more closely mimics endogenous insulin secretion with low day to day variability of glucose lowering action, to deliver improved glycaemic control with a reduced risk of hypoglycaemia relative to premixed insulin*' (as stated in the cover letter dated 20 September 2016).

## 2.4. Guidance

Refer to IDeg clinical evaluation report [see Attachment 2 for the Tresiba submission].[1]

## 2.5. Evaluator's commentary on the background information

The events that lead to the withdrawal of the original dossier for IDegAsp 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

## 3.1. Scope of the clinical dossier

The sponsor conducted a pre-submission meeting with the TGA on 20 June 2016, where it was agreed the dossier for IDegAsp would be resubmitted. In view of the previous evaluation, it was decided the dossier would be limited to data from the DEVOTE trial, synopses of studies completed since the previous submission rather than full clinical trial reports, and addressing any outstanding issues from the previous submission.

New studies:

- 10 new IDegAsp studies were submitted (compared with the original submission) as synopses. These included 7 Phase III trials (including 1 extension part) and 3 clinical pharmacology trials.
- Additional information was submitted in December 2016; this was the interim data from the cardiovascular outcomes DEVOTE trial (Study EX1250-4080).

Other key documents included:

- Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report IDegAsp (1 October 2014 to 30 September 2015).

The following documents were provided:

- Introduction
- Quality Overall Summaries
- Nonclinical overview for both IDegAsp and IAsp
- Clinical overview for IDegAsp, IDeg and IAsp
- Nonclinical summaries for IDegAsp

- Clinical summaries for IDegAsp and IDeg (including Summary of clinical safety addendum, IDegAsp)

## 3.2. Paediatric data

No paediatric data was been submitted; as of 30 September, 2014, 1 paediatric trial was ongoing. No paediatric indication is being sought in Australia. Paediatric data is relevant for this medicine as diabetes also occurs in infants and children.

## 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 (Section 7 of this report) 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, IDegAsp' which compared the updated data to a dataset with cut-off of 31 January 2011 contained within the document entitled 'Integrated Safety Summary' (24 August 2011). However the 'Integrated Safety Summary' was not submitted to the TGA with the original withdrawn submission; please see Section 7 for further discussion.

# 4. Pharmacokinetics

The PK profile of IDegAsp has been determined in the original withdrawn submission. A summary of the PKs of IDegAsp is provided in Table 3 below from the proposed PI.

**Table 3: Pharmacokinetics summary**

| | |
|---|---|
| **Absorption** | Following subcutaneous injection:<br>• IDeg: Stable multihexamers are formed, resulting in a depot of IDeg. IDeg monomers gradually separate resulting in a slower and continual release into the circulation. Steady state concentrations are reached after 2 to 3 days of daily IDegAsp administration<br>• IAsp: there is rapid release of IAsp monomers into the circulation. Insulin aspart appears 14 minutes after injection and peak concentration occurs after 72 minutes |
| **Distribution** | • IDeg: Plasma protein binding of > 99% in human plasma<br>• IAsp: Plasma protein binding of < 10% in human plasma. |
| **Metabolism** | Degradation of insulin degludec and insulin aspart is similar to that of human insulin. |
| **Excretion** | IDeg half-life: 25 hours<br>• independent of dose<br>• determined by rate of absorption from subcutaneous tissue. |

| | |
|---|---|
| **Absorption** | Following subcutaneous injection:<br>• IDeg: Stable multihexamers are formed, resulting in a depot of IDeg. IDeg monomers gradually separate resulting in a slower and continual release into the circulation. Steady state concentrations are reached after 2 to 3 days of daily IDegAsp administration<br>• IAsp: there is rapid release of IAsp monomers into the circulation. Insulin aspart appears 14 minutes after injection and peak concentration occurs after 72 minutes |
| **Linearity** | Total exposure with IDegAsp increases proportionally with increasing dose of the basal component (insulin degludec) and the mealtime component (insulin aspart) in type 1 and type 2 diabetes mellitus. |
| **Special populations** | No differences in PK parameters in hepatic and renal impairment compared to normal subjects. No differences in PK parameters between elderly and younger patients. |

As evidenced in the first and second round discussions in the original CER, the clinical evaluator for the original withdrawn submission stated bioequivalence between the IDegAsp fixed dose combination product and the IAsp component was not demonstrated, concluding the second round CER with:

> *'Clinical pharmacology studies have also shown that the fixed combination IDegAsp is not bioequivalent with co-administration of separate injections with respect to the IAsp component. The clinical implication would be that the reduction in post-prandial plasma glucose was statistically significantly less with IDegAsp compared to separate injections with IDeg and IAsp (as shown in the PK and PD Studies NN5401 -1959 and -1738)).'*

The sponsor's response to these comments included the following points:

- Study NN5401-1959 was designed to compare IDegAsp with corresponding actual doses of each of the components given as separate injection whereas Studies NN5401-3857 and NN5401-1977 were designed to compare IDegAsp with IDeg and IAsp at corresponding doses of each product to meet FDA requirement of documenting distinctiveness between IDegAsp and the individual component products IDeg and IAsp.
- When describing the glucose lowering effect profile of IDegAsp, the effect of the IAsp component in IDegAsp is mainly evident in the glucose infusion rate (GIR) profile during the first 6 hours after dosing. While it may be possible to find differences for subintervals of this 6 hour period, these only account for a smaller fraction of the IAsp effect.
- If considering the effect during the first 2 hours after dosing ($AUC_{GIR0\text{-}2h}$), as pointed to by the evaluator, the sponsor proposes that the results for Trial 1959 are amended with the dose normalised results of 3857 for the same endpoint. The reason is that, the $AUC_{GIR0\text{-}2h}$ was estimated to be 26% smaller with IDegAsp than IAsp in Trial 1959, it was estimated to be 23% greater in 3587 (results provided by the sponsor in the second round CER). In relation to the BE evaluation for the IAsp component, the sponsor proposes that the relative effect over the first 6 hour period after dosing ($AUC_{GIR0\text{-}6h}$) and maximum effect ($GIR_{max}$) is also emphasised. These are considered similar for IDegAsp and IAsp based on estimated ratios for $AUC_{GIR0\text{-}6h}$ (0.97 (0.88; 1.06)) and $GIR_{max}$ (0.94 (0.86; 10.3)) in Trial 1959.
- In Trial 3594/3645, subjects achieved similar long term glycaemic control (HbA1c) after basal bolus treatment with IDegAsp OD + IAsp at remaining meals (7.65%) compared with IDet + IAsp at all meals (7.72%). At end of trial, the total daily bolus dose was similar in both groups irrespective of whether IAsp was given as IDegAsp OD + IAsp at remaining meals (41 U) or as IDet + IAsp at all meals (43 U). Also at end of trial, the total dose of IDet + IAsp (82

U) was slightly higher than the total dose of IDegAsp OD + IAsp (72 U), which was solely attributed to a higher basal dose in the IDet group compared with the IDegAsp group.

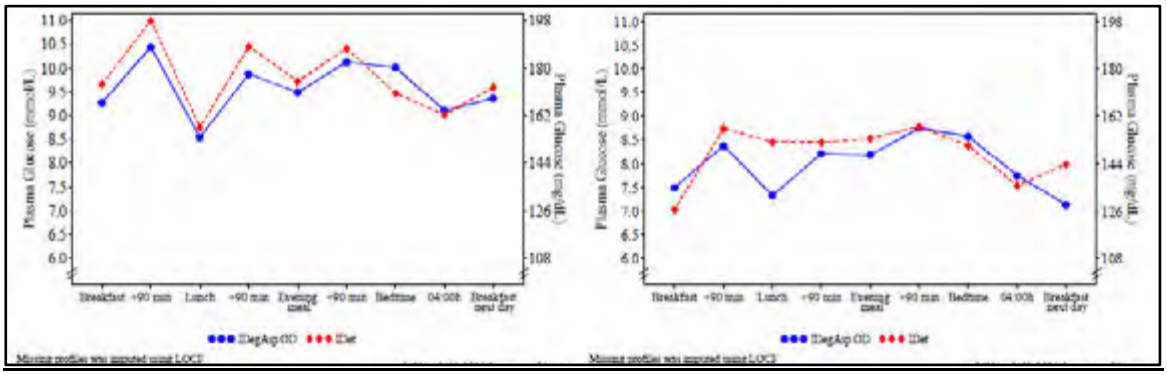
- In Trials 3592 and 3597, subjects achieved similar long-term glycaemic control (HbA1c) with IDegAsp (7.05 % and 7.07%, respectively) and NovoMix 30 (7.10% and 7.02%, respectively) at similar or lower dose levels at end of trial (90.3 and 55 U of IDegAsp and 97.7 and 68.3 U of NovoMix 30, respectively).

**Comment:** In terms of glucose lowering effect, the clinical evaluator of the original submission stated whilst matched doses of the co-formulation with separate injections of IDeg and IAsp resulted in similar $AUC_{GIR(0-6)}$ and $AUC_{GIR(0-24)}$, the $AUC_{GIR(0-2)}$ for the co-formulation was statistically significantly lower compared with the free injection, concluding the post-prandial component of glucose lowering is relatively blunted for the co-formulation.

From a clinical perspective, the key issue is whether these observed PK/PD differences are associated with clinically relevant effects.

The clinical evaluator of the original withdrawn submission noted the total daily insulin dose was 12% to 13% lower in the IDegAsp group than the IDet group. This was driven primarily by a lower basal insulin dose, as similar bolus doses of IAsp were reported for both groups (40 U and 42 U for IDegAsp and IDet respectively), with the clinical evaluator concluding T1DM subjects treated with IDegAsp achieved similar glycaemic control using a lower dose of insulin at end of trial compared with IDet treated subjects. The clinical evaluator stated the 9 point SMPG profile was similar between IDegAsp and IDet after 26 and 52 weeks, except before lunch and the evening meal where the mean plasma glucose value was lower for IDegAsp OD than for IDet. The 9 point SMPG after 26 weeks of treatment compared to Baseline was illustrated in a figure (see Figure 1, below).

**Figure 1: 9 point SMPG (mmol/L) at Baseline (left) and after 26 weeks (right); LOCF mean plot (FAS)**




From the above efficacy data, there is no evidence the identified concern regarding lack of bioequivalence of IDegAsp with the IAsp individual component was associated with a clinically meaningful effect. Further, this evaluator notes the Australian PI for the premixed insulin product Mixtard 30/70 (biphasic isophane insulin injection) states '*Mixtard 30/70 is not exactly equivalent to its component insulins*'.[5]

Given the comprehensive Phase III data provided with the submission, approval of the product will be contingent on the clinical data rather than PK parameters.

[5] Australian PI Mixtard 30/70 Biphasic isophane insulin injection neutral insulin (30%) and isophane insulin (70%).

## 4.1. New studies providing pharmacokinetic information

The PK data for IDegAsp has been evaluated in the original withdrawn submission. The current dossier contained synopses for 1 additional PD/PK trial (Study NN5401-1979) as discussed below and in Section 5.2 of this report.

## 4.2. Summary of pharmacokinetics

### 4.2.1. Pharmacokinetics in the target population

#### *4.2.1.1. Study NN5401-1979*

Study NN5401-1979 was a single centre, open label, multiple dose study to assess the PD and PK properties of IDegAsp (at steady-state) in 22 adult subjects with T1DM.

All subjects received a fixed subcutaneous dose of IDeg (0.42U/kg body weight) daily for 5 consecutive days (plus IAsp as bolus insulin as needed, dosage not specified) to achieve steady state for IDeg followed by a single fixed subcutaneous dose of IDegAsp (0.6 U/kg body weight, corresponding to 0.42 U/kg IDeg and 0.18 U/kg IAsp) on Day 6. PK properties were evaluated for 120 hours.

The mean total serum exposure of IDeg in IDegAsp at steady state during 1 dosing interval ($AUC_{IDeg,\tau,ss}$) was 72084 pmol.h/L and the mean $C_{max,IDeg\ ss}$ was 3938 pmol/L. Mean total serum exposure of IAsp in IDegAsp ($AUC_{IAsp,0-12h}$) was 1087 pmol.h/L and mean $C_{max,IAsp}$ was 326 pmol/L, with a median time to peak serum concentration of IAsp ($t_{max,IAsp}$) of 1.3 hours.

On visual inspection, the IAsp component of IDegAsp had a fast onset of appearance and a peak covering the prandial phase, whilst IDeg had a flat and evenly distributed pharmacokinetic profile over 24 hours. The mean ratio between $AUC_{IDeg,0\text{-}12h,SS}$ and $AUC_{IDeg,\tau,SS}$ was 0.51 indicating that exposure to IDeg in IDegAsp was similar for the first 12 hours compared to the following 12 hours of 1dosing interval at steady state.

The PD results for this study are discussed in Section 5.2 of this report.

**Comment:** The PK of IDeg at steady state in subjects with T1DM was determined in Studies 1991 and 1993 in the original withdrawn submission. The clinical evaluator for that submission noted IDeg exposure was similar for the first 12 hours compared to the following 12 hours of 1 dosing interval; the above results are consistent with these findings. However, as the half-life of IDeg is 25 hours, the PK parameters of the IDeg component of the IDegAsp would have been influenced by previous dosing of IDeg.

## 4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic characteristics of IDegAsp have been established in the original withdrawn submission.

The issue of bioequivalence has been addressed above within this section. It is recommended that the PI contain information as to the different PK parameters of IDegAsp compared to the individual components.

# 5. Pharmacodynamics

## 5.1. Studies providing pharmacodynamic information

The pharmacodynamic profile of IDegAsp has been described in the original withdrawn submission. The current submission included additional PD data for IDegAsp provided in Study NN5401-1979 as discussed below.

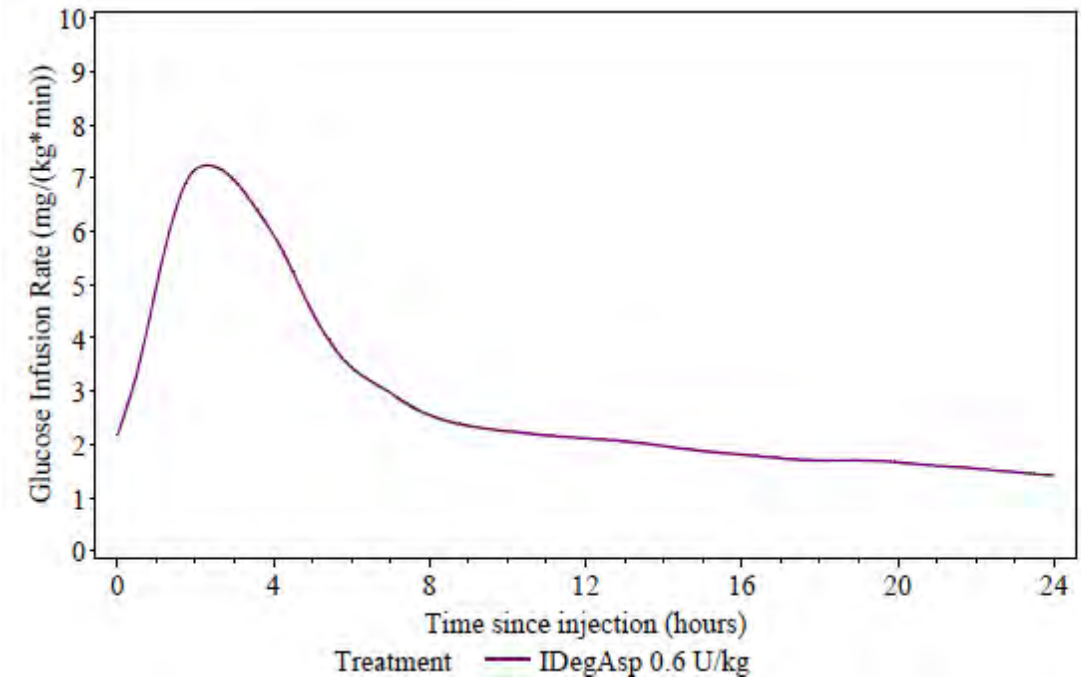
## 5.2. Summary of pharmacodynamics

### 5.2.1. Study NN5401-1979

Study NN5401-1979 was a single centre, open label, multiple dose study to assess the PD and PK properties of IDegAsp (at steady state) in 22 adult subjects with T1DM.

All subjects received a fixed subcutaneous dose of IDeg (0.42U/kg body weight) daily for 5 consecutive days (plus IAsp as bolus insulin as needed) to achieve steady-state conditions for IDeg. On Day 6, subjects received a fixed subcutaneous dose of IDegAsp (0.6 U/kg body weight, corresponding to 0.42 U/kg IDeg and 0.18 U/kg IAsp). After administration of IDegAsp the steady state PD response was evaluated during a 30 hour euglycaemic clamp. The primary endpoint was the glucose infusion rate (GIR) at steady state. The mean 24 hour smoothed pharmacodynamic GIR profile for the IDegAsp at steady state condition is shown in Figure 2, below.

**Figure 2: Mean 24 hour smoothed pharmacodynamic GIR profile for IDegAsp at steady state condition**




Following administration of IDegAsp at steady state conditions, the total glucose lowering effect (estimated mean $AUC_{GIR,\tau,SS}$) was 3859.1 mg/kg (95% CI: 3261.9 to 4565.6) and maximum glucose lowering effect (geometric mean $GIR_{max,SS}$) was 7.0 mg/(kg x min) with median time to maximal glucose infusion rate ($tGIR_{max,SS}$) 2.5 hours. At steady state, the glucose lowering effect of IDegAsp is characterised by a distinct peak action due to IAsp, and a separate and stable basal action from IDeg that is sustained for > 30 hours.

**Comment:** The PD properties of IDegAsp were investigated in the single dose Study NN5401-3539 evaluated in the original withdrawn submission. The PK parameters are as expected for a fixed dose product combining a basal and a fast acting insulin component.

### 5.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic effect of IDegAsp has been determined in the original withdrawn submission.

The concern raised by the clinical evaluator of that submission regarding the effect during the first 2 hours of dosing with IDegAsp compared to separate injections of IDeg and IAsp has been discussed above in Section 4 of this report

## 6. Clinical efficacy

There were 5 therapeutic confirmatory trials of similar design submitted and evaluated in the original withdrawn submission. The purpose of this evaluation is to address issues identified by the clinical evaluator of this submission, and discuss new data provided with the current submission.

A summary of the previously submitted confirmatory trials and issues regarding efficacy identified by the clinical evaluator of the original withdrawn submission are discussed below in Section 6.1 of this report. The main concerns raised by the clinical evaluator of the previous submission relate to choice of comparator in some studies and twice daily dosing of IDegAsp (see Section 6.1 of this report, below).

The new efficacy studies were provided as synopses (as per pre-submission meeting with the TGA) and discussed in Section 6.2.

### 6.1. Summary of previously submitted studies

A summary of the 5 therapeutic trials evaluated in the original withdrawn submission is provided below in Table 4. All trials were randomised, controlled, parallel group, open label, multinational, multicentre, treat to target studies comparing IDegAsp with an active comparator (IDet, IGlar or biphasic insulin aspart 30 (BIAsp 30; NovoMix 30)). 1 study was conducted in subjects with T1DM (Study NN5401-3594), and 4 studies in subjects with T2DM who were either insulin naïve (Study NN5401-3590) or insulin treated (Studies NN5401 -3592, -3593, and -3597) in combination with oral anti-diabetic drugs (OADs). A twice daily dosage regimen was used for insulin treated T2DM subjects in Studies Study NN5401-3592 and -3597. For the T2DM trials, OAD therapy with insulin secretogogues, α-glucosidase inhibitors (α–GI) and GLP-1 agonists was not permitted.

All studies were of 26 weeks duration, with 2 trials (Studies 3594 and 3590) extended by an additional 26 weeks to provide long term safety data. The trials were conducted using a treat to target principle, with insulin dose adjusted as per predefined titration algorithms, and a non-inferiority design applied. There were a total of 548 subjects with T1DM (IDegAsp = 366, comparator = 182) and 1866 subjects with T2DM (IDegAsp = 1004, comparator = 862) included in the 5 confirmatory studies.

The primary objective for all studies was to demonstrate efficacy of IDegAsp in controlling glycaemia, measured as the change from Baseline in HbA1c after 26 weeks of treatment. Non-inferiority of IDegAsp to the active comparator was considered demonstrated if the upper bound of the 2-sided 95% confidence interval for the estimated treatment difference for the mean change from baseline in HbA1c was ≤ 0.4%. Secondary efficacy parameters included FPG

and frequency of responders (HbA1c < 7.0%) without confirmed hypoglycaemia. Hypoglycaemic endpoints (confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia) were safety endpoints; these results are summarised in Table 4 (below) and are discussed further in Section 7. It is noted that patients were not blinded to their treatment allocation. 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 4: Summary of studies with IDegAsp**

| Parameter | Study 3594 | | Study 3590 | | Study 3593 | | Study 3592 | | Study 3597 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Design | 26 week (+ 26 week extension) efficacy and safety study comparing IDegAsp OD with IDet OD in adult subjects with T1DM. | | 26 week efficacy and safety study comparing IDegAsp OD with IGlar OD in insulin naïve adult subjects with T2DM currently treated with metformin. | | 26 week efficacy and safety study comparing IDegAsp OD and IGlar OD in insulin treated adult subjects with T2DM in combination with OADs (metformin ± pioglitazone ± DDP-4I) | | 26 week efficacy and safety study comparing IDegAsp BD and BIAsp 30 BD in adult subjects with T2DM treated with insulin ± OADs (± metformin ± DDP-4I ± pioglitazone) | | 26 week Pan-Asian efficacy and safety study comparing IDegAsp BD and BIAsp 30 BD in adult subjects with T2DM treated with insulin ± metformin. | |
| Treatments | Randomised 2:1 to IDegAsp OD + IAsp (n = 366); or IDet + IAsp (n = 182) | | Randomised 1:1 to: IDegAsp OD + metformin (n = 266); or IGlar OD + metformin (n = 264). | | Randomised 1:1 to IDegAsp OD + OADs (n = 230); or IGlar OD + OADs (n = 233). | | Randomised 1:1 to IDegAsp BD (n = 224) or BIAsp 30 BD (n = 223). | | Randomised 2:1 to IDegAsp (n = 280) or BIAsp 30 (n = 142). | |
| Treatment administration | IDegAsp 100 U/mL OD with main meal + IAsp with remaining meals; or IDet OD according to local label + IAsp as meal time insulin. A second dose of IDet could be added after 8 weeks if inadequate glycaemic control. | | IDegAsp 100 U/mL OD with morning meal; or IGlar OD according to local label ± metformin. | | IDegAsp 100 U/mL OD with any meal (evening meal or largest meal; same meal throughout study) or • IGlar OD according to local label ± metformin; ± pioglitazone; ± DDP-4I. | | IDegAsp 100 U/mL BD with breakfast and main evening meal; or BIAsp 30 BD with breakfast and main evening meal ± metformin; ± DDP-4I; ± pioglitazone. | | IDegAsp 100 U/mL with breakfast and main evening meal; or BIAsp 30 BD with breakfast and main evening meal; ± metformin. | |
| Primary efficacy endpoint | **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 (%)** | | **Mean change from Baseline in HbA1c after 26 weeks of treatment (%)** | |
| | IDegAsp | IDet | IDegAsp | IGlar | IDegAsp | IGlar | IDegAsp | BIAsp 30 | IDegAsp | BIAsp 30 |

| Parameter | Study 3594 | | Study 3590 | | Study 3593 | | Study 3592 | | Study 3597 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | -0.75 | -0.70 | -1.72 | -1.75 | -0.98 | -1.00 | - 1.31 | - 1.29 | -1.39 | -1.44 |
| | Mean treatment difference (IDegAsp – IDet) = -0.05 (95% CI: -0.18, 0.08)<br>Non-inferiority confirmed. Reduction in HbA1c maintained after 52 weeks | | Mean treatment difference (IDegAsp – IGlar) = 0.03 (95% CI: -0.14, 0.20)<br>Non-inferiority confirmed | | Mean treatment difference (IDegAsp – IGlar) = -0.03% (95% CI: -0.20, 0.14).<br>Non-inferiority confirmed | | Mean treatment difference (IDegAsp – BIAsp) = -0.03 % (95% CI: -0.18, 0.13).<br>Non-inferiority confirmed | | Mean treatment difference (IDegAsp– BIAsp) = 0.05% (95% CI: -0.10, 0.20)<br>Non-inferiority confirmed | |
| Secondary efficacy endpoint | **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)** | | **Mean change from baseline in FPG after 26 weeks of treatment (mmol/L)** | |
| | IDegAsp | IDet | IDegAsp | IGlar | IDegAsp | IGlar | IDegAsp | BIAsp 30 | IDegAsp | BIAsp 30 |
| | -1.65 | -1.88 | -3.5 | -4.02 | -1.60 | -1.93 | -2.80 | -1.65 | -2.51 | -1.45 |
| | Estimated mean treatment difference (IDegAsp– IDet) = 0.23 mmol/L (95% CI: -0.46, 0.91) | | Mean treatment difference (IDegAsp– IGlar) = 0.51 mmol/L (95% CI: 0.09, 0.93) | | Mean treatment difference (IDegAsp– IGlar) = 0.33 mmol/L (95% CI: -0.11, 0.77) | | Estimated treatment difference (IDegAsp - BIAsp) = -1.14 (95% CI: -1.53, -0.76) | | Estimated treatment difference (IDegAsp - BIAsp) = -1.06 (95% CI: -1.43, -0.70) | |
| Secondary efficacy endpoint | **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 (%)** | |
| | IDegAsp | IDet | IDegAsp | IGlar | IDegAsp | IGlar | IDegAsp | BIAsp 30 | IDegAsp | BIAsp 30 |
| | 4.5 | 3.0 | 23.6 | 30.7 | 20.9 | 23.5 | 21.8 | 14.9 | 21.9 | 13.2 |

| Parameter | Study 3594 | | Study 3590 | | Study 3593 | | Study 3592 | | Study 3597 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Estimated odds ratio (IDegAsp/IDet) = 1.53 (95% CI: 0.54, 4.38) | | Estimated odds ratio (IDegAsp/IGlar) = 0.61 (95% CI: 0.40,0.94) | | Estimated odds ratio (IDegAsp/IGlar) = 0.80 (95% CI: 0.50, 1.30) | | Estimated odds ratio (IDegAsp/BIAsp 30) = 1.60 (95% CI: 0.94, 2.72) | | Estimated odds ratio (IDegAsp/BIAsp 30) = 1.77 (95% CI: 0.97, 3.25) | |
| 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** | |
| | IDegAsp | IDet | IDegAsp | IGlar | IDegAsp | IGlar | IDegAsp | BIAsp 30 | IDegAsp | BIAsp 30 |
| | 371 | 572 | 19 | 46 | 82 | 101 | 74 | 253 | 111 | 155 |
| | Estimated rate ratio (IDegAsp/IDet) = 0.63 (95% CI: 0.49, 0.81) | | Estimated rate ratio (IDegAsp/IGlar) = 0.29 (95% CI: 0.13, 0.65) | | Estimated rate ratio (IDegAsp/IGlar) = 0.80 (95% CI: 0.49, 1.30) | | Estimated rate ratio (IDegAsp/BIAsp 30) = 0.27 (95% CI: 0.18, 0.41) | | Estimated rate ratio (IDegAsp/BIAsp 30) = 0.67 (95% CI: 0.43, 1.06) | |
| 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** | |
| | IDegAsp | IDet | IDegAsp | IGlar | IDegAsp | IGlar | IDegAsp | BIAsp 30 | IDegAsp | BIAsp 30 |
| | 3917 | 4434 | 423 | 185 | 431 | 320 | 972 | 1396 | 956 | 952 |
| | Estimated rate ratio (IDegAsp/IDet) = 0.91 (95% CI:0.76,1.09) | | Estimated rate ratio (IDegAsp/IGlar) = 2.17 (95% CI: 1.59, 2.94) | | Estimated rate ratio (IDegAsp/IGlar) = 1.43 (95% CI: 1.07, 1.92) | | Estimated rate ratio (IDegAsp/BIAsp 30) = 0.68 (95% CI: 0.52, 0.89) | | Estimated rate ratio (IDegAsp/BIAsp 30) = 1.00 (95% CI: 0.76, 1.32) | |

OD = once a day; BD = twice a day

The main issues regarding efficacy identified by the clinical evaluator of the original withdrawn submission are as follows:

1. Choice of comparators in the pivotal T2DM studies

The clinical evaluator stated the following regarding choice of comparators for the 4 pivotal T2DM studies:

a. In Study 3590 involving insulin naïve subjects with T2DM, comparison of a basal bolus combination (IDegAsp) with basal insulin only (IGlar OD) does not seem appropriate

as generally insulin naïve T2DM patients are usually first started off on basal insulin only.

b. With regard to twice daily dosing in subjects with T2DM, the evaluator provided the following comment in the CER: '*The major limitation of both Studies 3592 and 3597 was that the comparator chosen may not be appropriate as majority (70 to 90%) of the T2DM patients enrolled in these studies had used premix/self mix insulin BD with or without OADs (majority were treated with premix insulin BD in combination with at least 1 OAD). BIAsp 30 is a premixed insulin (containing a rapid acting and an intermediate acting insulin) while IDegAsp contains a long acting basal insulin IDeg in combination with rapid acting insulin aspart. While it is acknowledged that there is no available FDC of long-acting insulin+ rapid acting insulin, it does make interpretation of results difficult as the comparison is between 2 products in which the basal insulin component had different duration of action*'.

In response to the latter concern regarding IDegAsp BD dosing, the sponsor provided comments in the response to second round CER document. The sponsor's response included the following points:

- Pre-mixed insulins are recognised as a recommended therapeutic option in the Australian Diabetes Society guideline National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes.
- IDegAsp was designed as the first in class soluble co-formulation of a basal and a bolus insulin analogue to improve the treatment options for premix users. A premixed insulin product, such as BIAsp 30, was therefore the most relevant comparator for demonstrating the improved efficacy and safety of IDegAsp.
- The choice of comparator was discussed with the TGA at the end of Phase II meeting.

**Comment:** It is noted the sponsor sought the advice of the CHMP regarding choice of comparators in the proposed Phase III development program, namely IDet in subjects with T1DM, IGlar for once daily dosing in subjects T2DM and NovoMix 30 for BD dosing in subjects with T2DM. The CHMP stated the '*proposed clinical programme evaluating the potential use of SIAC* [IDegAsp] *in various conditions with different comparators is in general acceptable and in line with the CHMP NfG (CPMP/EWP/1080/00).*

The sponsor provided minutes of end of clinical Phase II meeting between TGA and the sponsor (5 March 2009) as referred to in the above response. The following points were discussed regarding comparators (note: SIBA and SIAC are synonymous with IDeg and IDegAsp respectively):

- Choice of comparators: TGA considered the comparators to be appropriate and realistic for the proposed studies. However, TGA was concerned regarding the dose equality (clinical potency) of SIBA (IDeg) and whether subjects would require a higher dose of bolus insulin compared to that used with other basal insulin analogues. NN clarified that overall the Phase II data suggested that both SIBA (IDeg) and SIAC (IDegAsp) were dose equivalent to insulin glargine. The Phase III data will confirm.
- NN clarified that SIAC (IDegAsp) once daily (OD) would be used both for initiation and intensification from basal insulin. Whereas SIAC (IDegAsp) twice daily (BD) would be reserved for switch from premixed insulin. Upon clarification of the OD dosing regimen for initiation and intensification as well as the BD dosing for switching from premixed insulin, TGA had no further concerns regarding the proposed dosing regimens.
- NN clarified that subjects would not initiate thiazolidinedione (TZD) treatment, but only continue on pioglitazone if already treated with a combination of insulin and TZDs.

- Following clarification, TGA were satisfied with the OAD combination programme.

In summary, the sponsor's response regarding choice of BIAsp 30 BD as comparator for BD dosing regimen is acceptable.

2. Concomitant OADs in T2DM Studies

The clinical evaluator for the previous withdrawn submission commented the efficacy and safety of IDegAsp in combination with insulin secretagogues, α-glucosidase inhibitors and GLP-1 agonists has not been evaluated.

**Comment:** The absence of data in combination with sulphonylureas was raised by the CHMP in the document EMA Scientific Advice NN5401 SIAC dated February 2009. The following question regarding proposed combination of OADs was put forward by the sponsor to the CHMP for comment:

*'Does the agency agree that the proposed trials investigating SIAC in combination with metformin, TZDs and DPP-4I's are sufficient for obtaining a general indication for the use of SIAC in combination with OAD agents?'*

The CHMP response included the following statements:

*'Although it is generally agreed that representative data on 1 substance and/or combination may be extrapolated to the further substances of the whole class of the compound, in serval instances the extrapolation may need justification, or can as such not be accepted (for example, different safety profiles).*

*There is no study including metformin and SU in combination with SIAC. The applicant should consider that metformin in combination with SU is widely used and thus and add on of SIAC to this combination with SU is widely used and thus, an add on of SIAC to this combination is clinically relevant. An additional treatment arm in Study NN5401-3592 investigating this combination should be considered. The number of patients included in the study should be large enough to allow meaningful subgroup analyses of the different concomitant OAD's'.*

The lack of data for metformin in combination with insulin secretagogues was considered acceptable by the EMA evaluator, as commented in the CHMP assessment report:

'*As insulin secretagogues were to be discontinued, there is no data on the combination of metformin and insulin secretagogues. However, since the combination of prandial insulin and insulin secretagogues is not recommended by the recognized clinical treatment guidelines, this is acceptable'.*

In the Australian clinical practice guideline General Practice Management of Type 2 Diabetes 2016 to 2018;[2,6] sulphonylureas remain a second line agent (and first line if metformin is contraindicated), with the comment '*SU are the usual initial agent to add to metformin. If SU are contraindicated or not tolerated another agent may be used*.' These agents include DPP-4I, sodium glucose co-transporter 2 inhibitors, GLP-1 receptor agonists, acarbose, thiazolidinedione and insulin. Whilst the availability of newer agents which are not associated with hypoglycaemia, such as DPP-4I and sodium glucose co-transporter 2 inhibitors, affords practitioners a greater choice of OADs to use in combination with insulin when treatment intensification is required, it is nevertheless not unreasonable to expect patients with T2DM to be on a combination of metformin and sulphonylureas in current clinical practice. Thus, the lack of data for IDegAsp in combination with sulphonylureas, as well of the risk of hypoglycaemia if

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

sulphonylureas are combined with a prandial insulin treatment, should be documented in the PI.

3. Efficacy of twice-daily dosing of IDegAsp

The clinical evaluator for the original withdrawn submission stated the following on in the supplementary CER: '*The evidence for efficacy of the new combination of IDegAsp was not conclusive especially with respect to the proposed twice daily dosing in patients with T2DM*'.

**Comment:** The sponsor has stated that in all of the confirmatory trials, non-inferiority of IDegAsp (OD or BD) versus the comparator product was demonstrated in terms of the primary efficacy endpoint (change in HbA1c). Non-inferiority of IDegAsp to respective comparators (IDet, IGlar and BIAsp30) in terms of reduction in HbA1c from Baseline was demonstrated in the pivotal studies previously evaluated in the original withdrawn submission. (see Table 4, above).

4. Efficacy and safety of IDegAsp in T2DM not evaluated beyond 26 weeks

The clinical evaluator for the original withdrawn submission noted the lack of studies in subjects with T2DM beyond 26 weeks.

**Comment**: It is noted the TGA adopted EU '*Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus'* states the comparative phase of confirmatory trials should usually be of 6 months duration and follow up data covering 12 months should be available for novel insulin analogues.[7] For IDegAsp, efficacy over 12 months has been demonstrated for subjects with T1DM in Study NN5401-3594.

The sponsor replied to this comment in the response document stating the clinical trial programme was discussed with the TGA at end of Phase II meeting and the 6 month exposure for IDegAsp was accepted.

The current dossier contains the synopsis for the 26 week extension of Study NN5401-3590 evaluating the efficacy and safety of IDegAsp in subjects with T2DM; this study is discussed below in Section 7.2 of this report. The sponsor adds further that long term data for IDeg are available in the concurrent submission for the mono-product, and IAsp is well established on the market.

The above reasoning is considered acceptable to this evaluator.

## 6.2. Studies providing new efficacy data

Synopses for 7 new studies providing efficacy data for subjects with T2DM were provided in the current dossier. This included the synopsis for the extension of the pivotal Study NN5401-3590, and 4 additional studies investigating twice daily dosing of IDegAsp. Although defined as safety endpoints, some of the hypoglycaemic parameters are included in the study summaries below to facilitate comparison with those results in earlier studies provided in Table 4.

### 6.2.1. Study NN5401-3726

Study NN5401-3726 is a 26 week extension of Study NN5401-3590 comparing the efficacy and safety of IDegAsp with IGlar in insulin naïve subjects with T2DM. The primary objective was to determine long-term safety and tolerability of IDegAsp, with efficacy endpoint secondary objectives. The extension study included 413 subjects (IDegAsp = 192, IGlar = 221).

[7] European Medicines Agency. 2012. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. CPMP/EWP/1080/00 Rev.1.

The estimated mean reduction in HbA1c after 52 weeks of treatment was 1.48% and 1.40% for the IDegAsp and IGlar treatment arms respectively, with an estimated mean treatment difference (IDegAsp - IGlar) of -0.08% (95% CI: -0.26, 0.09). The mean (SD) HbA1c was 7.5% (1.0) and 7.6% (1.1) with IDegAsp and IGlar respectively.

The estimated mean reduction from Baseline for FPG was similar between the 2 groups (3.50 mmol/L for IDegAsp and 3.77 mmol/L for IGlar), with an estimated mean treatment difference (IDegAsp - IGlar) of 0.28 mmol/L (95% CI: -0.14, 0.69). The observed proportion of subjects achieving HbA1c < 7% without confirmed hypoglycaemia was 23.6% and 20.9% with IDegAsp and IGlar respectively; the estimated odds ratio (IDegAsp/IGlar) was 1.15 (95% CI: 0.73, 1.81).

The observed rate of nocturnal confirmed hypoglycaemic episodes was lower in the IDegAsp group; 19 and 53 per 100 PYE for IDegAsp and IGlar respectively (estimated rate ratio (IDegAsp/IGlar) = 0.25 (95% CI: 0.14, 0.47)). The observed rate of confirmed hypoglycaemic episodes was higher for IDegAsp with 419 per 100 PYE versus 211 per 100 PYE for IGlar (estimated rate ratio (IDegAsp/IGlar) = 1.86 (95% CI: 1.42, 2.44)).

**Comment**: A persistent reduction in HbA1c was observed after 52 weeks of IDegAsp OD in insulin naïve patients with T2DM.

### 6.2.2. Study NN5401-3844

Study NN5401-3844 is a 26 week randomised, open label, multi-centre, 2 arm, and parallel group study to compare the efficacy and safety of 2 titration algorithms for IDegAsp OD in combination with metformin in insulin naïve subjects with T2DM. The primary objective was to confirm the efficacy of IDegAsp OD simple titration algorithm in controlling glycaemia by comparing the difference in change from baseline in HbA1c after 26 weeks of treatment between IDegAsp OD simple titration algorithm and IDegAsp OD the step wise algorithm (both in combination with metformin) to a non-inferiority limit of 0.4%.

The study population included insulin-naïve adults with T2DM for ≥ 24 weeks currently treated with metformin ± 1 or 2 other OADs, with HBA1c of 7.0 to 10.0% inclusive. There were 276 subjects randomised 1:1 to IDegAsp simple (n = 136) or IDegAsp step wise (n = 140). The simple titration algorithm involved twice weekly self-titration based upon pre-breakfast SMPG on the day of titration, with 3 to 4 days between titrations. In the step wise titration algorithm, subjects performed self-titration once weekly based on the lowest of 3 consecutive pre-breakfast SMPG values (2 days prior to titration and on the day of titration).

The treatment groups were well balanced with regard to baseline demographics, with the exception of distribution of sexes (greater proportion of males in the IDegAsp treatment arm).

Non-inferiority of IDegAsp simple to IDegAsp step-wise in terms of HbA1c reduction was demonstrated after 26 weeks of treatment (estimated mean treatment difference (IDegAsp simple - IDegAsp step wise) = -0.18% (95% CI: -0.38, 0.02). Mean FPG reduced in both groups with no statistically significant difference observed (estimated mean treatment difference (IDegAsp simple - IDegAsp step wise) = -0.42 mmol/L (95% CI: -0.93, 0.09)).

The rate of nocturnal confirmed hypoglycaemic episodes was similar in both groups (52 versus 41 events per 100 PYE, estimated rate ratio (IDegAsp simple/IDegAsp step wise) = 1.05 (95% CI: 0.45, 2.44). The rate of confirmed hypoglycaemic episodes was higher in the IDegAsp simple group than the IDegAsp step wise group (326 versus 207 events per 100 PYE, estimated rate ratio (IDegAsp simple/IDegAsp step wise) = 1.80 (95% CI: 1.14, 2.85)).

### 6.2.3. Study NN5401-3896

Study NN5401-3896 is a 26 week randomised, open label, multicentre, 2 arm, parallel group study to compare the efficacy and safety of IDegAsp OD and IGlar OD as monotherapy or in combination with OADs (excluding DPP-4I, sulphonylureas and glinides) in Japanese subjects

with T2DM. The study included 296 subjects randomised (1:1) to IDegAsp OD (n = 147) or IGlar OD (n = 149).

Superiority of IDegAsp to IGlar was demonstrated with regard to lowering HbA1c after 26 weeks, with the estimated mean change -1.61% in the IDegAsp group and -1.33% in the IGlar group (estimated treatment difference (IDegAsp-IGlar) = -0.28% (95% CI: -0.46, -0.10)). A similar reduction in mean FPG was observed in both groups after 26 weeks (estimated treatment difference (IDegAsp-IGlar) = 0.15 mmol/L (95% CI: -0.29, 0.60)). The observed proportion of subjects achieving HbA1c < 7.0% without confirmed hypoglycaemia was 43.3% with IDegAsp and 25.0% with IGlar.

The observed rate of nocturnal confirmed hypoglycaemic episodes was 39 and 53 per 100 PYE for IDegAsp and IGlar respectively (estimated rate ratio (IDegAsp/IGlar) = 0.75 (95% CI: 0.34, 1.64)). The observed rate of confirmed hypoglycaemic episodes was lower with IDegAsp compared to IGlar (191 vs. 271 episodes per 100 PYE; estimated rate ratio (IDegAsp/IGlar) = 0.73 (95% CI: 0.50, 1.08)).

## 6.3. Studies with twice daily dosing of IDegAsp

### 6.3.1. Study NN5401-3940

Study NN5401-3940 is a 26-week randomised, open label, multinational, 2 arm, parallel group, treat-to-target study to compare the efficacy and safety of IDegAsp BD and BIAsp 30 BD added to metformin in insulin naïve subjects with T2DM. The primary objective was to confirm the efficacy of IDegAsp added to metformin in controlling glycaemia by comparing change from baseline in HbA1c after 26 weeks of treatment to a non-inferiority limit of 0.4%. There were 394 subjects randomised 1:1 to IDegAsp (n = 197) or BIAsp 30 (n = 197). The trial population was considered well balanced with regard to baseline demographics.

Non-inferiority of IDegAsp to BIAsp 30 in terms of HbA1c reduction after 26 weeks of treatment was confirmed, with an estimated mean change in HbA1c from baseline of -1.71% with IDegAsp and -1.73% with BIAsp 30 (estimated mean treatment difference (IDegAsp- BIAsp 30) = 0.02% (95% CI: -0.12, 0.17)). The estimated mean change from baseline in FPG was -4.35 mmol/L and -3.34 mmol/L for IDegAsp and BIAsp 30 respectively (estimated treatment difference (IDegAsp-BIAsp 30) = -1.00 mmol/L (95% CI: -1.42, -0.59)). The observed proportion of subjects achieving HbA1c < 7.0% without confirmed hypoglycaemic episodes was 40.1% and 31.6% for the IDegAsp and BIAsp 30 groups respectively.

A lower rate of nocturnal confirmed hypoglycaemic episodes and confirmed hypoglycaemic episodes was observed for IDegAsp (63 and 580 episodes per 100 PYE) compared to BIAsp 30 (277 and 1301 episodes per 100 PYE). The estimated rate ratios (IDegAsp/BIAsp 30) were 0.25 (95% CI: 0.16, 0.38) and 0.46 (95% CI: 0.35, 0.61) for nocturnal confirmed and confirmed hypoglycaemic episodes respectively.

**Comment:** The efficacy of IDegAsp compared with BIAsp 30 BD in insulin-treated subjects with T2DM has been determined in the pivotal Study NN5401-3592 evaluated in the original withdrawn submission. The limited data provided in the current synopsis for BD dosing in insulin naïve subjects with T2DM demonstrate a similar trend to the results in Study NN5401-3592, *vis a vis* reductions in HBA1c, FPG and in the incidence of confirmed and nocturnal confirmed hypoglycaemic episodes.

### 6.3.2. Study NN5401-3996

Study NN5401-3996 is a 26-week randomised, controlled, open-label, multinational, parallel group, treat-to-target study to compare the efficacy and safety of IDegAsp BD with IDeg OD + IAsp in subjects with T2DM treated with OADs (except sulphonylureas and glinides) and basal insulin requiring treatment intensification with mealtime insulin. The primary objective was to

confirm the efficacy of IDegAsp BD in terms of glycaemic control by comparing the difference in the change in HbA1c from baseline between IDegAsp BD and IDeg OD + IAsp 2-4 times daily to a non-inferiority limit of 0.4%.

The study population included 274 subjects randomised 1:1 to IDegAsp BD (n = 138) or IDeg OD + IAsp (n = 136).

At randomisation, subjects in the IDegAsp BD treatment arm were switched unit-to-unit from previous daily total daily basal insulin dose to IDegAsp, with the total dose split into 2 daily doses of IDegAsp at the investigators' discretion also ensuring that the short-acting component was appropriate to the intended meal sizes. In the IDeg OD + IAsp arm, subjects previously on once daily basal insulin were switched unit-to-unit from their previous total daily basal insulin dose to IDeg OD and subjects on a twice daily insulin regimen previously were switched to IDeg OD. The dose of IDeg OD was reduced by 20% compared to previous total insulin dose. IAsp was administered with main meals 2-4 times daily.

It is noted at the end of the study the mean derived total daily basal insulin dose was similar between the 2 groups (IDegAsp BD = 75 U (0.78 U/kg) and IDeg OD+ IAsp = 73 U (0.74 U/kg)), whilst the mean derived total daily bolus insulin dose was numerically lower in the IDegAsp BD group (32 U (0.33 U/kg]) compared with the IDeg OD + IAsp group (58 U (0.61 U/kg]).

The estimated mean change from baseline in HbA1c after 26 weeks was -1.23% for IDegAsp BD and -1.42% with IDeg OD + IAsp. Non-inferiority of IDegAsp BD to IDeg + IAsp in terms of HbA1c reduction from baseline was not confirmed; the estimated treatment difference (IDegAsp BD – IDeg + IAsp) was 0.18% (95% CI: -0.04, 0.41). Non-inferiority was stated to have been demonstrated in sensitivity analyses.

There was a reduction in mean FPG from baseline in both groups, with an estimated treatment difference (IDegAsp BD – IDeg OD + IAsp) of -0.31 mmol/L (95% CI: -0.97, 0.34). After 26 weeks, the observed proportion of subjects with HbA1c < 7.0% was 56.5% subjects in the IDegAsp BD group and 59.6% subjects in the IDegAsp OD + IAsp group (treatment odds ratio (IDegAsp BD/IDeg OD + IAsp) of 0.83 (95% CI: 0.50, 1.38)).

There was no statistically significant difference in the rate of confirmed hypoglycaemic episode or nocturnal confirmed hypoglycaemic episodes between the 2 groups; estimated rate ratios (IDegAsp BD/IDeg OD + IAsp) were 0.81 (95% CI: 0.61, 1.07) and 0.80 (95% CI: 0.50, 1.29) respectively.

**Comment:** It is not clear why the dose of IDeg OD was reduced by 20% compared to previous insulin dose as stated in the synopsis. Non-inferiority of IDegAsp BD to IDeg OD + IAsp with regard to the primary endpoint was not confirmed. Sensitivity analyses were stated to be within the non-inferiority margin. Overall a reduction in HbA1c was observed in both groups as would generally be expected with intensification of insulin therapy, but it is difficult to draw any further conclusions based on a study synopsis.

### 6.3.3. Study NN5401-3941

Study NN5401-3941 is a 26 week randomised, open label, multinational, multicentre, 2 arm, parallel group, treat-to-target study to compare the efficacy and safety of 2 titration algorithms for IDegAsp BD subjects with T2DM previously treated with IGlar and up to 3 OADs (excluding SU's or glinides). Subjects in the IDegAsp BD simple titration algorithm arm performed self-titration twice weekly (at intervals of 3−4 days) based upon a single pre-breakfast and pre-dinner SMPG value, whilst for subjects in the IDegAsp stepwise titration algorithm arm, self-titration was performed once a week based on the lowest of 3 pre-breakfast SMPG values (measurements on 2 consecutive days prior to titration and on the day of titration) and 3 pre-dinner SMPG values (measurements on 3 consecutive days prior to titration).

There were 272 subjects randomised 1:1 to IDegAsp simple (n = 136) or IDegAsp step wise (n = 136). Non-inferiority of IDegAsp simple to IDegAsp step wise with respect to reduction in HbA1c after 26 weeks of treatment was confirmed, with the estimated treatment difference (IDegAsp simple – IDegAsp step wise) -0.11% (95% CI: -0.34, 0.11). FPG reduced from Baseline in both groups (estimated treatment difference (IDegAsp simple – IDegAsp, step wise) = 0.30 mmol/L (95% CI: -0.28, 0.88)).

Statistically significantly higher rates of both confirmed and nocturnal confirmed hypoglycaemic episodes were observed with IDegAsp simple titration than with IDegAsp stepwise titration (estimated rate ratios (IDegAsp simple/IDegAsp step wise) were 1.71 (95% CI: 1.21, 2.41) and 1.93 (95% CI: 1.04, 3.60) respectively).

#### 6.3.4. Study NN5401-4003

Study NN5401-4003 is a 26 week, randomised, open label, 2 arm, parallel, multinational, multicentre, treat-to-target study to assess the safety and efficacy of IDegAsp BD + IAsp OD versus basal bolus treatment with IDeg OD + IAsp TID both in combination with up to 2 OADs in subjects with T2DM qualifying for treatment intensification at the end of Study NN5401-3941. The primary objective was to compare the efficacy of IDegAsp BD + IAsp OD versus basal bolus treatment with IDeg OD + IAsp TID in controlling glycaemia by evaluating HbA1c.

The trial population included subjects from Study 3941 not achieving the glycaemic target of HbA1c < 7.0%. There were 40 subjects randomised (n = 20 to each treatment arm). The sponsor states 97 subjects were planned to be randomised, however fewer subjects than expected were screened due to more than 60% of subjects reaching glycaemic target in the preceding Study NN5401-3941. After 26 weeks, the estimated mean change in HbA1c from Baseline was 0.05% in the IDegAsp BD + IAsp OD group and -0.49% in the IDeg OD +IAsp TID group, with an estimated treatment difference of 0.54% (95% CI: 0.09, 0.99).

**Comment**: The sample size of this study was too small to draw any meaningful conclusions. Better glycaemic control with regimes allowing more flexible titration of components would be expected.

## 6.4. Evaluator's conclusions on clinical efficacy

The efficacy of IDegAsp in terms of HbA1c reduction was demonstrated in the pivotal studies evaluated in the original withdrawn submission (with non-inferiority of IDegAsp to comparators in subjects with both T1DM and T2DM demonstrated. Additional 52 week data for subjects with T2DM provided in the synopsis for Study NN5401-3726 demonstrate maintenance of effect in terms of HbA1c reduction.

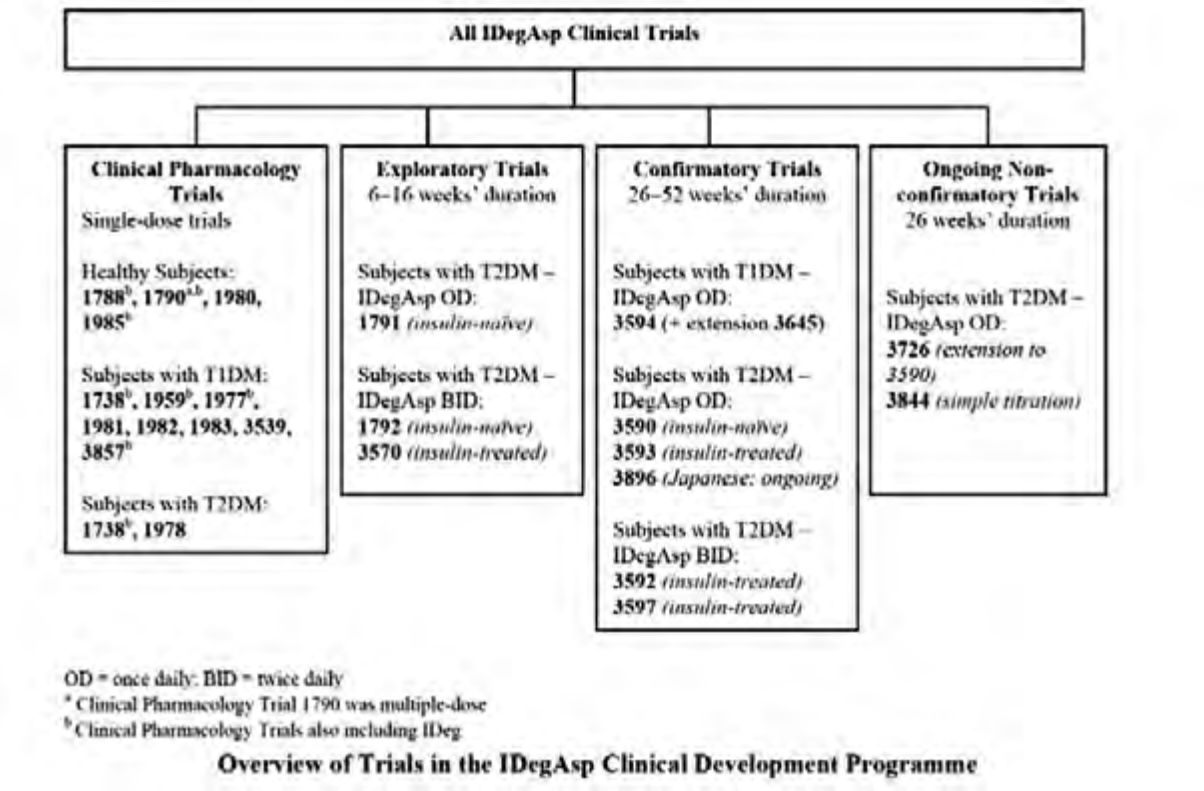
Outstanding issues regarding efficacy identified in the original submission are considered to have been adequately addressed, with particular regard to the efficacy of twice daily dosing of IDegAsp in subjects with T2DM. The synopses provided in the current dossier for an additional 4 studies comparing IDegAsp BD and BIAsp 30 BD confirmed non-inferiority of IDegAsp to BIAsp 30 with respect to reduction in HbA1c in 2 studies. A reduction in HbA1c was observed, although non-inferiority of IDegAsp BD to BIAsp 30 BD not confirmed, in 1 study and the remaining study comprised a sample size too small to draw any meaningful conclusions. These findings need to be considered in accordance with safety data.

The external validity of the clinical trials is a major concern. The results of the clinical trials describe an average response for the population in terms of glycaemic control and hypoglycaemia. However, in clinical practice insulin doses are individualised based on type of diabetes, residual insulin secretion, insulin sensitivity, carbohydrate composition of meals, age and co-morbidities. Thus, the extrapolation of dosing regimens and outcomes need to be interpreted with caution.

# 7. Clinical safety

In the original withdrawn submission, the following completed trials with a cut-off date of 31 January 2011 were submitted, as shown in Figure 3.

**Figure 3: Completed trials with cut-off date 31 January 2011**




**Overview of Trials in the IDegAsp Clinical Development Programme**

Since the original withdrawn 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 IDegAsp, which contain data up until 30 September, 2014. These 2 documents provide integrated safety data from the updated data set (cut off 30 September 2011); although the Safety Update IDegAsp appears to contain additional details compared to the Summary of Clinical Safety Addendum. The safety section of this CER references data presented in these 2 documents. These 2 documents compare the updated data to data contained within the Integrated Safety Summary (ISS) which was not submitted in the original withdrawn Australian submission of IDegAsp but assumed to be similar to the data evaluated in that submission.

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

- The cut-off date for the data submitted in the original withdrawn Australia IDegAsp submission and the US submitted ISS are both 31 January 2011.
- The submissions appear to include the same completed clinical pharmacology, exploratory and confirmatory trials.
- 'All subject' safety analysis dataset presented in the original Australian clinical evaluation for the IDegAsp group and the comparator group for all therapeutic confirmatory trials contains the same number of patients as that contained within the US FDA ISS dataset (taken form a table in Summary of clinical safety addendum).

- Adverse event summary table for both the original Australian evaluation and the ISS are identical (taken 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 (taken from a table in second round CER and a table in the Summary of Clinical Safety Addendum respectively).

One discrepancy was found: with regards to the ongoing confirmatory trials at the time of the evaluation, there is a discrepancy in the categorisation of 1 of the studies listed in the original Australian clinical evaluation report (dated 13 August, second round report) and the US submitted ISS: the US ISS lists Study NN5401-3726 (an extension of Study NN5401-3590) but this is likely to have no impact on the data.

Therefore, with the exception of the discrepancy described above, the datasets evaluated in the original Australian clinical evaluation report and the ISS appear to be very similar.

## 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, 2 have safety as the sole primary outcome:

- Study EX1250-4080 (the DEVOTE trial), a dedicated cardiovascular outcomes study. This study randomised subjects to either IDeg or IGlar (an IDegAsp arm was not included). See Section 7.2 (below) for further details and also the IDeg CER [available as Attachment 2 of the Tresiba submission].[1]
- Study NN5401-3726 ('BOOST: START1' study), an extension study (26 weeks) which continued to follow subjects with T2DM who were in Study NN 5401-3509 who received IDegAsp or IGlar. See Section 7.2 (below) for further details.

### 7.1.2. Other studies

In the original CER for the original withdrawn submission, 5 therapeutic confirmatory studies and 3 exploratory studies (completed as of 31 January 2011) and ongoing studies (with a cut-off date as of 31 March 2011) provided evaluable safety data. The 5 pivotal/confirmatory studies counted for most of the overall exposure in the original withdrawn submission. Of the additional data contained within this submission, 1 extension trial (Study NN5401-3726) of the original pivotal Study NN5401-3590 is included.

As of 30 September 2014, a total of 31 trials and extension trials have been completed with IDegAsp; 1 paediatric was trial ongoing, as shown below in Table 5.

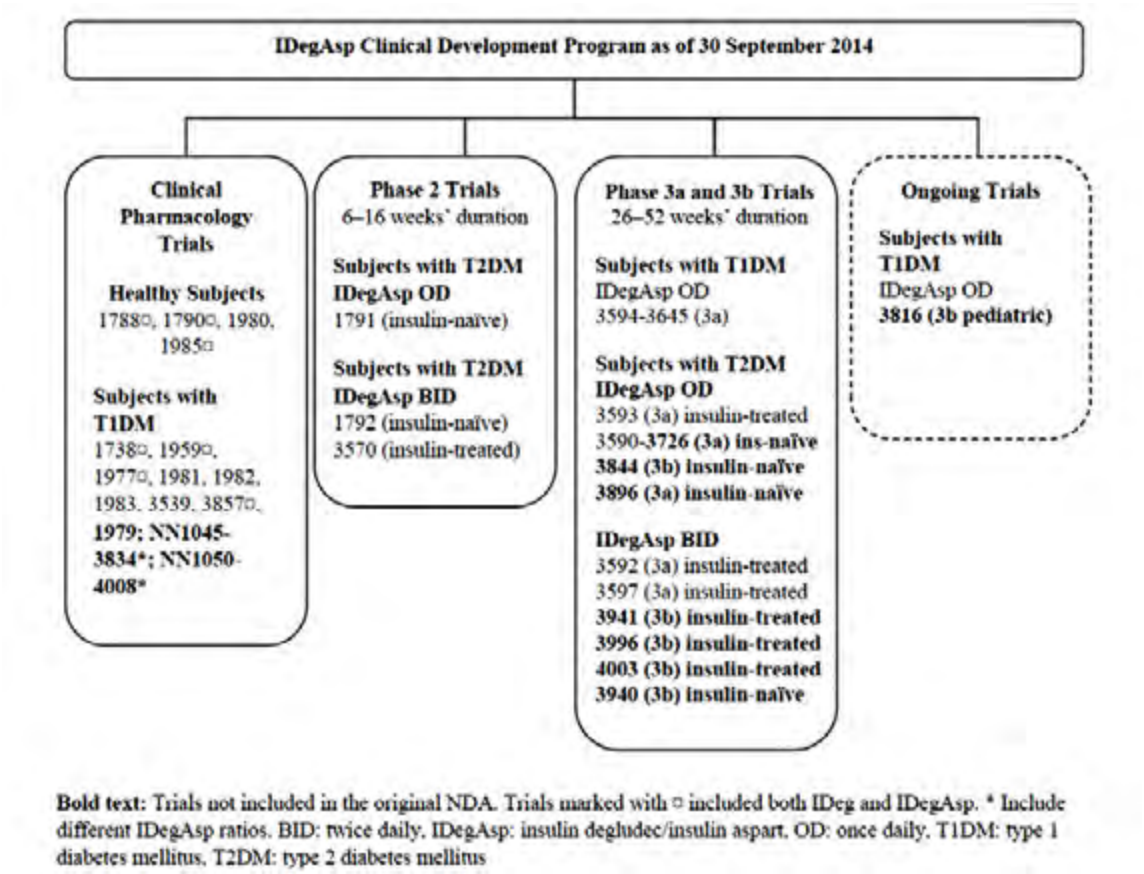
**Table 5: Summary of completed IDegAsp studies as of 30 September 2014**

| | T1DM | T2DM (daily dosing) | T2DM (twice daily dosing) |
|---|---|---|---|
| Phase III | 1 | 4 | 6 |
| Clinical pharmacology | 17 (includes healthy subject trials and T1DM trials) | | |
| Phase II trials | 0 | 1 | 2 |
| Ongoing trial | 1 | 0 | 0 |

Of the 31 completed trials, 10 trials have been completed since the Integrated Safety Summary (ISS): 7 Phase III trials (including 1 extension part) and 3 clinical pharmacology trials. The cut-off date for data included in this safety update for both completed and ongoing trials was 30 September 2014.

Figure 4 (shown below) is a summary of the IDegAsp clinical development program as of 30 September 2014 and indicates new trials as presented in the Summary of Clinical Safety Addendum.

**Figure 4: IDegAsp clinical development program as of 30 September 2014; indicating new trials**




**Bold text:** Trials not included in the original NDA. Trials marked with ¤ included both IDeg and IDegAsp. * Include different IDegAsp ratios. BID: twice daily, IDegAsp: insulin degludec/insulin aspart, OD: once daily, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus

It is noted that there are 2 studies listed in the submission ('Comparison of data submitted with the original and current application') of the current Australian submission which carry the study number prefix of 'NN5401', denoting IDegAsp studies, which are not listed in the above figure extracted from the Summary of clinical safety addendum (IDegAsp). These studies are Study NN5401-1718 and Study NN5401-1719; both designated as patient PD and PK/PD study reports; Study NN5401-1718 is in healthy male subjects and Study NN5401-1719 is in T2DM and T1DM subjects and both were previously submitted to the TGA. It is not clear why there is a discrepancy.

This safety evaluation is mainly based on the Phase III trials; a complete list of the completed Phase III trials as of 30 September 2014 can be found below in Table 6. It should be noted that Study EX1250-4080 (the DEVOTE trial) is not included in this list since it is ongoing.

**Table 6: Completed IDegAsp Phase III trials as of 30 September 2014**

| Trial ID | Type of subjects | Treatment duration (weeks) | Phase | Design Randomized (IDeg : Comp) | Test drug | Comparator | Exposed subjects |
|---|---|---|---|---|---|---|---|
| 3594-3645 | T1DM | 26 + 26 | 3a | parallel (2:1)[#] | IDegAsp OD + IAsp at remaining meals | IDet OD/BID + IAsp at all meals | IDegAsp: 362 IDet: 180 |
| 3590-**3726** | T2DM | 26 + **26** | 3a | parallel (1:1)[#] | IDegAsp OD + met | IGlar OD + met | IDegAsp: 265 IGlar: 261 |
| 3593 | T2DM | 26 | 3a | parallel (1:1) | IDegAsp OD + OADs | IGlar OD + OADs | IDegAsp: 230 IGlar: 233 |
| **3896 (Japan)** | T2DM | **26** | 3a | parallel (1:1) | IDegAsp OD ± OADs | IGlar OD ± OADs | IDegAsp: 147 IGlar: 149 |
| 3597 | T2DM | 26 | 3a | parallel (2:1) | IDegAsp BID ± met | BIAsp 30 BID ± met | IDegAsp: 279 BIAsp 30: 141 |
| 3592 | T2DM | 26 | 3a | parallel (1:1) | IDegAsp BID ± OADs | BIAsp 30 BID ± OADs | IDegAsp: 224 BIAsp 30: 222 |
| **3844** | T2DM | **26** | 3b | parallel (1:1) | IDegAsp OD ± met simple titration | IDegAsp OD ± met stepwise titration | IDegAsp simple: 134 IDegAsp stepwise: 140 |
| **3940** | T2DM | **26** | 3b | parallel (1:1) | IDegAsp BID + met | BIAsp 30 BID + met | IDegAsp: 196 BIAsp 30: 195 |
| **3941** | T2DM | **26** | 3b | parallel (1:1) | IDegAsp BID + met simple titration | IDegAsp BID + met stepwise titration | IDegAsp simple: 135 IDegAsp stepwise: 134 |
| **3996** | T2DM | **26** | 3b Repor -ting | parallel (1:1) | IDegAsp BID ± OADs | IDeg OD + IAsp TID ± OADs | IDegAsp: 136 IDeg: 135 |
| **4003** | T2DM | **26** | 3b | parallel (1:1) | IDegAsp BID + IAsp OD | IDeg OD + IAsp TID | IDegAsp: 20 IDeg: 20 |

**Bold text:** Trials not submitted as part of the original NDA, BID: twice daily; Comp: comparator; IAsp: insulin aspart; IDeg: insulin degludec; IDegAsp: insulin degludec/insulin aspart; BIAsp 30: biphasic insulin aspart 30; IDet: insulin detemir; IGlar: insulin glargine; met: metformin; OD: once daily; OAD, Ped: pediatric; TID: three times daily
[#]Randomization ratio at start of the main trial period – entry into extension required new informed consent.

## 7.2. Studies that assessed safety as the sole primary outcome

### 7.2.1. Study EX1250-4080, the DEVOTE trial

Please see Section 7.2 in the Tresiba/IDeg clinical evaluation report for a discussion of this study [available as Attachment 2 for this submission].[1]

**Comment:** It should be noted that the DEVOTE trial did not specifically include an IDegAsp arm. Although it is acknowledged that IDeg is the new chemical entity in this combination, and therefore of greater interest to explore its impact on cardiovascular outcomes, it is nevertheless noted that the original FDA cardiovascular analysis which showed a potential cardiovascular signal included both IDeg patients and IDegAsp patients.

Although some patients did receive IDeg plus IAsp (but not the IDegAsp combination product) in the DEVOTE trial, the study report does not specify what proportion of patients on either arm received IAsp. Furthermore, the study was not designed to explore the impact of a combination of IDeg and IAsp on cardiovascular outcomes.

Thus, although the results from the DEVOTE trial are somewhat reassuring from the viewpoint of IDegAsp, it is difficult to know to what degree the results can be extrapolated to the combination product, IDegAsp.

It was also noted in the DEVOTE trial that the patients who received IAsp developed a higher rate of Event Adjudication Committee (EAC) confirmed hypoglycaemia compared to those not receiving IAsp, more than 3 times the rate. In terms of the individual arms, the IDeg + IAsp arm had a lower rate (7.23 events per 100 patient years of observation) compared to the IGlar arm + IAsp (11.16 events per 100 patient years of observation) although it is noted that the actual proportion of subjects affected were similar (2.7% on IDeg and 3.0% on IGlar). However there are no further details available regarding this subset analysis and it is difficult to draw any conclusions.

Thus, although the results of DEVOTE trial are reassuring from a cardiovascular point of view with regards to the use of IDeg, the implications for IDegAsp are less clear.

### 7.2.2. Study NN 5401-3726, the BOOST: START1 trial

This study was an extension trial of Study NN5401-3590 and followed subjects for a further 26 weeks after the main trial of 26 weeks (52 weeks total). The full study report was not included in the submission and therefore not evaluated. See Section 6.2 above for a summary of efficacy results.

In terms of adverse events, it is noted that the rate of adverse events, possibly or probably related adverse events and serious adverse events was higher in the IDegAsp group compared to the IGlar group, as shown below in Table 7.

**Table 7: Adverse events in Studies NN5401-3590 and NN5401-3726 (extension)**

| | Study NN5401-3590 | | Study NN5401-3726 (ext) | |
|---|---|---|---|---|
| | IDegAsp | IGlar | IDegAsp | IGlar |
| Rate of adverse events | 352 | 269 | 313 | 238 |
| Rate of possibly or probably related adverse events | 24 | 19 | 18 | 13 |
| Rate of serious adverse events | 16 | 5 | 17 | 9 |

Note: Rate = number of events per 100 patient year exposure.

The reason for this discrepancy is not clear from the data in the synopsis, however it is noted that a similar pattern was seen in the main Study NN5401-3590, of which Study NN5401-3726 is an extension. The observed mean (SD) body weights at Baseline and at the end of the trial were 85.1 kg (18.0) and 88.7 kg (18.3) in the IDegAsp group, that is, a weight increase of 3.6 kg; and 85.2 kg (18.6) and 87.4 kg (18.9) in the IGlar group, that is, a weight increase of 2.2 kg, respectively. The rate of confirmed hypoglycaemic episodes was higher in the IDegAsp group compared to the IGlar group (419 and 211 per 100 PYE for IDegAsp and IGlar groups, respectively), however the rate of nocturnal confirmed hypoglycaemic episodes was lower for IDegAsp (19 and 53 per 100 PYE for IDegAsp and IGlar groups respectively). Rates of severe and nocturnal severe hypoglycaemia were too low in either arm to draw any meaningful conclusion. The sponsor will be asked to comment on the difference in rates of confirmed hypoglycaemic episodes.

It is also noted that the mean daily insulin dose after 52 weeks was higher in the IDegAsp group (70 U) compared with the IGlar group (62 U). The ratio of IDegAsp/IGlar mean daily insulin dose (U) after 52 weeks was 1.13.

## 7.3. Patient exposure (integrated data)

The following integrated patient exposure data is taken from the Summary of Clinical Safety Addendum and the Safety Update IDegAsp, which contain data up until 30 September 2014. These 2 documents compare the updated data to data contained within the Integrated Safety Summary (ISS), with a cut-off of 31 January 2011.

Per the Summary of Clinical Safety Addendum which has a cut-off date of 30 September 2014:

- 3139 subjects have been exposed to IDegAsp in 31 completed clinical trials and extension trials, of which 10 trials have been completed since the 31 January 2011: 7 Phase III trials all in T2DM (1 extension part, 5 Phase III trials) and 3 clinical pharmacology trials. This has resulted in an 1100 additional subjects compared to the original Integrated Safety Summary (ISS; data up to 31 January 2011 (please see Section 7.4 for information regarding the ISS)).
- The only ongoing IDegAsp trial as of 30 September 2014 is a paediatric trial.
- 10 773 subjects have been exposed to IDeg and/or IDegAsp in all completed IDeg/IDegAsp trials (a small number of subjects were exposed to both IDeg and IDegAsp).
  - This includes an additional 167 subjects exposed in 6 Phase I trials completed with IDeg and IDegAsp since the ISS (data up to 31 January 2011).
  - Subjects participating in the main and extension parts of a trial were counted only once in the subject exposure calculation.

Table 8 that follows is a summary of all subjects from completed trials for both IDeg and IDegAsp (from Summary of Clinical Safety Addendum IDegAsp).

**Table 8: Exposure in all completed trials (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

Table 9 (below) gives an indication of exposure to IDegAsp by exposure duration in the completed Phase III trials as of 30 September 2014.

**Table 9: Exposure to IDegAsp in completed Phase III trials**

| | % of patients with any exposure (N) | % of patients with exposure ≥ 6 months | % of patients with exposure ≥ 12 months (N) | Total exposure in subject years |
|---|---|---|---|---|
| **All subjects** | | | | |
| IDegAsp | 100 (2382) | 88.6 | 18.1 (431) | 1340.3 |
| Comparators | 100 (1381) | 89.1 | 23.7 (327) | 815.8 |
| **T1DM** | | | | |
| IDegAsp | 100 (362) | 89.0 | 64.9 (235) | 296.9 |
| Comparators | 100 (180) | 87.2 | 63.3 (114) | 145.5 |
| **T2DM** | | | | |

| | % of patients with any exposure (N) | % of patients with exposure ≥ 6 months | % of patients with exposure ≥ 12 months (N) | Total exposure in subject years |
|---|---|---|---|---|
| IDegAsp | 100 (2020) | 88.6 | 9.7 (196) | 1043.4 |
| Comparators | 100 (1201) | 89.4 | 17.7 (213) | 670.3 |
| **Insulin naive T2DM** | | | | |
| IDegAsp | 100 (882) | 91.0 | 20.5 (181) | 514.1 |
| Comparators | 100 (605) | 91.4 | 35.2 (213) | 398.9 |
| **Insulin treated T2DM** | | | | |
| IDegAsp | 100 (1138) | 86.6 | 1.3 (15) | 529.3 |
| Comparators | 100 (596) | 87.4 | 0 | 271.4 |

N = number of patients. Reference: Safety update IDegAsp (16 December 2014), includes Studies 3590-3726, 3592, 3593, 3594-3645, 3597, 3844, 3896, 3940, 3941, 3996, 4003

It is also noted that some trials included only IDeg and IDegAsp and no other comparator.

Compared to the ISS (cut-off date of 31 January 2011), an additional 930 subjects have been exposed to IDegAsp for 6 months, and additional 196 subjects for 12 months or more. The additional subjects who have been exposed for more than 6 months were enrolled on extension Study NN5401-3726 and therefore were all insulin naïve T2DM subjects receiving daily IDegAsp. It is noted that the maximum duration of the trials (as per Figure 4, above) is 52 weeks therefore, even though a sizable proportion of the T1DM population and less percentages of the T2DM population are reported to have been exposed for ≥ 12 months, it is not expected that the subjects would have been exposed for any longer than 12 months. It is also noted that a very small number of insulin treated T2DM subjects have been treated for 12 months or more; the reason for this is not clear. Furthermore, of the subjects with T2DM who have been exposed for 12 months or more, the majority of these are in the comparator group. However, it is not clear why there is such a large difference in terms of those who have been exposed for ≥ 12 months (9.7% IDegAsp compared to 17.7% comparator) and this is not reflected as clearly in terms of completion of extension trials which showed that 92.4% of subjects completed the extension trials in the IDegAsp group compared to 93.9% of those in the comparator group. A question will be asked of the sponsor to clarify this.

In terms of subject disposition in the completed Phase III trials for IDegAsp, 87.5% of subjects on the IDegAsp group completed the main trials compared with 88.3% on the comparator group; the most common reason for withdrawal on the IDegAsp arm was 'other' (5.65%), Fulfilling withdrawal criteria (4.2%) and adverse events (1.4%). Similar rates were seen on the comparator arm except there were fewer (2.7%) withdrawing due to 'fulfilling withdrawal criteria'. Of the subjects included in the extension trials (446 on the IDegAsp, 343 on comparator arms), 92.4% completed the trial on IDegAsp and a slightly higher number on the comparator arm (93.9%). The most common reason for withdrawal was 'other' (4% for

IDegAsp and 3% for comparators); 1.3% withdrew due to adverse events on the IDegAsp compared to 0.9% on the comparator arm. It is noted that the sponsor has indicated that in some of the new completed trials, new withdrawal criteria have been included and this may have resulted in disproportionate reporting of withdrawals on the IDegAsp group since several trials had IDegAsp in both arms and there were no 'comparator' groups.

No new information was included regarding demographic characteristics in the Summary of Clinical Safety Addendum for IDegAsp.

## 7.4. Adverse events (integrated data)

The following integrated safety analyses are summarised from data presented in the Summary of Clinical Safety Addendum, dated 20 January 2015. The data presented in this Summary compares the cumulated safety information for IDegAsp with a cut-off date of 30 September 2014, with that was submitted in the original FDA New Drug Application in the Integrated Safety Summary (ISS) which has a cut-off date of 31 January 2011. Please see Section 7.3 for further information about the reference to the Integrated Safety Summary in this document.

The safety evaluation of IDegAsp is mainly based on the Phase III trials, since these represent the major component of IDegAsp exposure. 2 trials (Studies NN5401-3996 and NN5401-4003) compared IDegAsp with IDeg + IAsp; both arms are included in the analysis for AEs as part of the IDegAsp arm but only IDegAsp is included in the IDegAsp group for hypoglycaemic episodes. Comparators in Phase III trials included IDet daily/twice daily + IAsp, IGlar, BIAsp 30, IDeg + IAsp and IDegAsp + metformin stepwise titration. For T2DM trials, oral anti-diabetic drugs were also allowed (some allowing only metformin). It is assumed that the comparator arms of IDegAsp + metformin stepwise is not included in the comparator group for the purposes of the Integrated Safety Summary however this is not expressly stated in the Summary of Clinical Safety Addendum document. It is also noted that all Phase III trials were open label and therefore there is a risk of bias inherent in these trials.

The trials have been pooled into the following subgroups: subjects with T1DM, subjects with T2DM, T2DM insulin treated (twice daily dosing) and T2DM insulin naïve (once daily dosing) for the analysis of SAE and hypoglycaemic data. SAE and AE data has also been pooled for all subjects and subjects with T2DM.

No new information is available for Phase II trials with IDegAsp (none were conducted); Phase II trial data is pooled with Phase III for rare events.

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 2 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 clinical evaluation report.

The only ongoing trial is a paediatric trial and data for SAEs, SAEs leading to withdrawal and pregnancies from this trial was presented in a blinded manner.

IDegAsp data has been pooled with IDeg data for all subjects from Phase III trials from either IDeg or IDegAsp for analysis of deaths, cardiovascular events, immunological events, neoplasms and rare events. It should be noted that Study EX1250-4080, the dedicated cardiovascular outcomes study, was ongoing as of 30 September 2014 and therefore not included in the integrated safety data for completed trials.

2 analysis sets were described in the Summary of Clinical Safety Addendum:

- Safety analysis set: includes all subjects who received at least 1 dose of the investigational drug or its comparator and they are evaluated 'as treated'. Descriptive safety data is based on the safety analysis set.
- Full analysis set: includes all randomised subjects and are evaluated as randomised. In exceptional cases, subjects could be excluded however it had to be justified and documented in individual study reports.

It is also noted that the version of MedDRA used in the Clinical Safety Summary Addendum IDegAsp cut-off date of 30 September 2014 is 17.0, whereas the version used in the ISS was 13.1 and the versions used in the Australian dossier were 13.0 and 13.1. Some preferred terms have changed from 1 system organ class to another between versions, including some which relate to hypoglycaemia.

Finally, adverse events that occurred in individual studies have not been summarised in this CER unless noted.

### 7.4.1. All adverse events (irrespective of relationship to study treatment)

#### *7.4.1.1. Integrated safety analyses (cut-off date of 30 Sept 2014)*

Table 10 (below) is a summary of all adverse events that have occurred in completed Phase III IDegAsp trials (from Summary of Clinical Safety Addendum IDegAsp, with cut-off date of 30 September 2014).

**Table 10: Adverse events (completed Phase III IDegAsp trials)**

| | IDegAsp | | | | Comparator | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Safety analysis set | 2557 | | | | 1381 | | | |
| All Adverse Events | 1641 | ( 64.2) | 5210 | 369.3 | 862 | ( 62.4) | 2741 | 336.0 |
| Serious Adverse Events | 194 | ( 7.6) | 248 | 17.6 | 104 | ( 7.5) | 130 | 15.9 |
| Adverse Events leading to Death | 11 | ( 0.4) | 11 | 0.8 | 3 | ( 0.2) | 5 | 0.6 |
| Adverse Events Possibly or Probably Related to IMP | 297 | ( 11.6) | 449 | 31.8 | 175 | ( 12.7) | 289 | 35.4 |
| Severity | | | | | | | | |
| Mild | 1380 | ( 54.0) | 3746 | 265.5 | 760 | ( 55.0) | 2035 | 249.4 |
| Moderate | 661 | ( 25.9) | 1223 | 86.7 | 298 | ( 21.6) | 547 | 67.1 |
| Severe | 171 | ( 6.7) | 239 | 16.9 | 97 | ( 7.0) | 159 | 19.5 |
| Unknown | 2 | ( 0.1) | 2 | 0.1 | 0 | | | |
| Adverse Events withdrawals | 42 | ( 1.6) | 46 | 3.3 | 23 | ( 1.7) | 33 | 4.0 |

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, Trials: 3590-3726, 3592, 3593, 3594-3645, 3597, 3844, 3896, 3940, 3941, 3996, 4003

The rate of all adverse events is slightly higher on the IDegAsp arm (369.3 per 100 subject years of exposure compared to 336.0 on comparator); the rate of serious adverse events is relatively similar (17.6 per 100 subjects years of exposure compared to 15.9). The rate of related adverse events is 31.8 per 100 subject years of exposure on the IDegAsp compared to 35.4 per 100 subject years of exposure on the comparator arm. A similar pattern is seen in the ISS (cut-off date 31 January 2011; data not shown). It is noted that the rates of mild and moderate adverse events were relatively similar across both the IDegAsp and comparator groups in the ISS (31 January 2011), however in the updated data (30 September 2014), mild and moderate events were more common in the IDegAsp group compared to the comparator.

*T1DM*

No updated data for Phase III trials was provided for the T1DM population in the Summary of Clinical Safety Addendum IDegAsp (cut-off date of 30 September 2014).

*T2DM*

The parameters of all adverse events, as well as mild and moderate adverse events are more common in the IDegAsp group compared to the comparator group.

*Most frequently reported adverse events*

The most frequently reported events in the IDegAsp group were nasopharyngitis, upper respiratory tract infections and headache. Headache occurs at a higher rate in the IDegAsp group compared to the comparator (17.0 events per 100 subject years of exposure compared to 13.2).

### 7.4.2. Treatment related adverse events (adverse drug reactions)

#### *7.4.2.1. Integrated safety analyses (cut-off date of 30 September 2014)*

In the updated data, the most frequently reported groups of AEs that were assessed to be related to IDegAsp were events (multiple terms) related to hypoglycaemia; for comparators, events (multiple terms) related to hypoglycaemia and injection site reactions were most common.

No single preferred term was reported more than 2% of subjects in completed Phase III trials on the IDegAsp arm. Hypoglycaemia and weight increase were reported in ≥ 1% of subjects in the IDegAsp group. The most common related adverse event (in terms of preferred terms) was hypoglycaemia, however this occurred at a decreased rate compared to the comparator arm (4.7 events per 100 subject years of exposure in IDegAsp group compared to 8.1 in comparator group; comparators included IDet daily/twice daily + IAsp, IGlar and biphasic insulin aspart 30). Furthermore, this rate of hypoglycaemia may, in part, reflect the monitoring program used in clinical trials, which is likely to be more rigorous than normal clinical practice.

The rate at which adverse events possibly or probably related to the treatment occurred was 31.8 per 100 subject years of exposure; not too dissimilar to the comparator arm (35.4 events per 100 subjects years of exposure). The rate of possible/probably related adverse events in the updated data (cut-off date of 30 Sept 2014) is relatively similar to that seen in the ISS (32.9 events per 100 subject years of exposure) for the IDegAsp arm and has numerically reduced for the comparator arm since the ISS.

For subjects with T2DM, rate at which adverse events possibly or probably related to the treatment occurred was 30.3 per 100 subject years of exposure; and again, not too dissimilar to the comparator arm (28.2 events per 100 subjects years of exposure).

No updated data was reported for the T1DM population.

### 7.4.3. Deaths and other serious adverse events

#### *7.4.3.1. Integrated safety analyses (cut-off date of 30 September 2014)*

*Deaths*

15 deaths were reported in the completed IDegAsp trials, 14 in Phase III trials and 1 in a Phase II trial, and of these deaths, 11 were treated with IDegAsp (0.4%) compared to 3 on the comparator arm (0.2%) and 9 have been reported since the ISS (cut-off date 31 January 2011); all were T2DM trials. Of these 9 deaths reported in the period since 31 January 2011, 1 event of coronary artery disease in a subject with a history of hypertension, hypercholesteremia and 18 year history of T2DM was assessed to be possibly related to the study drug IDegAsp but considered to be unlikely related by the sponsor.

The proportion of deaths in the ISS (cut-off date 21 January 2011) was similar: 0.3% for IDegAsp and 0.1% for comparators.

**Table 11: Deaths in IDegAsp trials**

| | IDegAsp (proportion of subjects) | Comparator (proportion of subjects) |
|---|---|---|
| All Deaths (all completed trials) | N = 15 | |
| All Deaths (completed Phase III) | 0.4% (n = 11) (out of total n = 2557) | 0.2% (n = 3) (out of total n = 1381) |
| Deaths reported in original Integrated Safety Summary (completed clinical trials with IDeg; cut-off date 31 January 2011)[1] | 0.3% (n = 4) | 0.1% (n = 1) |
| MACE (including UAP) deaths | 0.2% (n = 5) | 0.1% (n = 2) |
| Deaths in T1DM group | 0 | 0 |
| Deaths in T2DM group | 0.5% (n = 11) (total n = 2195) | 0.2% (n = 3) (total n = 1201) |

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.

It is noted that all deaths that have occurred on the IDegAsp trials were in the T2DM population. The proportion of subjects who have died on the IDegAsp is numerically higher (0.4%) compared to the comparator (0.2%), however this is similar to the ISS data; it is noted that this difference is slightly greater in the T2DM population, 0.5% versus 0.2%.

For deaths that occurred on both IDeg and IDegAsp trials, please see Section 7.4 of the Tresiba IDeg CER [available as Attachment 2 of the Tresiba submission].

*Other serious adverse events*

Serious adverse events that occurred on the completed Phase III trials are summarised in Table 12, shown below.

**Table 12: Serious adverse events in completed IDegAsp Phase III trials**

| | IDegAsp N | (%) | E | R | Comparator N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Safety analysis set | 2557 | | | | 1381 | | | |
| Serious Adverse Events | 194 | ( 7.6) | 248 | 17.6 | 104 | ( 7.5) | 130 | 15.9 |
| Adverse Events leading to Death | 11 | ( 0.4) | 11 | 0.8 | 3 | ( 0.2) | 5 | 0.6 |
| Adverse Events Possibly or Probably Related to IMP | 49 | ( 1.9) | 67 | 4.7 | 25 | ( 1.8) | 29 | 3.6 |
| Severity | | | | | | | | |
| Mild | 19 | ( 0.7) | 19 | 1.3 | 17 | ( 1.2) | 18 | 2.2 |
| Moderate | 74 | ( 2.9) | 85 | 6.0 | 36 | ( 2.6) | 43 | 5.3 |
| Severe | 112 | ( 4.4) | 144 | 10.2 | 57 | ( 4.1) | 69 | 8.5 |
| Adverse Events withdrawals | 33 | ( 1.3) | 35 | 2.5 | 16 | ( 1.2) | 20 | 2.5 |

N = Number of subjects with adverse events, % = Proportion of subjects in analysis set having adverse events, E = Number of adverse events, R = Number of events divided by subject years of exposure multiplied by 100, IMP = Investigational medicinal product
Trials: 3590-3726, 3592, 3593, 3594-3645, 3597, 3844, 3896, 3940, 3941, 3996, 4003

The general trends of the data for IDegAsp and the comparator arm as seen in the table in relation to each other above have not changed significantly since the ISS, although overall the rates have decreased for both groups.

The most frequently reported SAEs were events related to hypoglycaemia (included multiple preferred terms) with a rate of 4.0 events per 100 subject years of exposure reported in the IDegAsp arm and 3.7 on the comparator arm; the most commonly reported single preferred terms in the IDegAsp group were hypoglycaemia and hypoglycaemic unconsciousness (rates on the IDegAsp of 2.6 and 1.0 respectively, and similar on the comparator arm). Apart from hypoglycaemia events, no other serious adverse event occurred at a rate greater than 1 per 100 subject years of exposure.

*T2DM*

With respect to T2DM, the rates of SAEs, SAEs probably or possibly related to study drug, severity and withdrawals due to SAEs are generally consistent with the overall population. The rate of events related to hypoglycaemia (multiple terms) occurring on the IDegAsp arm was 1.7 events per 100 subject years of exposure, compared to 2.4 on the comparator arm and were the most commonly occurring events. This is slightly lower than the overall population.

The most commonly reported preferred terms for serious adverse events (proportion of subjects having adverse event ≥ 0.5%) occurring with IDegAsp in the T2DM population was hypoglycaemia with a similar rate in both groups.

### 7.4.4. Discontinuations due to adverse events

#### *7.4.4.1. Integrated safety analyses (cut-off date of 30 September 2014)*

The proportion of subjects withdrawing due to adverse events was similar in the IDegAsp and comparator group. The majority of the events leading to withdrawal were serious adverse events on both arms and in the IDegAsp group; the most common reasons for withdrawal were related to hypoglycaemia. The percentage of SAEs which lead to withdrawals remained relatively similar to the Integrated Safety Summary (ISS) in both the IDegAsp and comparator groups current dataset: 1.3% versus 1.4% (ISS) for IDegAsp and 1.2% versus 1.1 (ISS) for comparators.

It is noted that the most frequently reported preferred term leading to withdrawal on the IDegAsp arm almost all occurred at a numerically higher rate in the IDegAsp group although the numbers were small. Hypoglycaemia was the commonest reason for withdrawal and occurred

in the IDeg group more than double the rate of the comparators (0.2%/rate 0.3 versus comparator n = 0 0.0%/rate 0.0). The number of patients who withdrew due to an adverse event that was possibly/probably related to the study treatment was not presented.

## 7.5. Evaluation of issues with possible regulatory impact

The cut-off date was 30 September 2014 unless otherwise specified for the following findings:

### 7.5.1. Liver function and liver toxicity

#### *7.5.1.1. Integrated safety analyses*

No subjects across either the IDeg or IDegAsp programs have met the criteria for Hy's law. 1 subject in the IDeg program developed a simultaneous increase in ALT and total bilirubin in associated with an increase in alkaline phosphatase and a carcinoma in the common bile duct.

### 7.5.2. Renal function and renal toxicity

#### *7.5.2.1. Integrated safety analyses*

No new information was included in the Summary of Clinical Safety Addendum (IDegAsp).

### 7.5.3. Other clinical chemistry

#### *7.5.3.1. Integrated safety analyses*

No new information was included in the Summary of Clinical Safety Addendum (IDegAsp).

### 7.5.4. Haematology and haematological toxicity

#### *7.5.4.1. Integrated safety analyses*

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

It is noted that 3 adverse events of preferred term 'thrombocytopaenia' were reported, including 2 on the IDegAsp group, however none were considered to be related to the study drug.

### 7.5.5. Other laboratory tests

#### *7.5.5.1. Integrated safety analyses*

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

### 7.5.6. Electrocardiograph findings and cardiovascular safety

#### *7.5.6.1. Integrated safety analyses*

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 for the dedicated cardiovascular outcomes trial (see Section 7.2 above), 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).

Pooled data for IDegAsp and IDeg was presented in Summary of Clinical Safety Addendum in terms of cardiovascular data and it is the same which was presented for in the Summary of Clinical Safety Addendum IDeg. Please refer to section 7.5 in the Tresiba IDeg CER [available as Attachment 2 of the Tresiba submission].[1]

In terms of the IDegAsp specific data, the EAC evaluated 62 events (4.4 events per 100 subject years of exposure) in the IDegAsp group and 30 events (3.7 events per 100 subject years of exposure) in the comparator group.

A numerically higher rate of MACE(ISA) was seen on the IDegAsp group (1.9 per 100 subject years of exposure) compared to comparator group (1.5), however the difference is small. Data for MACEs assessed as possibly or probably related to trial product were not presented for the IDegAsp group only.

No new information regarding electrocardiograph findings was included in the Summary of Clinical Safety Addendum (IDegAsp).

### 7.5.7. Vital signs and clinical examination findings

#### *7.5.7.1. Integrated safety analyses*

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

### 7.5.8. Immunogenicity and immunological events

#### *7.5.8.1. Integrated safety analyses*

Only pooled data for IDegAsp and IDeg was presented in Summary of Clinical Safety Addendum and it is the same which was presented in the Summary of Clinical Safety Addendum for IDeg. Please refer to Section 7.4 of the Tresiba IDeg CER [available as Attachment 2 of the Tresiba submission].[1] It is noted that for this pooled data, 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.

Relating to the narrow and narrow + broad scope searches completed, the sponsor has stated that the outcomes seen for immunogenicity in patients with T1DM and T2DM and the IDegAsp trials only was similar to that seen in the pooled data however no data was available to clarify this.

### 7.5.9. Serious skin reactions

#### *7.5.9.1. Integrated safety analyses*

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

It is noted that 2 adverse events of photosensitivity reaction was reported in the completed Phase III trials for IDegAsp, 1 each on IDegAsp and the comparator group, but neither were considered to be possibly or probably related to the study drug.

### 7.5.10. Neoplasms

#### *7.5.10.1. Integrated safety analysis*

Only pooled data for IDegAsp and IDeg was presented in Summary of Clinical Safety Addendum which is the same as that presented in the Summary of Clinical Safety Addendum for IDeg, please refer to Section 7.4 in the Tresiba IDeg CER [available as Attachment 2 of the Tresiba submission].[1]

In terms of IDegAsp specific data in Phase III trials, there were varying degrees of discrepancy in the overall rate of neoplasms reported for the IDegAsp groups and the comparators, the rates were numerically higher in the IDegAsp group for all IDegAsp Phase III trials (2.8 events per 100 subjects years of exposure for IDegAsp compared to 2.3) and T2DM (3.2 events per 100 subjects years of exposure for IDegAsp compared to 1.8) however for the T1DM subset, the rate was lower in the IDegAsp group, 1 event per 100 subjects years of exposure for IDegAsp compared to 4.8.

In terms of externally classified neoplasms (assessed by an independent consultant for blinded evaluation), the rate of benign neoplasms was numerically higher in the IDegAsp group (2.9 per 100 subject years of exposure for IDegAsp compared to 2.2) but for malignant neoplasms, the rates were numerically lower in the IDegAsp group (0.5 events per 100 subjects years of

exposure for IDegAsp compared to 0.9 on the comparator group). Data was not presented by T1DM and T2DM subset for the externally classified neoplasms.

Overall, numerical differences between the groups are noted, however the differences are mostly relatively small, the rates are relatively low and it is unknown whether these are true differences. It is also noted that in the PSUR submitted for this evaluation that both neoplasms and colon cancer are being monitored as part of an Evaluation of Authority Request requested by the SwissMedic and EMA respectively (see Section 7.7 for further information) and this should continue to be monitored.

### 7.5.11. Hypoglycaemic episodes

Definitions:

- *Severe hypoglycaemia* is an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (American Diabetes Association classification).
- *Documented symptomatic hypoglycaemia* is an episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (American Diabetes Association classification).
- *Confirmed hypoglycaemic* episodes are either severe (that is, requiring assistance from another person) or where plasma glucose was biochemically confirmed to be < 3.1 mmol/L with or without symptoms consistent with hypoglycaemia.
- *Nocturnal:* time of onset between 00.01 and 5.59 inclusive.

T1DM data has not been updated since the Integrated Safety Summary (cut off 31 January 2011) and thus no further data included in this report.

T2DM; Insulin naïve on daily therapy: Rates of confirmed and documented symptomatic hypoglycaemia are higher in the IDegAsp group compared to the comparator; but reduced when looking specifically at nocturnal episodes.

T2DM; Insulin naive treated on twice a day treatment): Rates of confirmed and documented symptomatic hypoglycaemia, including nocturnal episodes, are lower in the IDegAsp group compared to the comparator. Few episodes of severe hypoglycaemia occurred on either arm.

T2DM; Insulin treated on daily therapy: Rates of nocturnal confirmed and documented symptomatic (24 hour and nocturnal) hypoglycaemic episodes were lower in the IDegAsp group compared to the comparator group. However, the rate of confirmed episodes (24 hours) was higher in the IDegAsp group. Relatively low rates of severe episodes occurred on both arms.

T2DM; Insulin treated on twice daily therapy: The IDegAsp group had lower rates of all types of hypoglycaemic episodes, including nocturnal.

Thus, in summary, it is noted that there were

- Overall, less nocturnal hypoglycaemic episodes with IDegAsp compared to the comparator group.
- More hypoglycaemic episodes overall in patients on twice daily dosing.
- In terms of the once daily dosing, there were possibly more confirmed or symptomatic hypoglycaemic episodes, but similar rate of severe episodes with IDegAsp.
- More hypoglycaemic episodes in insulin treated patients overall (expected).

The subgroups in which IDegAsp had higher rates of hypoglycaemia were all T2DM and all receiving the daily dose as indicated in Table 13, below.

**Table 13: Hypoglycaemia parameters in which the rate of hypoglycaemia was higher in the IDeg than the comparator group**

| | IDegAsp (rate) | Comparator (rate) |
|---|---|---|
| T2DM insulin naïve on daily therapy: confirmed hypoglycaemia (24 hours) | 332 | 225 |
| T2DM insulin naïve on daily therapy: documented symptomatic hypoglycaemia (24 hours) | 673 | 565 |
| T2DM insulin treated on daily therapy: confirmed hypoglycaemia (24 hours) | 431 | 420 |

Rate: number of episodes per 100 subject years of exposure

### 7.5.12. Other safety parameters

#### *7.5.12.1. Integrated safety analyses*

*Other adverse events highlighted in the Summary of Clinical Safety Addendum*

- Medication errors: the rate of medication error on IDegAsp arm was 3.3 events per 100 PYE compared to comparator rate of 2.2 events; the ISS rate (cut off 31 January 2011) was 5.2 for IDegAsp and 3.2 for the comparators. The most frequent medication error (according to preferred term) was 'wrong drug administered' (0.8% of subjects, rate 1.6 per 100 subject years of exposure in the IDegAsp group'; 0.4% of subjects 0.7 per 100 subjects years of exposure in the comparator group) noted to be twice as common in the IDegAsp group compared to the comparator group, followed by incorrect dose administered (0.5% of subjects, rate 1.1 per 100 subject years of exposure in the IDegAsp group'; 0.4% of subjects, 0.7 per 100 subjects years of exposure in the comparator group). The rates of medication errors assessed to be probably or possibly related to the trial drug were 1.2 events per 100 patient years of exposure for IDegAsp and 0.7 for the comparators.
- Injection site reactions: rates of injection site reactions with IDegAsp and comparators were 4.3 and 8.0 events per 100 PYE, respectively (decreased rate compared to the integrated safety summary). The rates of injection site reactions assessed as possibly or probably related to study drug by the investigator were 2.7 events per 100 PYE in the IDegAsp group and 7.0 with the comparators.
- Lipodystrophy: The rate of lipodystrophy in the IDeg and comparator group was 0.1 events per 100 PYE and 1.3 events per 100 PYE respectively; the Integrated Safety Summary reported rates of 0.3 and 1.9 respectively. AEs assessed as possibly or probably related to the study drug on the IDeg arm occurred at a rate of 0.0 events per 100 PYE versus 0.6 events on the comparator arm).
- Peripheral oedema: the rate of peripheral oedema was 3.8 events per 100 PYE on the IDeg arm and 2.6 events for the comparator arm; the preferred term 'local swelling' was also assessed and the event rates were the same on both each arm (0.9). It is noted that the frequency of local swelling in the ISS (cut-off date 31 January 2011) was 0.1 events per 100 PYE for both groups, however it is unclear whether there is a true increase in frequency or whether this is secondary to the MedDRA version updates that have occurred between the

ISS and the safety update leading to some events of oedema peripheral being recoded to local swelling. Rate of related (possibly or probably) peripheral oedema events were 0.8 and 0.4 per 100 patient years of exposure for the IDegAsp group and comparators respectively, a doubling of the rate on the IDegAsp arm.

## 7.6. Other safety issues

### 7.6.1. Safety in special populations

#### *7.6.1.1. Paediatrics*

As of 30 September 2014, 1 clinical pharmacology trial with IDegAsp has been completed and 1 Phase III trial is ongoing.

In the ongoing trial (3816), 5.5% of subjects (pooled and blinded data; 20 subjects reported 23 events) have reported an SAE; the SAEs reported by more than 1 subject are hypoglycaemia (7 subjects), diabetic ketoacidosis (2 subjects) and viral infection (2 subjects). No SAEs have led to trial withdrawal.

#### *7.6.1.2. Pregnancy and lactation*

As of 30 September 2014, 6 pregnancies have been reported on completed IDegAsp trials (1 since the integrated safety summary) including 4 pregnancies in subjects in the IDegAsp group.

Table 14 (below) is a summary of the pregnancies that have occurred in the IDegAsp trials.

**Table 14: Pregnancies in subjects receiving IDegAsp**

| Pregnancy | Study drug | Reported event | Outcome |
|---|---|---|---|
| 1 | IDegAsp + IAsp | Abortion (spontaneous) | Spontaneous abortion at 6 weeks. |
| 2 | IDegAsp + IAsp | Pregnancy | Termination of pregnancy due to social circumstances. |
| 3 | IDegAsp + IAsp | Pregnancy | Health infant born gestational age 34 weeks. Caesarean section performed as infant was trapped by umbilical cord; weight of newborn was low (1970 g). |
| 4 *(new since 31 January 2011)* | IDegAsp | Pregnancy | Infant delivered; infant had hypoglycaemia 28 mg/dL) but recovered. |

The number of events that have occurred on the IDegAsp clinical trials is low; no robust conclusions can be drawn.

#### *7.6.1.3. 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.

#### *7.6.1.4. Safety related to drug-drug interactions and other interactions*

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

## 7.7. Post marketing experience

### 7.7.1. Insulin degludec/insulin aspart periodic safety update report (PSUR)/periodic benefit–risk evaluation report (PBRER)

- Date: From 1 October 2014 to 30-September 2015.

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

#### *7.7.1.1. Worldwide marketing authorisation status*

IDegAsp has been approved in more than 55 countries and marketed in 5 countries (Denmark, Switzerland, India, Bangladesh and Mexico).

#### *7.7.1.2. 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 IDegAsp; DEVOTE trial results are required to confirm the cardiovascular safety of the products.

#### *7.7.1.3. Clinical trial data*

Clinical trial data has already been summarised, 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 in this reporting period (there are no ongoing clinical trials).

*Completed clinical trials*

1 Phase IIIb paediatric clinical trial (Study NN5401-3816) was completed in this reporting period: a 16 week multinational, open label, 2 arm, parallel group, randomised, treat to target, efficacy and safety trial with IDegAsp once daily with main meal and insulin asp for the remaining meals vs. insulin detemir and mealtime IAsp in subjects with T1DM aged 1 to < 18 years old.

Key safety findings are shown below in Table 15.

**Table 15: Key safety findings in Study NN5401-3816**

| Key safety finding | IDegAsp | Insulin determir |
|---|---|---|
| **Deaths** | 0 | 0 |
| **AE rate** | 915 events per 100 patient years of exposure | 853 events per 100 patient years of exposure |
| **SAEs (% of patients who reported an event)** | 14 events in 11 subjects (6.1%); rate 26 events per 100 patient years of exposure | 7 events in 7 subjects (3.9%); rate 13 events per 100 patient years of exposure |
| **Confirmed hypoglycaemic episodes** | 4623 events per 100 patient years of exposure | 4955 events per 100 patient years of exposure |
| **Severe hypoglycaemic episodes** | 26 events per 100 patient years of exposure | 7 events per 100 patient years of exposure |

Higher rates of AEs, SAEs and severe hypoglycaemic episodes are noted in this paediatric population for the IDegAsp arm.

### 7.7.2. Post marketing exposure

It is estimated that there has been 12,902 patient years of exposure to IDegAsp until 30 September 2015 ('cumulative exposure') and of these, 11,644 patient years of exposure have occurred during the current PSUR reporting period.

- Cumulatively, 91 adverse drug reactions have been reported in 41 spontaneous case reports, of which 4 reports were serious. 79 adverse drug reactions were reported in this PSUR period.
- One serious event of hypoglycaemia was received from non-interventional post-marketing studies and other solicited sources and is included as an adverse drug reaction.
- Most frequently reported events (5 events each) were injection site reactions (SOC general disorders and administration site conditions), hypoglycaemia, hyperglycaemia (both of SOC Metabolism and nutrition disorder) and blood glucose increased (SOC investigations).
- No cases of MACE or neoplasms have been reported.
- No fatal cases have been reported.
- Lack of efficacy: 3 reports were reported and all of these cases were associated with non-serious events of blood glucose increased or hyperglycaemia.
- Allergic reactions: 4 cases with 7 non-serious allergic reactions in the cumulative period; 4 events from this reporting period.
- Medication errors: 8 case reports with 9 non-serious events; 7 events (6 reports) from this reporting period: multiple use of single use product, wrong technique in administration (4 events), drug dose omission and incorrect storage of the product. No case of a mix-up of bolus insulin with IDegAsp was reported in this reporting period; 1 has been reported cumulatively.

The PSUR/PBRER states that *'no specific pattern or clustering of events was observed…. single or few events (by PT) were reported' … and 'overall, no significant new safety concerns were identified with Ryzodeg from marketing experience, up until 30 Sep 2015.'*

Off label use: Cumulatively, 6 case reports have been received relating to the use of IDegAsp in children, all of which are from this reporting period. 1 report was associated with an event of 'blood glucose abnormal'; the others had no adverse event reported. There are no reported post marketing cases of IDegAsp use in pregnant or lactating women.

Data relating to IDegAsp components:

- IDeg: Please refer to Section 7.7 (PSUR/PBRER summary) in the Tresiba IDeg CER [available as Attachment 2 of the Tresiba submission].[1]
- IAsp: The most recent DSUR and PSUR for IAsp were for the period of 1 October 2014 to 30 September 2015. According to the sponsor (PBRER/PSUR) *'Overall, the clinical trial safety data for IAsp remain in accordance with the cumulative experience as described in the current reference safety information. No reasons for new safety concerns were identified in connection with the administration of IAsp in clinical trials in the reporting period. No change was made to the existing safety concerns for IAsp'.*

Other safety information; the PSUR states that:

- *'No new nonclinical safety findings were reported during the period of this PSUR for Ryzodeg.'*

- *'No new significant safety findings or concerns specifically for Ryzodeg were identified based on the results of the review of the scientific literature'.*

It is noted that no non-interventional studies were initiated or completed for IDegAsp in this reporting period.

### 7.7.3. Signal review and Evaluation of authority request

1 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 of 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 IDegAsp trials were sent to an external, independent and blinded consultant for classification into malignant, benign and unclassifiable neoplasms and post marketing data was analysed.

### 7.7.4. Summaries of safety concerns

No new potential or important risks have been identified in this PSUR period.

**Table 16: Summary of safety concerns as stated in PSUR**

| Category of safety concern | Safety concerns | Comments |
|---|---|---|
| Important identified risks | Hypoglycaemia | No new significant information identified |
| | Immunogenicity related events (allergic reactions) | No new significant information identified |
| Important potential risks | Medication errors due to mix up between IDegAsp and bolus insulin | No new significant information identified according to the PSUR.<br>However, it is noted that 10 medication errors resulting in a mix up between IDegAsp and bolus insulin have occurred in therapeutic confirmatory trials, including 3 events which were considered to be possibly/probably related to the trial product and 1 that was serious.<br>It is also noted that the number of adult subjects at risk in the table entitled 'Overview of all treatment emergent mix ups in therapeutic confirmatory trials, T1DM + T2DM, adult population' within [a specified table] is very low, n |

| Category of safety concern | Safety concerns | Comments |
|---|---|---|
| | | = 382 for IDegAsp and 180 for comparator; the reason for this is unclear. |
| | Immunological events, formation of neutralising insulin antibodies | No new significant information identified. |
| Missing information | Pregnant and lactating women | No new significant information identified. |
| | Children and adolescents < 18 years | As noted above, a Phase IIIb trial was completed in a paediatric population (aged 1 to < 18 years). The PSUR notes that a variation application has been submitted to the EMA related to the use of IDegAsp in children and adolescents.<br>It is noted that the Product information available on the EMA website indicates that Ryzodeg is now indicated for the treatment of adolescents |

| Category of safety concern | Safety concerns | Comments |
|---|---|---|
| | | and children form the age of 2 years.[8] |
| | Hepatic impairment | No new significant information identified. |
| | Moderate and severe renal impairment | No new significant information identified. |
| | Elderly patients (> 75 years) with T1DM | No new significant information identified. |
| | Co-administration of GLP-1 receptor agonists | No new significant information identified. |

As highlighted above, it is noted that medication errors due to a mix-up with IDegAsp and bolus insulin is an Important potential risk, however several related cases have been reported, especially in the T2DM population. The evaluator would recommend this be changed to an identified risk in the Australian Specific Annex and risk mitigation strategies employed.

It is also noted that the EMA has a recently approved paediatric indication and that there are completed clinical trials in children. The evaluator would recommend the sponsor submit an extension of indications application to extend the indication for use in children.

## 7.8. Evaluator's overall conclusions on clinical safety

The important identified risks of IDeg Asp as noted in the PSUR/PBRER are hypoglycaemia and immunogenicity-related events (allergic reactions). A safety concern arising from the original withdrawn submission for IDegAsp related to cardiovascular outcomes and a core component of the safety data submitted in this resubmission of IDegAsp 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 withdrawn 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 that the DEVOTE trial does not provide data specific either to the T1DM population or patients receiving IDegAsp.

New integrated safety data with cut-off date of 30 September 2014 has been presented for IDegAsp 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 from the FDA dossier. The evaluator has assumed that this data is the same as that in the original Australian dossier.

The updated dataset contained 10 new completed trials, of which 7 were Phase III trials, resulting in exposure of an additional 1100 subjects. There were no new Phase III data for T1DM (neither new nor ongoing patients). Of the Phase III trials relating to T2DM, 7 were new trials and 1 (a paediatric trial) was ongoing. In total, 3139 subjects have been exposed to IDegAsp in completed clinical trials as of 30 September 2014. It is noted that there were a

[8] European Public Assessment Report (EPAR) for Ryzodeg insulin degludec/insulin aspart, 18 October 2012 EMA/700472/2012. Committee for Medicinal Products for Human Use (CHMP) Procedure No. EMEA/H/C/002499; Product Information, as per EMA website, last updated on 30 August 2016.

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 and received either a daily or twice daily dose. 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, data 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 IDegAsp.

Based on the updated data presented, there do not appear to be any new significant safety signals that have emerged since the original withdrawn submission in terms of integrated safety data. Hypoglycaemia related adverse events continue to be the most frequently occurring possibly or probably related to study drug adverse events, serious adverse events and adverse event (preferred term) leading to withdrawal on the IDegAsp arm. This is not surprising, given the therapeutic action of IDegAsp; prescriber and patient education is important to ensure appropriate use. In general, the rate of hypoglycaemic events tended to be relatively similar in the IDegAsp group compared to the comparator group although there were some exceptions:

- Preferred term of hypoglycaemia leading to withdrawal (although the rates are low, therefore the significance is unclear) was higher in the IDegAsp group.
- in terms of the specific hypoglycaemic analysis, confirmed hypoglycaemia episodes over 24 hours for T2DM insulin naïve, confirmed hypoglycaemia episodes over 24 hours in insulin treated subjects and documented symptomatic hypoglycaemic episodes over 24 hours for T2DM insulin naïve subjects were all higher in the IDegAsp group, all only in the group of subjects who received daily insulin.

In terms of nocturnal confirmed hypoglycaemia, IDegAsp had lower rates compared to the comparator group in all disease and dosing subgroups.

Subset analyses for T2DM are reported, although the T1DM dataset has not been updated. Overall, the rates seen for AEs, overall SAEs, possibly/probably related SAEs and hypoglycaemic events were consistent with those seen in the overall population. It is noted that the proportion of subjects with the event of death was slightly higher on the T2DM IDegAsp arm compared to the IDegAsp arm in the overall population; this is because all of the deaths that have occurred in IDegAsp trials have occurred in the T2DM population.

It is noted that in the updated data set, there is additional data with longer follow up (up to 52 weeks) than was available in the original withdrawn submission. However, the proportion of subjects with T2DM in particular with data for 12 months remains limited and the majority of these are in the comparator group, although the reason for this discrepancy is not clear. More specifically, there are very few insulin treated subjects with T2DM were followed up for 12 months or more. Long term data is of relevance given that the use of IDegAsp in this population is expected to be administered for years rather than months in this population and highlights the importance of post marketing monitoring.

A number of specific analyses made by the sponsor such as immunological, MACE and neoplastic related events have not been discussed in detail this CER as only pooled data (IDegAsp + IDeg) was presented and this is presented in the IDeg clinical evaluation report. Although reference was made to IDegAsp only data for MACE and neoplastic events, no data for IDegAsp relating to immunological events was presented for review.

Post marketing experience is somewhat limited; the majority of the cumulative post marketing reports have been submitted in the year of the PSUR report. The paediatric study is noted and would be of interest for Australia in view of the relatively high prevalence of T1DM in children. It is also noted that there are 2 ongoing safety signal evaluations as detailed in the PSUR:

1. Neoplasms/colon cancer: refer to the Tresiba IDeg CER for specific discussion relating to pooled data available as Attachment 2 of the Tresiba submission].[1] Ongoing monitoring should be maintained.
2. Cardiovascular events: as previously discussed.

It has also been noted that medication errors due to a mix up with IDegAsp and bolus insulin is an Important potential risk, however several related cases have been reported, especially in the T2DM population.

# 8. First round benefit-risk assessment

## 8.1. First round assessment of benefits

Table 17 summarises the assessment of benefits at the first round.

**Table 17: First round assessment of benefits**

| Benefits | Uncertainties |
|---|---|
| Overall, non-inferior efficacy for glycaemic control compared to IDet, IGlar and BIAsp30. | The recommended dosing algorithm based on FPG only ignores the impact of the aspart component on post prandial BGLs. Although FPG is the most important parameter, dosing considerations for the prandial component should also be considered. |
| The sponsor has proposed flexible dosing as a benefit. Although the glycaemic control in a clinical trial setting is similar for such a dosing regimen, the ability to extrapolate this to real life setting is unknown (see also risks). | Flexible dosing has potential to be of benefit if a dose is forgotten. |
| Rate of nocturnal hypoglycaemia generally lower compared to comparators | |
| Interim analysis of the DEVOTE trial provided supportive evidence for non-inferiority of CV endpoints | |

## 8.2. First round assessment of risks

Table 18 summarises the assessment of risks at the first round.

**Table 18: First round assessment of risks**

| Risks | Uncertainties |
|---|---|
| Hypoglycaemia: Hypoglycaemia and events related to hypoglycaemia, commonly occurred with the use of IDegAsp in the clinical trials. It is recognised that hypoglycaemia is an inherent risk associated with all insulins, however due to the 'ultra long' action, the period following a single dose in which hypoglycaemia may occur is longer than other insulins.<br>However, it is also acknowledged that the aetiology of hypoglycaemia is multifactorial and the type of insulin used is only 1 important component. Thus education of prescribers and patients again will play an important part in mitigating this risk. | |
| Exclusion of some oral anti-diabetic drugs in Phase III trials. | There is uncertainty regarding the use of some oral anti-diabetic drugs in combination with IDegAsp since GLP-1 receptor agonists, sulfonylureas, glinides and alpha glucosidase inhibitors were excluded from the Phase III trials. There were no studies with SGLT-2 inhibitors.<br>This should be also noted in the Product Information. |
| Routine use of flexible dosing is not consistent to overall approach to diabetes management and applicability into the 'real world' setting in unclear (see also benefits above). | |
| Cardiovascular events (MACE): Although the outcomes of the interim analysis for the DEVOTE trial 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). | IDegAsp was not used in the DEVOTE trial and therefore the specific cardiovascular risk in patients receiving IDegAsp is unknown and can only be extrapolated from the IDeg data.<br>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. |
| Dosing errors related to mixing basal and bolus insulin.<br>It is noted that the dosing errors due to mixing basal and bolus insulin is an important potential risk, however there are a number of adverse events that have been reported relating to this in clinical trials. | |

| Risks | Uncertainties |
|---|---|
| | Neoplasms/colon cancer: Neoplasms and colon cancer are the subject of an ongoing review as requested by SwissMedic and the EMA respectively. Further monitoring should be continued. |

### 8.3. First round assessment of benefit-risk balance

Overall, the benefit-risk balance is positive for IDegAsp provided appropriate steps for education of prescribers and patients are undertaken and consideration of the upgrade from important potential risk to identified risk should be made for dosing errors related to mixing basal and bolus insulin, as well as active ongoing monitoring for detected signals.

## 9. First round recommendation regarding authorisation

At this stage, the clinical evaluator has no major concerns for the approval of the registration of IDegAsp 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

No questions.

### 10.2. Pharmacodynamics

No questions.

### 10.3. Efficacy

No questions.

### 10.4. Safety

#### 10.4.1. Question 1

Regarding Study NN5401-3726, please comment on the difference in rates of confirmed hypoglycaemic episodes.

#### 10.4.2. Question 2

Please comment on the discrepancy in terms of T2DM subjects who were exposed to study drug for ≥ 12 months (9.7% IDegAsp compared to 17.7% Comparator). This is not reflected as clearly in terms of completion of extension trials which showed that 92.4% of subjects completed the extension trials in the IDegAsp group compared to 93.9% of those in the comparator group.

#### 10.4.3. Question 3

For the insulin naïve subjects (daily and twice daily dosing), please provide data which indicates what proportion of the hypoglycaemic episodes that occurred were post meal for both groups.

#### 10.4.4. Question 4

Please provide additional details specific to the 10 documented events of mix up between bolus and IDegAsp (from a table of the PSUR [not included here]). Please also explain why only the number of adult subjects at risk is so small in the table (n = 382 for IDegAsp and 180 for comparator) entitled 'Overview of all treatment-emergent, mix-ups in therapeutic confirmatory trials, T1DM + T2DM, adult population'.

#### 10.4.5. Question 5

In relation to the use of IDegAsp in T2DM, does the sponsor have any data on the use of insulin aspartate in patients with T2DM in Australia?

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

The sponsor's response to the Clinical Questions was received and has been summarised below with evaluator comments.

## 11.1. Question 1

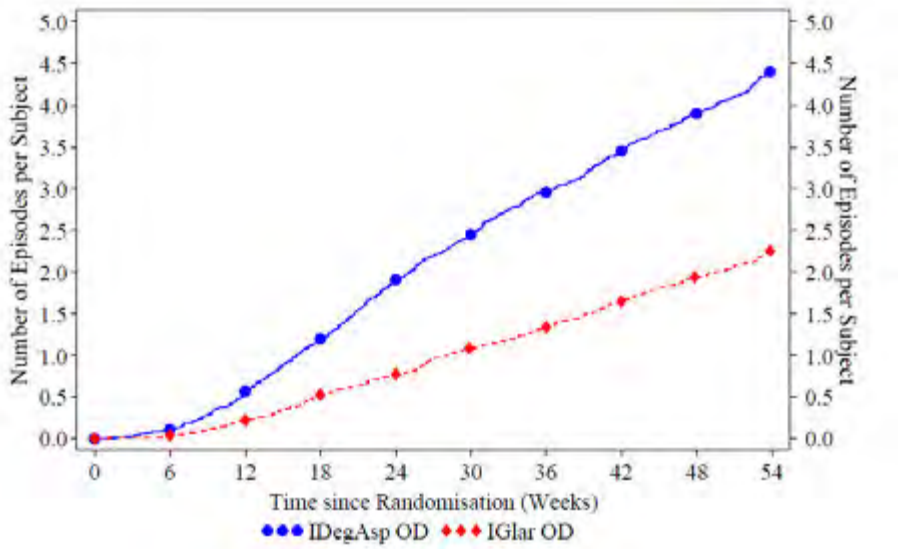
*'Regarding Study NN5401-3726, please comment on the difference in rates of confirmed hypoglycaemic episodes.'*

#### 11.1.1. Sponsor's response

During the main trial period, the IDegAsp treatment group received dosing at breakfast; this was independent of intake. In the extension study (that is, Study NN5401-3726) IDegAsp could be taken either with breakfast or the largest meal. Subjects in the IGlar treatment group received dosing according to approved labelling throughout the trial (no further details provided).

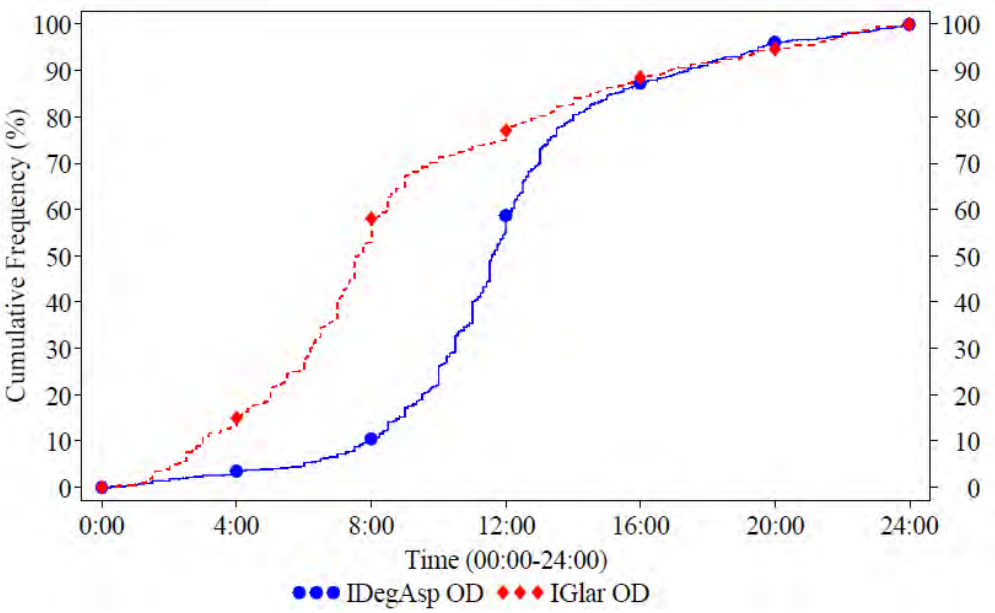
As seen in the following graph, the rate of confirmed hypoglycaemic episodes was similar in the initial 6 weeks of the combined trials, however thereafter a higher rate is seen in the IDegAsp group.

**Figure 5: Confirmed hypoglycaemic episodes, treatment emergent; mean cumulative function (Safety analysis set, Study NN5401-3726)**




The difference in timing of hypoglycaemic episodes is seen in the graph below. The sponsor notes that the timing of the confirmed hypoglycaemic episodes differed between the 2 treatment groups; most hypoglycaemic episodes in the IDegAsp group occurred between 08:00 and 12:00, whereas on the IGlar arm, they tended to occur between 04:00 and 08:00. The sponsor hypothesised that this may be because IDegAsp was predominantly administered at breakfast which may not have been the main meal and that the IAsp component of the IDegAsp is likely to have caused this. This also gives an indication as to why the IGlar arm had a higher rate of nocturnal (defined as occurring between 00:01 and 05:59) confirmed hypoglycaemia episodes.

**Figure 6: Confirmed hypoglycaemic episodes, treatment emergent; cumulative frequency over day (Safety analysis set, Study NN5401-3726)**




The proposed product information will state that *'Ryzodeg can be administered once or twice daily with the main meal(s). When needed, the patient can change the time of administration as long as Ryzodeg is dosed with the largest meal when taken once daily.'*

### 11.1.2. Evaluator's comment

Cumulative data across the main and extension studies showed that the hypoglycaemic episodes associated with IDegAsp tend to be more common in the timeframe after breakfast compared to IGlar.

The sponsor has suggested that the difference in hypoglycaemia seen between the IDegAsp and IGlar arms may be due to the dosing instructions in the main study, which were subsequently changed in the extension study. However, the sponsor did not present hypoglycaemia data for Study NN5401-3726 only (extension); combined data for the main-extension trial only was presented. Therefore, the impact of changed dosing instructions (if any) on the hypoglycaemia pattern cannot be assessed.

It is noted in Figure 5 (see above) that the gradient for confirmed hypoglycaemic episodes on the IDegAsp arm is greatest in the first 26 weeks (timeframe of the main study) and this does seem to decrease slightly in the next 26 weeks, which coincides with the change in the protocol allowing dosing of IDegAsp to be dosed with the main meal in the extension study. However, the discrepancy in rates between the IDegAsp arm and IGlar arms does not appear to completely resolve in the latter 26 weeks (although exact gradient has not been calculated) and the timeframe of when these hypoglycaemia episodes occurred over the day is not clear.

No further information is sought.

## 11.2. Question 2

*'Please comment on the discrepancy in terms of T2DM subjects who were exposed to study drug for ≥ 12 months (9.7% IDegAsp compared to 17.7% comparator). This is not reflected as clearly in terms of completion of extension trials which showed that 92.4% of subjects completed the extension trials in the IDegAsp group compared to 93.9% of those in the comparator group.'*

### 11.2.1. Sponsor's response

The percentage of T1DM and T2DM subjects completing the extension trials was calculated as a proportion of subjects included in the extensions.

The percentage of T2DM subjects who were exposed to study drug for ≥ 12 months was calculated as a proportion of all subjects exposed to study drug regardless of planned study duration. As the majority of the studies in T2DM were 6 months in duration (only 2 were 12 months in duration) and due to 2:1 randomisation, more subjects were exposed to IDegAsp than the comparator. This has resulted in a skewed distribution across the treatment groups.

When considering only the 2 T2DM 12-month duration trials, the percentage of subjects with T2DM who were exposed for ≥ 12 months was 92% for IDegAsp and 96% for comparator (no comparator including in the pooled analysis from 1 of these trials, Study NN5401-4003).

### 11.2.2. Evaluator's comment

No further information is sought.

## 11.3. Question 3

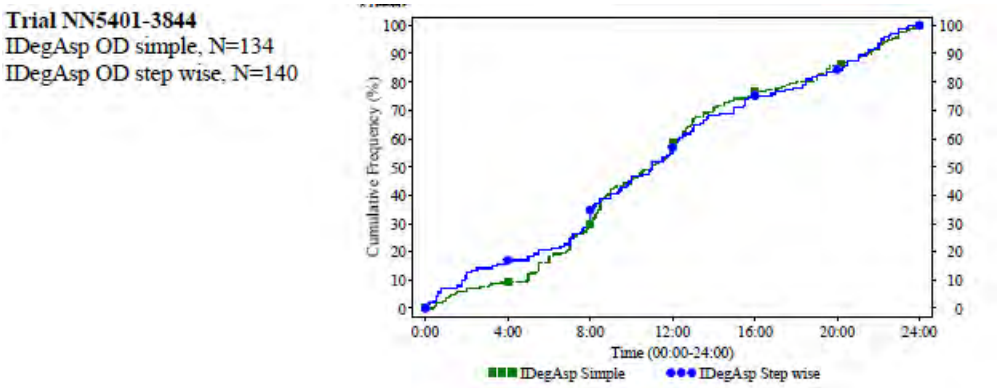
*'For the insulin naïve subjects (daily and twice daily dosing), please provide data which indicates what proportion of the hypoglycaemic episodes that occurred were post meal for both groups'.*

### 11.3.1. Sponsor's response

*Once daily therapy:* 3 IDegAsp trials included insulin-naïve subjects with T2DM on daily dosing:

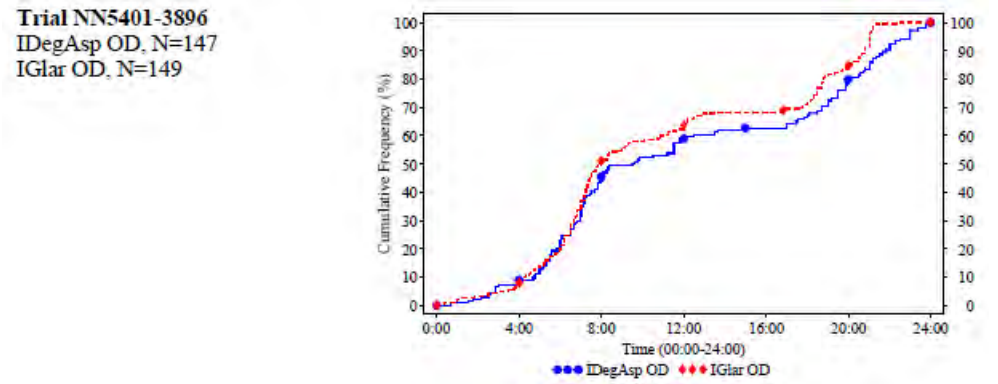
- Study NN5401-3726 (main and extension): see Figure 5 and question above.
- Study NN5401-3844: this trial compared simple versus stepwise titration IDegAsp, episodes outside of nocturnal period did not appear to cluster around a specific meal time (see Figure 7, below).

**Figure 7: Confirmed hypoglycaemic episodes, treatment emergent; cumulative frequency over day (Subjects with T2DM, insulin naïve, OD regimen; Safety analysis set, Study NN5401-3844)**



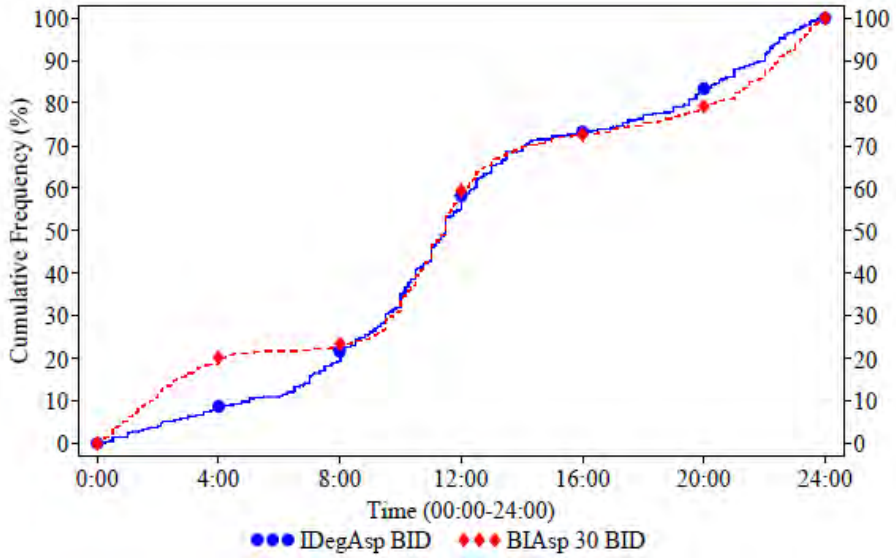

- Study NN5401-3896: this trial compared IDegAsp daily with IGlar daily; according to the study synopsis, IDegAsp was dosed prior to the largest meal of the day. In both groups, confirmed hypoglycaemic episodes mainly occurred approximately between 04:00 and 08:00 (pre-breakfast/ breakfast period) and between 18:00 and 24:00 (evening meal/post-evening meal period) (see Figure 8, below).

**Figure 8: Confirmed hypoglycaemic episodes, treatment emergent; cumulative frequency over day (Subjects with T2DM, insulin naïve, OD regimen; Safety analysis set, Study NN5401-3896)**




*Twice daily:* There was 1 IDegAsp trial which included insulin-naïve subjects with T2DM on twice daily dosing (Trial NN5401-3940). This trial compared IDegAsp twice daily with BIAsp 30 twice daily. In both treatment groups, the confirmed hypoglycaemic episodes mainly occurred between approximately 08:00 and 12:00 (breakfast/post-breakfast period) and between approximately 20:00 and 24:00 (evening meal/post-evening meal period) (see Figure 9, below).

**Figure 9: Confirmed hypoglycaemic episodes, treatment emergent; mean cumulative function (Subjects with T2DM, insulin naïve, BD regimen, Safety analysis set; Study NN5401-3940)**




### 11.3.2. Evaluator's comment

In Study NN5401-3896, patients were dosed daily with IDegAsp prior to the largest meal of the day and may be receiving up to 2 oral antidiabetic drugs. Despite dosing prior to the largest meal, hypoglycaemia was seen around the time of breakfast and after dinner for the IDegAsp arm.

In Study NN5401-3940, twice daily dosing of IDegAsp occurred at breakfast and the main evening meal and was given in combination with metformin. Hypoglycaemia episodes coincided with these timeframes.

As noted previously, in Study NN5401-3726 (main and extension) hypoglycaemia episodes occurred mostly in the breakfast/post breakfast timeframe. Although it is acknowledged that in the main study dosing occurred with breakfast which was not necessarily the largest meal of the day, this was changed in the extension trial. However, data for the extension study only was not provided by the sponsor.

From these studies, it can be seen that post meal hypoglycaemia is seen with IDegAsp, both with daily dosing or twice daily dosing, even in a clinical trial setting and even when IDegAsp is given before the largest meal. Although it is acknowledged that there are other factors influencing hypoglycaemia occurrence, not just insulin administration, it is important that the PI and CMI contain adequate information to reduce the risk of hypoglycaemia in the 'real world' setting.

No further information is sought.

## 11.4. Question 4

*'Please provide additional details specific to the 10 documented events of mix up between bolus and IDegAsp (from a table from the PSUR). Please also explain why only the number of adult subjects at risk is so small in the table (n = 382 for IDegAsp and 180 for comparator) entitled 'Overview of all treatment-emergent, mix-ups in therapeutic confirmatory trials, T1DM+ T2DM, adult population''.*

### 11.4.1. Sponsor's response

- Number of subjects included in the summary of mix ups.

The table in the PSUR includes data from 2 completed Phase III trials (Studies NN5401-3645 and NN5401-4003) which included a basal bolus regimen (IDegAsp + IAsp) in which there was therefore a potential risk of mix up between IDegAsp and bolus insulin.

- Additional details on the 10 mix ups

10 events of mix ups (preferred term 'wrong drug administered') were reported in 9 subjects, all in Study NN5401-3645. Of these, 1 event was considered to be serious by the investigator. In 8 events, IAsp was injected instead of IDegAsp and in the other two events IDegAsp was injected instead of IAsp. In most cases, hypoglycaemia was avoided by subjects adjusting their oral intake and monitoring blood glucose more intensely; 4 mix ups (all IAsp administration instead of IDegAsp) resulted in non-serious symptomatic hypoglycaemic episodes.

### 11.4.2. Evaluator's comment

The sponsor has indicated that there are 2 trials in which there was potential risk of mix up; however, all of the reported events occurred in Study NN5401-3645. It is noted that the other trial, Study NN5401-4003 was small with only 40 subjects randomised in total. No further information sought.

See also comment regarding the sponsor's response arising from the Summary of safety concerns comments below, which is related to this question.

## 11.5. Question 5

*'In relation to the use of IDegAsp in T2DM, does the sponsor have any data on the use of insulin aspartate in patients with T2DM in Australia?'*

### 11.5.1. Sponsor's response

Data from the Pharmaceutical Benefits Scheme (PBS) 10% dataset (a standardised dataset from the PBS) for Q4 2016 indicated that IAsp was the most frequently prescribed short acting insulin for patients with T2DM (see Table 19, below), however there are a number of limitations associated with using this data as the patient population definitions are derived from demographic factors and prescribing patterns (not actual diagnoses) and the population of T1DM patients tends to be underestimated in comparison to reports from the Australian National Diabetes Services Scheme.

**Table 19: Number of T1DM and T2DM patients in PBS 10% dataset who were prescribed short acting insulins by brand name; Q4 2016**

| Brand name | Description | T1DM patients | T2DM patients |
|---|---|---|---|
| NovoRapid® | Insulin aspart | 52,848 | 75,916 |
| ActRapid®/Humulin® R[a] | Human insulin | 3,152 | 5,792 |
| Humalog® | Insulin lispro | 12,178 | 7,000 |
| Apidra® | Insulin glulisine | 1,617 | 6,959 |
| NovoMix® 30 | Insulin aspart/protamine-crystallised insulin aspart in the ratio 30/70 | 3,766 | 62,509 |

[a] Data for ActRapid® and Humulin® R were combined in the data provided to Novo Nordisk.

### 11.5.2. Evaluator's comment

No further information sought.

# 12. Second round benefit-risk assessment

## 12.1. Second round assessment of benefits

No change to assessment of benefits.

## 12.2. Second round assessment of risks

In the first round report, hypoglycaemia was identified as a risk. Assessment of this risk is updated below in Table 20 (new text in *italics*); assessment of other risks identified in the first round remains unchanged.

**Table 20: Second round assessment of risks**

| Risks | Uncertainties |
|---|---|
| Hypoglycaemia: Hypoglycaemia and events related to hypoglycaemia, commonly occurred with the use of IDegAsp in the clinical trials. It is recognised that hypoglycaemia is an inherent risk associated with all insulins, however due to the 'ultra long' action, the period following a single dose in which hypoglycaemia may occur is longer than other insulins.<br>*It is also noted that hypoglycaemia episodes appear to occur around mealtimes in insulin naïve patients, even when IDegAsp is administered with the largest meal.*<br>However, it is also acknowledged that the aetiology of hypoglycaemia is multifactorial and the type of insulin used is only 1 important component. Thus education of prescribers and patients again will play an important part in mitigating this risk. | |

## 12.3. Second round assessment of benefit-risk balance

Overall, the benefit-risk balance is positive for IDegAsp provided appropriate steps for education of prescribers and patients are undertaken and active ongoing monitoring for detected signals is maintained.

# 13. Second round recommendation regarding authorisation

At this stage, the clinical evaluator has no major concerns for the approval of the registration of IDegAsp for the treatment of diabetes subject to PI comments [discussed elsewhere and beyond the scope of this document].

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